Contents lists available at ScienceDirect





Science of the Total Environment

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

Ambient NO₂ exposure hinders long-term survival of Chinese middle-aged and older adults



Yaqi Wang ^{a,1}, Siqi Luo ^{a,1}, Jing Wei ^b, Zhiming Yang ^c, Kejia Hu ^d, Yao Yao ^e, Yunquan Zhang ^{a,f,*}

^a Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University of Science and Technology, Wuhan, Hubei, China

- ^b Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park 20742, USA
- ^c School of Economics and Management, University of Science and Technology Beijing, Beijing 100083, China
- ^d Institute of Big Data in Health Science, School of Public Health, Zhejiang University, Hangzhou 310058, China
- ^e China Center for Health Development Studies, Peking University, Beijing 100191, China

^f Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology, Wuhan 430065, China

HIGHLIGHTS

- National study to assess association between long-term NO₂ exposure and mortality in China.
- No evident violation for linear relationship was found at a range of 7.4–45.0 μg/m³.
- Estimated NO₂-mortality association was robust to additional adjustment of copollutants.
- Elevated mortality risk was only identified among participants aged 65 and over.

ARTICLE INFO

Editor: Scott Sheridan

Keywords: Nitrogen dioxide All-cause mortality Cohort study Long-term exposure China





ABSTRACT

Introduction: Serval longitudinal investigations have reported relationships between long-term nitrogen dioxide (NO_2) exposure and mortality. In developing countries such as China, however, the cohort evidence was extremely rare. In this study, we aimed to establish the concentration-response relationship between long-term exposure to NO_2 and mortality in Chinese adults.

Methods: We conducted a prospective cohort study followed up from 2011 to 2018, by enrolling 15,440 participants aged \geq 45 years from 28 provincial regions of China. NO₂ concentration estimates were derived from high-quality spatiotemporal datasets developed by machine learning methods and were assigned for each participant according to their residential cities. We applied Cox proportional hazard models with time-varying exposures to assess the association of all-cause death with long-term NO₂ exposure. Subgroup analyses were performed to identify effect modifications.

Results: A total of 1646 death events occurred during 105,478.5 person-years follow-up (median 7.1 years). No evident violation for linear NO₂-mortality relationship (*P* nonlinear = 0.332) was observed at a range of 7.4–45.0 μ g/m³. Per 10- μ g/m³ rise in NO₂ was associated with an hazard ratio of 1.220 (95% confidence interval: 1.103–1.350) for all-cause mortality. The association between NO₂ and mortality was generally robust after adjusting for co-pollutants including fine particulate matter or/and ozone. Only participants aged 65 and over (1.351 [1.193–1.531]) suffered from increased risks of death associated with NO₂ exposure, and an evident effect modification by age (*P* = 0.008) was identified. The elevated risk of death induced by NO₂ was also observed in participants living in rural areas and those with elementary school education or below, though effect modifications were non-significant in these subgroups.

* Corresponding author at: Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University of Science and Technology, Wuhan 430065, China. *E-mail address*: YunquanZhang@wust.edu.cn (Y. Zhang).

¹ Yaqi Wang and Siqi Luo were co-first authors who contributed equally to this work.

http://dx.doi.org/10.1016/j.scitotenv.2022.158784

Received 13 May 2022; Received in revised form 25 August 2022; Accepted 11 September 2022 Available online 15 September 2022 0048-9697/© 2022 Elsevier B.V. All rights reserved. *Conclusions*: This study provided novel evidence that long-term NO₂ exposure could be an independent risk for mortality among Chinese middle-aged and older adults. Our findings highlighted the importance of controlling air pollution induced by vehicle emissions.

1. Introduction

Nitrogen dioxide (NO₂) predominantly stemming from fuel combustion and vehicle emission (Qian et al., 2021) has raised growing concern across the globe in the context of transportation development (Weichenthal et al., 2021). Several systematic reviews have reported a positive association between long-term exposure to NO₂ and mortality (Beelen et al., 2014; Huang et al., 2021; Huangfu and Atkinson, 2020). However, the majority of studies came from developed areas such as North America and Europe (Huang et al., 2021), with considerably sparse evidence from low- and middle-income countries where people were projected to have high vulnerability to air pollution. In order to facilitate the global assessment of disease burden related to NO₂ exposure, more population-based studies are of great necessity and significance in less-developed regions.

With the implementation of ongoing clean air actions (e.g., The Air Pollution Prevention and Control Action Plan), ambient NO₂ level in China has declined over the past few years (Cui et al., 2019; Lin et al., 2021). Nevertheless, current NO₂ concentration in China still far exceeds the updated guideline ($10 \ \mu g/m^3$) recommended by World Health Organization (WHO, 2021). To date, only three studies have explored the association between long-term NO₂ exposure and mortality in China (Chen et al., 2016b; Yang et al., 2018; Zhang et al., 2022), but great heterogeneity existed. Specifically, a national investigation reported an increased risk of mortality associated with long-term NO₂ exposure (Zhang et al., 2022), whereas no positive association was observed in two regional studies (Chen et al., 2016b; Yang et al., 2018). To better support environmental health policymaking in the context of accelerated aging in China in the coming decades (Vollset et al., 2020), high-quality evidence regarding the chronic effects of NO₂ on the survival of older adults is highly warranted.

Here, we conceived a nationally representative prospective cohort study in mainland of China, using face-to-face computer-assisted personal interview survey data of ~15,000 middle-aged and older adults. The primary aim of our study was to establish the concentration-response relationship between long-term NO₂ exposure and all-cause mortality in Chinese adults. The secondary purpose was to identify susceptible populations by comparing estimated mortality risk across subgroups.

2. Methods

2.1. Study data and cohort design

The data of this study was derived from the China Health and Retirement Longitudinal Study (CHARLS), an ongoing national survey for persons 45 years of age and older in mainland of China. Study participants of CHARLS were chosen from 450 communities at 150 country-level units within 28 provinces through multistage probability sampling (Chen et al., 2015; Zhao et al., 2014). The baseline survey among 17,708 participants was conducted between June 2011 and March 2012, and participants were generally followed up every 2–3 years through health examination and questionnaire investigation (Zhao et al., 2014). The CHARLS study has been approved by the Ethics Committee of Peking University Health Science Center, and all participants gave written informed consent before participation.

To date, the CHARLS has publicly released the baseline (2011 - 2012) and three waves of follow-up survey data during 2013–2018 (http://charls.pku.edu.cn/en/, accessed on April 14th, 2022). Therefore, the data of CHARLS from 2011 to 2018 was included for cohort design in this study. Verbal autopsies were used to identify the death information of deceased CHARLS participants (Chen et al., 2015), which were ascertained from their family members in consequent interviews. Due to

the lack of clinical diagnoses prior to the events of death (Zhang et al., 2020), about 25% of relatives could not provide specific death information for these decedents. In view of those unknown or indefinable causes of death, therefore, only mortality outcome from all causes was considered in this study. Participants were excluded due to lost to follow-up during 2013–2018 (n = 765), invalid or erroneous death date (n = 25), younger than 45 years (n = 347), and missing information on crucial variables (n = 1131) (Fig. S1). Finally, a total of 15,440 individuals from 125 cities (Fig. 1a) were assembled into our cohort analysis, and the number of individuals per province was geographically illustrated in Fig. 1b.

2.2. Exposure assessment

The ChinaHighNO₂ data of monthly ground-level NO₂ concentration during 2005-2018 were obtained from the China High Air Pollutants (CHAP) database (https://weijing-rs.github.io/product.html, accessed on April 14th, 2022), a full-coverage and high-quality gridded data with a spatial resolution of $0.25^{\circ} \times 0.25^{\circ}$. The dataset was originally generated from OMI Tropospheric NO₂ products based on satellite remote sensing and machine-learning methods. Estimates of this dataset have a good consistency with the values from ground monitoring stations, with a crossvalidation coefficient of determination (CV-R²) of 0.72 and a root-meansquare error (RMSE) of 9.97 μ g/m³. Modeling details could be found in our prior publications (Wei et al., 2021, 2022a, 2022b). Owing to privacy concerns, village- or street-level residential addresses for participants were concealed from publicly released CHARLS data. We thus performed exposure assessments at the city-level by linking participants to 125 cities. Monthly mean NO₂ concentrations for 125 cities during 2005-2018 were calculated through aggregating cell grid estimates into city-level averages. Using monthly mean concentrations of these cities, we evaluated annual average exposures for each calendar year and each city during the study period.

To account for the confounding effects of co-pollutants, we derived annual estimates of fine particulate matter (PM_{2.5}) and ozone (O₃) concentrations at a 0.1° × 0.1° resolution from the Global Burden of Disease Study 2019 (https://ghdx.healthdata.org/gbd-2019, accessed on April 14th, 2022). PM_{2.5} concentrations were estimated by using Data Integration Model for Air Quality. Modeling testing results showed a median R² value (0.9) and median population-weighted RMSE (10.1 μ g/m³) (Murray et al., 2020). M³Fusion and Bayesian Maximum Entropy methods were applied to estimate global O₃ concentrations, with a good prediction accuracy (R² = 0.63, RMSE = 10.86 μ g/m³) (DeLang et al., 2021). Details of these prediction models could be found in previously published articles (Hu et al., 2018; van Donkelaar et al., 2016). Participants were assigned annual average city-level exposures to each pollutant for each calendar year during the study periods.

2.3. Covariates

In consistency with previous studies (Shi et al., 2022; Stieb et al., 2021), we considered a series of potential confounders, including demographic characteristics (e.g., sex, age, education attainment, marital status), behavior factors (e.g., smoking and alcohol drinking), physical conditions (e.g., chronic diseases and body-mass index [BMI]), and geographic distribution (residence and region). In particular, education attainment was grouped into elementary school and below (0–6 yrs), middle school and above (\geq 7 yrs). Marital status was categorized as married and living, married but separated, and single or divorced and widowed. Chronic diseases included cardiovascular disease (CVD) and respiratory diseases. BMI was classified into three groups according to Chinese standard (Zhou et al., 2002):

Y. Wang et al.



Fig. 1. Geographical distributions of participants and NO₂ annual average concentrations. (a) location of 125 survey cities; (b) the number of subjects by province; (c) and (d) annual average NO₂ concentration in 2011 and 2018, respectively. Abbreviation: NO₂, nitrogen dioxide.

underweight (<18.5 kg/m²), normal weight (18.5 kg/m² \leq BMI < 24 kg/m²), and overweight (\geq 24 kg/m²).

2.4. Statistical analysis

Cox proportional hazard models with time-varying exposures on the annual time scale were applied to assess the long-term association between NO₂ exposure and all-cause mortality. We calculated personyears of follow-up from study enrolment to loss to follow-up, the end of this study, or date of death, whichever came first. One observation was created for each person for each year of mortality follow-up (Zanobetti et al., 2012). Considering the long-term time-trend of NO₂ concentration, we use calendar year as the time-scale in our Cox model (Griffin et al., 2012). All models were stratified by sex and age (i.e., 44–54, 55–64, 65–74, 75–84 and \geq 85), adjusting aforementioned confounders as well. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated for an increase of 10-µg/m³ in NO₂ exposure.

Restricted cubic spline (RCS) with 3 knots was used to smooth the concentration-response (C-R) curve between NO_2 exposure and all-cause mortality (Bentayeb et al., 2015; Cesaroni et al., 2013). We selected the

knot number for RCS smoothing via the Akaike information criterion (AIC) and Bayesian information criterion (Li et al., 2018; Liang et al., 2020) (Table S1). Nonlinearity of C-R curve was checked by comparing the model fit of treating NO₂ as linear and nonlinear term through a likelihood ratio test. To identify vulnerable subpopulations, we performed subgroup analyses stratified by sex, age (45–64 versus \geq 65 yrs), smoking and alcohol drinking status, CVD and respiratory diseases (yes or no), residence (rural versus urban), region (north versus south), and education attainment (0–6 versus 7 + yrs).

Sensitivity analyses were conducted to examine the robustness of NO₂mortality associations. First, we excluded participants who died within the first year since baseline survey to investigate potential reverse causality bias. Second, we applied bi-pollutant and tri-pollutant (NO₂ plus PM_{2.5} or/and O₃) models in an analysis to eliminate the confounding effects of co-pollutants, because existing epidemiologic evidence has associated mortality with long-term PM_{2.5} and O₃ exposure (Di et al., 2017; Zhang, 2021). Third, we used directed acyclic graph (DAG) to determine a minimal sufficient adjustment set of variables and estimated the association of NO₂-mortality using variables depicted in Fig. S2. DAG was widely used to select covariates for minimizing confounding bias in epidemiological studies (Textor et al., 2016). We performed all statistical analyses in R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), using "survival" package for the Cox modeling and "rms" package for RCS smoothing. Two-sided tests with *P*-value <0.05 were considered to be statistically significant.

3. Results

Table 1 describes basic characteristics of 15,440 study participants included in this cohort. During 105,478.5 person-years follow-up (median 7.1 years), a total of 1646 death events occurred. The mean (\pm SD [standard deviation]) age of participants was 59.5 \pm 9.8 years, and 52.9% of participants were women. Study subjects enrolled from rural regions shared 61.1%, and 44.4% lived in northern provinces. Smokers and alcohol drinkers accounted for 38.1% and 30.6%, respectively. Approximately one-third and a tenth of respondents reported the prevalence of CVD and respiratory diseases at the baseline, respectively. There were three in five subjects whose BMI was within the normal weight range (18.5 kg/m² \leq BMI < 24 kg/m²).

Table 2 gives the summary statistics of air pollutants exposures for 125 study cities during 2011–2018. Annual average concentration of NO₂ for surveyed cities varied substantially from 7.4 µg/m³ to 44.7 µg/m³, showing an overall decline of 3.0μ g/m³ from 2011 (20.6 µg/m³, Fig. 1c) to 2018 (17.6 µg/m³, Fig. 1d). Specifically, 118 of the 125 cities (Table S2) experienced a reduction in NO₂ levels during 2011–2018, with an over 20% decline in nearly a quarter of survey cities and the greatest decline in the Beijing-Tianjin-Hebei region (Fig. S3). During the study period, ambient levels for O₃ and PM_{2.5} in China generally exhibited a downward trend (Fig. S4), with 8-year mean concentrations of 101.1 µg/m³ (range:

Table 1

Variables	Statistics
Persons, n (%)	15,440
Death, n (%)	1646 (10.7)
Total person-years	105,478.5
Median year of follow-up	7.1
Age (mean \pm SD), yrs	59.5 ± 9.8
Sex, n (%)	
Male	7272 (47.1)
Female	8168 (52.9)
Education level, n (%)	
Elementary school and below	10,418 (67.5)
Middle school and above	5022 (32.5)
Marital status, n (%)	
Married and living	12,625 (81.8)
Married but separated	895 (5.8)
Single, divorced or widowed	1920 (12.4)
BMI (kg/m^2) , n (%)	
<18.5	900 (5.8)
[18.5, 24]	9442 (61.2)
≥24	5098 (33.0)
Smoking status, n (%)	
Non-smoker	9560 (61.9)
Smoker	5880 (38.1)
Drinking status, n (%)	
Non-drinker	10,709 (69.4)
Drinker	4731 (30.6)
Residence, n (%)	
Rural	9431 (61.1)
Urban	6009 (38.9)
Regional distribution, n (%)	
North	6850 (44.4)
South	8590 (55.6)
Cardiovascular diseases, n (%)	
Yes	5375 (34.8)
No	10,065 (65.2)
Respiratory diseases, n (%)	.,,
Yes	1802 (11.7)
No	13,638 (88.3)

Abbreviations: SD, standard deviation; $\mathrm{NO}_2,$ nitrogen dioxide, BMI, bodymass index.

Table 2

Descriptive characteristics of air pollutants at participants' residential cities during 2011–2018 and Spearman's rank correlation coefficients among the air pollutants.

	Mean ± SD Min.		Quartile			Max.	Correl	ation co	efficient
(µg/m ³)			P ₂₅	P ₅₀	P ₇₅		NO_2	O_3	PM _{2.5}
NO_2	21.2 ± 6.3	7.4	16.5	20.3	25.2	44.7	1.00		
O ₃	101.1 ± 14.8	60.7	90.2	101.2	111.0	142.4	0.45	1.00	
$PM_{2.5}$	52.8 ± 18.2	16.1	38.8	51.0	65.7	102.4	0.77	0.59	1.00

Abbreviations: SD, standard deviation; NO₂, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; O₃, ozone.

60.7–142.4) and 52.8 μ g/m³ (16.1–102.4), respectively (Table 2). NO₂ was moderately correlated with O₃ (r = 0.45), and the correlation coefficient was 0.77 between NO₂ and PM_{2.5}.

Fig. 2 outlines the C-R curve between long-term NO₂ exposure and allcause mortality. An approximately linear NO₂-mortality association (*P* nonlinear = 0.332) was observed at a range of 7.4–45.0 μ g/m³, with a slightly moderated slope at concentrations above 20 μ g/m³. Per 10- μ g/m³ increase in annual average NO₂ concentration was associated with an HR of 1.220 (95% CI: 1.103–1.350). The look-up table of HR estimates based on C-R function stemming from our study was available in Table S3. NO₂mortality association remained robust to modeling adjustments in our sensitivity analyses (Table S4). DAG-based analysis provided a comparable HR estimate of 1.192 (1.070–1.328) to fully adjusted model. NO₂-related risk increased slightly when excluding participants who died within the first year since baseline survey (1.242, 1.118–1.381), and performing analyses using bi-pollutant and tri-pollutant models.

Fig. 3 summarizes HR estimates in subgroup analyses stratified by behavioral characteristics, geographical distribution, and health status. For a 10-µg/m³ increase in annual NO₂ exposure, we observed overlapped risks of mortality between sex, with an HR of 1.258 (1. 098–1.441) for males and 1.167 (1.002–1.359) for females. Only participants aged 65 and over (1.351 [1.193–1.531]) suffered from increased risk of death associated with NO₂ exposure, and an evident effect modification by age (*P* = 0.008) was identified. A significant NO₂-mortality association was found among participants with elementary school education and below, with a corresponding HR of 1.270 (1.133–1.424). Only those living in rural and southern areas had a significantly increased risk associated with NO₂, and participants with cardiovascular and respiratory diseases suffered greater NO₂-related risks of death. Positive and highly comparable associations were seen between subgroups stratified by smoking and alcohol drinking status.

4. Discussion

To our knowledge, this is the first nationwide prospective cohort study to examine the association between long-term exposure to NO_2 and allcause mortality among Chinese middle-aged and older adults. Our findings suggested that long-term exposure to NO_2 may play an independent risk in triggering death. Stratified analyses revealed that the mortality risk of exposure to NO_2 differed across age, indicating a significantly greater vulnerability among those aged 65 and older.

In line with documented studies (Beelen et al., 2014; Chen et al., 2013; Huangfu and Atkinson, 2020), we found a positive association between mortality risk and NO₂ exposure, with an HR of 1.220 (95% CI: 1.103–1.350) for a 10- μ g/m³ rise. This association was stronger than an estimated risk of 1.127 (1.042–1.219) in a younger cohort (45.6 ± 16.3 yrs) enrolled in 162 Chinese counties (Zhang et al., 2022). In contrast, a regional analysis of adults aged 23–89 years conducted in northern China reported a negative NO₂-mortality relation (Chen et al., 2016b), while the Hong Kong cohort research failed to find a positive association among the elderly (\geq 65 yrs) (Yang et al., 2018). This inconsistency may be related to differences in demographic characteristics (e.g., population age) and exposure assessment methods (e.g., model- or station-based). Based on



Fig. 2. Concentration-response relationship of mortality with annual average NO_2 exposure modeled using a restricted cubic spline function with 3 knots. Abbreviation: NO_2 , nitrogen dioxide.

Characteristics	Subgroup	Hazard Ratio [95% CI]		P for interaction
All		1.220 [1.103–1.350] ***		
Sex	Male	1.258 [1.098–1.441] ***	F	[Ref.]
	Female	1.167 [1.002–1.359] *		0.470
Age group, yrs	45–64	1.013 [0.851–1.206]	⊢	[Ref.]
	≥65	1.351 [1.193–1.531] ***	⊢ − − 1	0.008
Education attainment, yrs	0–6	1.270 [1.133–1.424] ***	F	[Ref.]
	≥7	1.097 [0.877–1.371]		0.251
Smoking status	Yes	1.178 [1.019–1.362] *	⊢ I	[Ref.]
	No	1.228 [1.067–1.414] **	⊢	0.686
Alcohol consumption	Yes	1.255 [1.054–1.493] *	H	[Ref.]
	No	1.208 [1.067–1.367] **	F	0.727
Residence	Urban	1.105 [0.937–1.302]	⊢┼╼╌┤	[Ref.]
	Rural	1.274 [1.120–1.449] ***	F	0.181
Region	South	1.178 [1.004–1.383] *		[Ref.]
	North	1.177 [0.999–1.386]		0.992
CVD	Yes	1.259 [1.085–1.461] **	F =	[Ref.]
	No	1.165 [1.014–1.339] *		0.456
Respiratory diseases	Yes	1.366 [1.060–1.761] *	H	[Ref.]
	No	1.187 [1.063–1.325] **	F	0.319

Fig. 3. Subgroup analyses of hazard ratios (with 95% CIs) of all-cause mortality associated with a $10-\mu g/m^3$ increase in annual average NO₂ exposure. Notes: ** *P* < 0.01, *** *P* < 0.001. Abbreviations: CI, confidence interval; NO₂, nitrogen dioxide; CVD, cardiovascular disease.

current cohort evidence, the association of NO_2 -mortality is inconclusive in China. Therefore, further investigations with a larger representative population sample are needed to explore the relationship between long-term exposure to NO_2 and mortality in China.

The majority of existing NO2-mortality studies failed to investigate C-R association (Eum et al., 2019; Hvidtfeldt et al., 2019). Three older cohorts of the American Medicare population reported a linear C-R association between NO₂ and mortality, indicating no apparent evidence of a safe threshold value (Ma et al., 2022; Qian et al., 2021; Shi et al., 2022). Meanwhile, two European large-scale cohorts in adults aged \geq 30 years showed no evidence of deviation from linearity for non-accidental death in relation to NO₂ exposure (Cesaroni et al., 2013; Fischer et al., 2015). Within NO₂ level of 6.9–57.4 μ g/m³, our prior cohort study (Zhang et al., 2022) in Chinese population (age ≥ 16 years) reported an approximately linear C-R relationship (P nonlinear = 0.273). Here, we also did not identify significant evidence (P = 0.332) for nonlinear NO₂-mortality association at an exposure range of 7.4–45.0 μ g/m³ (Fig. 2). Given the scarcity of populationbased evidence for NO₂-mortality association in China, more large-scale cohort studies in next decades should be warranted to facilitate assessment of diseases burden with regard to NO2 exposure.

Our stratified analyses revealed the potential effect modification by the prevalence of pre-existing cardiovascular or respiratory diseases in association between mortality and long-term exposure to NO₂, in spite of nonsignificant difference in susceptibility. Prior studies have suggested that persons with pre-existing cardiorespiratory diseases were more susceptible to air pollution (Lee et al., 2014; Rajagopalan et al., 2018; Shi et al., 2022), and their long-term survival may be subject to obstruct. The underlying biological mechanisms such as systemic oxidative stress and inflammatory (de Bont et al., 2022; Liang et al., 2020) may have played an essential role in increasing mortality, and these responses may have a larger impact on participants who have already compromised cardiorespiratory systems compared to healthy population (Chen et al., 2016a; de Bont et al., 2022; Schikowski et al., 2007). Stratified analyses only identified an elevated mortality risk associated with NO2 exposure among participants aged 65 and over, exhibiting a significant effect modification by age. The overall decline in physical function of the elderly makes them less able to protect themselves against the hazards of NO2 exposure. Moreover, cardiovascular and respiratory diseases prevalence in this study were higher in participants aged 65 and over (44.7% and 17.5%) than in those 45-64 years (30.3% and 9.4%), which may also be a potential explanation for the vulnerability in the older population (de Bont et al., 2022).

Serval limitations should be noted in the present study. First, we failed to evaluate the associations between cause-specific deaths and long-term exposure to NO2 given the unknown or indefinable causes of death. Our analysis could not exclude accidental deaths that were traditionally unlinked with air pollution exposure, but we don't think this issue will change the direction of the association between long-term NO2 exposure and mortality risk for two reasons: 1) the low proportion of accidental deaths in the total death cases, and 2) highly similar C-R relationships for all-cause and non-accidental mortality reported in prior air pollution cohort studies (Eum et al., 2022; Villeneuve et al., 2015). Second, owing to the unavailability of detailed residential addresses, participants' exposures were assessed at city level rather than residential addresses, which may lead to unavoidable exposure bias. Third, NO2 may be a proxy of traffic-related pollution such as traffic noise and trace dust (Hales et al., 2021). We could not rule out potential influence of these confounding factors, even though these unmeasured variables may still drive the NO2-mortality relationship. Fourth, since our cohort population is middle-aged and older adults, our findings may not be generalizable to the younger generations.

5. Conclusions

In summary, this nationwide cohort provided crucial evidence of NO₂mortality association among Chinese middle-aged and older adults. Our results suggested that long-term exposure to NO₂ may play an independent risk in triggering death, posing a great health threat among older adults in particular. Further population-based investigations should fully take advantage of fine spatial-temporal exposure datasets, so as to help guide air quality policymaking suitable for Chinese public.

CRediT authorship contribution statement

Yaqi Wang: Writing – original draft, Writing – review & editing, Methodology, Formal analysis. Siqi Luo: Writing – review & editing, Validation, Visualization. Jing Wei: Resources, Data curation. Zhiming Yang: Software, Visualization. Kejia Hu: Writing – review & editing. Yao Yao: Conceptualization, Validation. Yunquan Zhang: Writing – review & editing, Supervision, Funding acquisition.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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.

Acknowledgments

This study was supported by Hubei Provincial Natural Science Foundation of China (Grant No. 2021CFB032), Humanities and Social Sciences Research Project of Hubei Provincial Department of Education (Grant No. 21Q031), and Youth Fund Project of Humanities and Social Sciences Research of the Ministry of Education (Grant No. 21YJCZH229). We sincerely thank to the National Development Research Institute of Peking University and China Social Science Research Center of Peking University for providing CHARLS data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.scitotenv.2022.158784.

References

- Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., et al., 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet. 383 (9919), 785–795.
- Bentayeb, M., Wagner, V., Stempfelet, M., Zins, M., Goldberg, M., Pascal, M., et al., 2015. Association between long-term exposure to air pollution and mortality in France: a 25-year follow-up study. Environ. Int. 85, 5–14.
- de Bont, J., Jaganathan, S., Dahlquist, M., Persson, A., Stafoggia, M., Ljungman, P., 2022. Ambient air pollution and cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. J. Intern. Med. 291 (6), 779–800.
- Cesaroni, G., Badaloni, C., Gariazzo, C., Stafoggia, M., Sozzi, R., Davoli, M., et al., 2013. Longterm exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ. Health Perspect. 121 (3), 324–331.
- Chen, H., Goldberg, M.S., Burnett, R.T., Jerrett, M., Wheeler, A.J., Villeneuve, P.J., 2013. Long-term exposure to traffic-related air pollution and cardiovascular mortality. Epidemiology. 24 (1), 35–43.
- Chen, X., Smith, J., Strauss, J., Wang, Y., Zhao, Y., 2015. China Health and Retirement Longitudinal Study (CHARLS). Encyclopedia of Geropsychology, pp. 1–8.
- Chen, H., Burnett, R.T., Copes, R., Kwong, J.C., Villeneuve, P.J., Goldberg, M.S., et al., 2016a. Ambient fine particulate matter and mortality among survivors of myocardial infarction: population-based cohort study. Environ. Health Perspect. 124, 1421–1428.
- Chen, X., Zhang, L.W., Huang, J.J., Song, F.J., Zhang, L.P., Qian, Z.M., et al., 2016b. Long-term exposure to urban air pollution and lung cancer mortality: a 12-year cohort study in northern China. Sci. Total Environ. 571, 855–861.
- Cui, Y., Zhang, W., Bao, H., Wang, C., Cai, W., Yu, J., et al., 2019. Spatiotemporal dynamics of nitrogen dioxide pollution and urban development: satellite observations over China, 2005–2016. Resour. Conserv. Recycl. 142, 59–68.
- DeLang, M.N., Becker, J.S., Chang, K.L., Serre, M.L., Cooper, O.R., Schultz, M.G., et al., 2021. Mapping yearly fine resolution global surface ozone through the bayesian maximum entropy data fusion of observations and model output for 1990–2017. Environ. Sci. Technol. 55, 4389–4398.

Y. Wang et al.

- Di, Q., Wang, Y., Zanobetti, A., Wang, Y., Koutrakis, P., Choirat, C., et al., 2017. Air pollution and mortality in the Medicare population. N. Engl. J. Med. 376, 2513–2522.
- van Donkelaar, A., Martin, R.V., Brauer, M., Hsu, N.C., Kahn, R.A., Levy, R.C., et al., 2016. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. Environ. Sci. Technol 50, 3762–3772.
- Eum, K.D., Kazemiparkouhi, F., Wang, B., Manjourides, J., Pun, V., Pavlu, V., et al., 2019. Long-term NO₂ exposures and cause-specific mortality in American older adults. Environ. Int. 124, 10–15.
- Eum, K.D., Honda, T.J., Wang, B., Kazemiparkouhi, F., Manjourides, J., Pun, V.C., et al., 2022. Long-term nitrogen dioxide exposure and cause-specific mortality in the U.S. Medicare population. Environ. Res. 207, 112154.
- Fischer, P.H., Marra, M., Ameling, C.B., Hoek, G., Beelen, R., de Hoogh, K., et al., 2015. Air pollution and mortality in seven million adults: the Dutch Environmental Longitudinal Study (DUELS). Environ. Health Perspect. 123, 697–704.
- Griffin, B.A., Anderson, G.L., Shih, R.A., Whitsel, E.A., 2012. Use of alternative time scales in Cox proportional hazard models: implications for time-varying environmental exposures. Stat. Med. 31, 3320–3327.
- Hales, S., Atkinson, J., Metcalfe, J., Kuschel, G., Woodward, A., 2021. Long term exposure to air pollution, mortality and morbidity in New Zealand: cohort study. Sci. Total Environ. 801, 149660.
- Hu, L., Keller, C.A., Long, M.S., Sherwen, T., Auer, B., Da Silva, A., et al., 2018. Global simulation of tropospheric chemistry at 12.5 km resolution: performance and evaluation of the GEOS-chem chemical module (v10–1) within the NASA GEOS earth system model (GEOS-5 ESM). Geosci. Model Dev. 11, 4603–4620.
- Huang, S., Li, H., Wang, M., Qian, Y., Steenland, K., Caudle, W.M., et al., 2021. Long-term exposure to nitrogen dioxide and mortality: a systematic review and meta-analysis. Sci. Total Environ. 776, 145968.
- Huangfu, P., Atkinson, R., 2020. Long-term exposure to NO₂ and O₃ and all-cause and respiratory mortality: a systematic review and meta-analysis. Environ. Int. 144, 105998.
- Hvidtfeldt, U.A., Sorensen, M., Geels, C., Ketzel, M., Khan, J., Tjonneland, A., et al., 2019. Long-term residential exposure to PM_{2.5}, PM₁₀, black carbon, NO₂, and ozone and mortality in a Danish cohort. Environ. Int. 123, 265–272.
- Lee, B.J., Kim, B., Lee, K., 2014. Air pollution exposure and cardiovascular disease. Toxicol. Res. 30, 71–75.
- Li, T., Zhang, Y., Wang, J., Xu, D., Yin, Z., Chen, H., et al., 2018. All-cause mortality risk associated with long-term exposure to ambient PM_{2.5} in China: a cohort study. Lancet Public Health. 3, e470–e477.
- Liang, F., Liu, F., Huang, K., Yang, X., Li, J., Xiao, Q., et al., 2020. Long-term exposure to fine particulate matter and cardiovascular disease in China. J. Am. Coll. Cardiol. 75, 707–717.
- Lin, C., Lau, A.K.H., Fung, J.C.H., Song, Y., Li, Y., Tao, M., et al., 2021. Removing the effects of meteorological factors on changes in nitrogen dioxide and ozone concentrations in China from 2013 to 2020. Sci. Total Environ. 793, 148575.
- Ma, T., Yazdi, M.D., Schwartz, J., Réquia, W.J., Di, Q., Wei, Y., et al., 2022. Long-term air pollution exposure and incident stroke in American older adults: a national cohort study. Glob. Epidemiol. 4, 100073.
- Murray, C.J.L., Aravkin, A.Y., Zheng, P., Abbafati, C., Abbas, K.M., Abbasi-Kangevari, M., et al., 2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 396, 1223–1249.
- Qian, Y., Li, H., Rosenberg, A., Li, Q., Sarnat, J., Papatheodorou, S., et al., 2021. Longterm exposure to low-level NO₂ and mortality among the elderly population in the southeastern United States. Environ. Health Perspect. 129, 127009.
- Rajagopalan, S., Al-Kindi, S.G., Brook, R.D., 2018. Air pollution and cardiovascular disease: JACC state-of-the-art review. J. Am. Coll. Cardiol. 72, 2054–2070.

- Schikowski, T., Sugiri, D., Ranft, U., Gehring, U., Heinrich, J., Wichmann, H.E., et al., 2007. Does respiratory health contribute to the effects of long-term air pollution exposure on cardiovascular mortality? Respir. Res. 8, 20.
- Shi, L., Rosenberg, A., Wang, Y., Liu, P., Danesh Yazdi, M., Requia, W., et al., 2022. Lowconcentration air pollution and mortality in American older adults: a national cohort analysis (2001–2017). Environ. Sci. Technol. 56 (11), 7194–7202.
- Stieb, D.M., Berjawi, R., Emode, M., Zheng, C., Salama, D., Hocking, R., et al., 2021. Systematic review and meta-analysis of cohort studies of long term outdoor nitrogen dioxide exposure and mortality. PLoS One. 16, e0246451.
- Textor, J., van der Zander, B., Gilthorpe, M.S., Liskiewicz, M., Ellison, G.T., 2016. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int. J. Epidemiol. 45, 1887–1894.
- Villeneuve, P.J., Weichenthal, S.A., Crouse, D., Miller, A.B., To, T., Martin, R.V., et al., 2015. Long-term exposure to fine particulate matter air pollution and mortality among Canadian women. Epidemiology. 26, 536–545.
- Vollset, S.E., Goren, E., Yuan, C.W., Cao, J., Smith, A.E., Hsiao, T., et al., 2020. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. Lancet. 396 (10258), 1285–1306.
- Wei, J., Li, Z., Lyapustin, A., Sun, L., Peng, Y., Xue, W., et al., 2021. Reconstructing 1-kmresolution high-quality PM_{2.5} data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens. Environ. 252, 112136.
- Wei, J., et al., 2022a. Ground-level NO₂ surveillance from space across China for high resolution using interpretable spatiotemporally weighted artificial intelligence. Environ. Sci. Technol. 56 (14), 9988–9998.
- Wei, J., et al., 2022b. Full-coverage mapping and spatiotemporal variations of ground-level ozone (O₃) pollution from 2013 to 2020 across China. Remote Sens. Environ. 270, 112775.
- Weichenthal, S., Dons, E., Hong, K.Y., Pinheiro, P.O., Meysman, F.J.R., 2021. Combining citizen science and deep learning for large-scale estimation of outdoor nitrogen dioxide concentrations. Environ. Res. 196, 110389.
- WHO, 2021. WHO Global Air Quality Guidelines. Particulate matter (PM_{2.5} and PM₁₀), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization.
- Yang, Y., Tang, R., Qiu, H., Lai, P.C., Wong, P., Thach, T.Q., et al., 2018. Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. Environ. Int. 117, 99–106.
- Zanobetti, A., O'Neill, M.S., Gronlund, C.J., Schwartz, J.D., 2012. Summer temperature variability and long-term survival among elderly people with chronic disease. Proc. Natl. Acad. Sci. U. S. A. 109, 6608–6613.
- Zhang, Y., 2021. All-cause mortality risk and attributable deaths associated with long-term exposure to ambient PM_{2.5} in Chinese adults. Environ. Sci. Technol. 55, 6116–6127.
- Zhang, Y.S., Hu, P., Strauss, J.A., Zhao, Y., Wang, Y., Crimmins, E.M., 2020. Ascertaining cause of mortality among middle-aged and older persons using computer-coded and expert review verbal autopsies in the China Health and Retirement Longitudinal Study. Glob. Health Action 13, 1768502.
- Zhang, Y., Li, Z., Wei, J., Zhan, Y., Liu, L., Yang, Z., et al., 2022. Long-term exposure to ambient NO₂ and adult mortality: a nationwide cohort study in China. J. Adv. Res https://doi.org/10.1016/j.jare.2022.02.007.
- Zhao, Y., Hu, Y., Smith, J.P., Strauss, J., Yang, G., 2014. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int. J. Epidemiol. 43 (1), 61–68.
- Zhou, B.F., Chen, C.M., Zhao, X.H., Wu, Y.F., Zhao, L.C., Li, X., et al., 2002. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed. Environ. Sci. 15, 83–96.