Longitudinal association between ambient nitrogen dioxide exposure and all-cause mortality in Chinese adults

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Research Article

Abstract

A number of population-based studies have investigated long-term effects of nitrogen dioxide (NO_2) on mortality, while great heterogeneities exist between studies. In highly populated countries in Asia, cohort evidence for NO_2-mortality association was extensively sparse. This study aimed to quantify longitudinal association of ambient NO_2 exposure with all-cause mortality in Chinese adults. A national cohort of 30,843 adult men and women were drawn from 25 provincial regions across mainland China, and followed up from 2010 through 2018. Participants' exposures to ambient air pollutants were assigned according to their residential counties at baseline, through deriving monthly estimates from high-quality gridded datasets developed by machine learning methods. Cox proportional hazards models with time-varying exposures were utilized to assess the association of all-cause mortality with long-term exposure to ambient NO_2. An approximately linear NO_2-mortality relation (p=0.273 for nonlinearity) was identified across a broad exposure range of 6.9–57.4 µg/m^3. Per 10-µg/m^3 increase in annual NO_2 exposure was associated with an hazard ratio of 1.127 (95% confidence interval: 1.042–1.219, p<0.003) for all-cause mortality. Risk estimates remained robust after additionally adjusting for the confounding effects of co-pollutants (i.e., $PM_{2.5}$ or O_3). In 2018, 1.65 million deaths could be attributed to ambient NO_2 exposure (national average 17.3 µg/m^3) in China, representing a decrease of 4.3% compared with the estimate of 1.72 million in 2010 (20.5 µg/m^3). This cohort study provided national evidence for elevated risk of all-cause mortality associated with long-term exposure to ambient NO_2 in Chinese adults.

1. Introduction

Ambient nitrogen dioxide (NO_2) is a common air pollutant primarily originating from fuel combustion and traffic. As a precursor to ground surface ozone, NO_2 is also involved in the secondary generation of fine particles ($PM_{2.5}$). In recent decades, health assessments on NO_2's independent impact raised great research interests across the globe in the context of rapid urbanization and transportation development. Systematic reviews of epidemiologic studies have well documented short-term effects of NO_2 exposure on a variety of morbidity[1−6] and mortality[2−4, 7] outcomes, including cardiovascular (e.g., stroke and ischemic heart disease) and respiratory diseases (e.g., chronic obstructive pulmonary disease and pneumonia). A recent multi-country analysis[8] from 398 cities, for instance, provided robust evidence for independent NO_2-mortality associations from co-pollutants, linking a significant increase of 0.37−0.47% for total, cardiovascular, and respiratory mortality with per 10-µg/m^3 rise in daily NO_2 concentration. These findings highlighted the great significance and urgency for policy making to quantify the chronic effects of NO_2 exposure on human life expectancy.

During past decades, longitudinal associations between NO_2 exposure and mortality have been investigated in a large number of population-based cohort studies, whereas great heterogeneities were identified between regions and studies[9−12]. The majority of existing studies came from the western world[9, 10] including North America and the Europe, suggesting strong evidence for NO_2-induced risk of

all-cause death. In highly populated countries in Asia, cohort evidence for longitudinal NO_2-mortality association was extensively sparse[9, 10], thus introducing great uncertainty when performing the pooled analysis. In China, only two regional cohorts investigated chronic impacts of NO_2 exposure on mortality, identifying null associations among the Hong Kong elderly[13] but a protective effect in four northeast cities[14]. These mixed findings warranted more high-quality and large-scale longitudinal investigations across mainland China, for the sake of better understanding of mortality burden due to ambient NO_2 in Chinese population.

In this study, we conceived a nationwide prospective cohort of ~ 30,000 Chinese adult men and women, utilizing population-based survey data through 2010 to 2018 from the China Family Panel Studies spanning across 126 prefecture-level cities. Our primary purpose was to quantify the association of long-term exposure to ambient NO_2 with all-cause mortality in Chinese adults; A secondary purpose was to depict the spatiotemporal patterns of NO_2-attributable deaths between 2010 and 2018 in China, on the basis of dose-response function derived from our cohort analysis.

2. Materials And Methods

2.1 Study population and design

Study population in this study was drawn from the China Family Panel Studies (CFPS) [15], an ongoing national survey across 25 provincial regions in mainland China. Using a multi-stage probability strategy with stratification [16], the CFPS baseline survey during April, 2010 through February, 2011 totally included 33,600 adult men and women ages 16–110 years, and follow-up investigations were conducted every two years during 2012–2020. Face-to-face interviews were performed aided by computer-assisted personal interviewing technology, and participants' data (e.g., demographic and socioeconomic characteristics, lifestyle, behavioral patterns, and health status) were thoroughly collected by well-trained investigators through standard questionnaires. The CFPS study has been ethically approved by the Peking University Biomedical Ethics Review Committee (Approval number: IRB00001052-14010), and all participants signed informed consent forms.

In purpose of investigating long-term NO_2-mortality association, we conceived a longitudinal cohort design using the CFPS baseline (CFPS-2010) and four consequent waves of follow-up data (CFPS-2012, 2014, 2016, and 2018), which were publicly available at the Peking University Open Research Data Platform (https://opendata.pku.edu.cn/dataverse/CFPS/). Death information (e.g., date and cause of death) for deceased CFPS participants were ascertained from their family members in the follow-up interviews. We only considered death events from all causes in this study, because some unknown or indeterminable causes of death were identified.

From 33,600 adult participants totally involved at CFPS baseline, we excluded those who had no follow-up data during 2012–2018 (n = 2549) and objects whose information on death date was invalid or

logically erroneous (n = 25). To avoid bias from selection of participants, we also excluded participants who died within the first year from the baseline interview[17, 18] (n = 183). A national cohort of 30,843 adult men and women were finally involved in our study, and distribution of the investigated subjects was geographically illustrated in Fig. 1.

2.2 Exposure assessment and covariates

2.2.1 Exposure assessment

CFPS redacted detailed residential address from the public-access data due to privacy considerations, exposure assessments for air pollutants were thus performed at the county level as a proxy. For each CFPS participant, we identified a county-level geographic unit using uniform 6-digit administrative codes in mainland China, and linked participants in our cohort to 162 counties in 25 provincial regions [19]. Based on administrative polygons of the 162 CFPS counties, we calculated monthly concentrations during 2005−2018 for ambient air pollutants (NO_2, $PM_{2.5}$, and O_3) through aggregating gridded estimates at spatiotemporal scales into county-level averages.

Ground surface concentrations of monthly NO_2 at a 0.25°×0.25° resolution were derived from the full-coverage and high-quality datasets for near-surface air pollutants in China. Gridded datasets for NO_2 (https://doi.org/10.5281/zenodo.3988349, ChinaHighNO$_2$) were originally generated from the OMI/Aura Tropospheric Column NO_2 products based on satellite remote sensing and machine-learning method (Space-Time Extra-Trees model, STET)[20]. Estimates from ChinaHighNO$_2$ datasets showed high consistency with nationwide ground monitors across China from 2013 to 2019, with an overall cross-validation coefficient of determination (CV-R^2) of 0.72 and root mean square error (RMSE) of 9.97 µg/m^3. Modelling details could be found in our previous publications[20, 21].

Monthly mean ozone concentrations at a 0.1°×0.1° resolution were estimated using a nationwide prediction model based on eXtreme Gradient Boosting (XGBoost) trees[22]. The prediction model was trained and validated using observations from 1713 sites between 2013−2017, and externally tested with regional monitors during 2005−2012 and nationwide measurements in 2018. Model testing results of monthly O_3 estimates showed high R^2 values (0.60−0.87) and low RMSEs (12.94−18.41 µg/m^3) in different years[22].

Ground monthly estimates of $PM_{2.5}$ concentrations at a 0.1°×0.1° resolution were extracted from a full-coverage high-resolution air pollutant dataset of Tracking Air Pollution in China (TAP, http://tapdata.org). As the first near real-time air pollutant database in China[23], TAP $PM_{2.5}$ developed by Tsinghua University is estimated based on a two-stage random forest model coupled with the synthetic minority oversampling technique and a tree-based gap-filling method[24]. This machine learning-based model exhibits good agreements with the ground monitors, with an out-of-bag CV-R^2 of 0.80−0.88 and RMSE of 13.9 − 22.1 µg/m^3 for different years.

2.2.2 Covariates

In light of prior cohort studies assessing NO_2-mortality associations[9, 10], we considered a rich set of potential confounders, including demographic characteristics (sex, age, ethnicity, education attainment, urbanicity, marital status, and employment status), lifestyle (smoking, alcohol consumption, physical activity, and sleep duration), health status (body-mass index [BMI], chronic disease prevalence, and depressive symptom), and household characteristics (annual household income, and household air pollution from solid fuels).

Specifically, ethnicity was defined as a dichotomous variable indicating Han or minority. Education attainment was grouped into illiteracy, primary or middle school, and high school or above. Smokers and alcohol drinkers referred to former and current status of regular smoking or drinking. Sleep duration was categorized into three groups: <6 h, 6−8 h, and more than 8 h. Physical activity was a dummy variable indicating whether a participant was a regular physical exerciser. Body-mass index was calculated by dividing weight in kilogram by squared height in m^2, and grouped into < 18.5, 18.5−24, and $24 + kg/m^3$. Chronic disease prevalence was coded as 1 if a participant had one or more doctor-diagnosed chronic diseases such as hypertension, stroke, and diabetes. Depressive status was measured by the K6 screening instrument of Center for Epidemiological Studies-Depression (CES-D) scale [25], and defined as depression episode if the CES-D score is higher than a cut-off of 24. Household income was categorized into three groups of < 15000 RMB, 15000−40000 RMB, and ≥ 40000 RMB generally based on its quartile distribution.

2.3 Statistical analysis

Baseline characteristics of study populations were presented as percentages for categorical variables or mean ± standard derivation (SD) for continuous variables. We assessed the long-term association between ambient NO_2 exposure and all-cause death using time-varying Cox proportional hazards models, and quantified temporal and spatial changes in estimates of deaths attributable to ambient NO_2 between 2010 and 2018. We did analyses with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and p-value < 0.05 was considered to be statistically significant.

2.3.1 Main multivariate analysis

Cox proportional hazards models with time-varying exposures on the annual time scale, were used to quantify long-term associations of NO_2 exposure with all-cause mortality. Person-years of follow-up were calculated as the intervals from the dates of baseline interviews (i.e., study enrolment) to the dates of death occurrence, loss to follow-up (the last follow-up interviews during 2012−2018), or the end of CPFS 2018, whichever came first. Motivated by prior investigations suggesting the potential for biased risk estimates using time-on-study time-scales [26−28], we adopted attained age as the time scale given the interpretability of the hazard ratio as a function of age[29]. All models were stratified by sex and age at baseline[30], which was grouped into 10-year intervals (i.e., 15−24, 25−34, 35−44, 45−54, 55−64, 65−74,

and ≥ 75) to allow for sufficient sample sizes for assessing interactions. We assessed hazard ratios (HRs) of all-cause death and corresponding 95% confidence intervals (CIs) associated with a 10-μg/m³ increase in exposure to annual NO_2 concentration, adjusting for aforementioned confounders.

To investigate the shape of concentration-response (C-R) curve for NO_2-mortality association, we input the term of annual NO_2 exposure as a restricted cubic spline (RCS) with 3 knots in the multivariate-adjusted model. The number of knots for RCS smoothing was selected according to Akaike information criterion and Bayesian information criterion [31, 32] (Table S1). Nonlinearity of concentration-response curve was examined through comparing the model fit of the linear and RCS models via a likelihood-ratio test [33–35].

2.3.2 Subgroup and sensitivity analyses

We performed subgroup analyses stratified by sex, age, smoking and drinking status, and physical activity. Two-sample z-tests [34, 36] were applied to identify potential effect modifications. Several sensitivity analyses were conducted to examine the robustness of $PM_{2.5}$-mortality associations estimated in our main analysis. First, to disentangle the effects of co-pollutants, we included two pollutants simultaneously (NO_2 plus $PM_{2.5}$ or O_3) in an analysis using a consistent annual scale for time-varying exposures. Second, we incorporated time-varying exposure for environmental temperature (e.g., annual average temperature) into our survival analysis to account for the long-term effects of weather conditions. Given emerging evidence with regard to nonlinear effects of temperature on mortality [37], we adjusted for annual average temperature through an RCS function with 3 knots[38]. Specifically, we first derived China's daily gridded temperatures (0.1°×0.1°) during 2010–2018 from the ERA5 climate reanalysis datasets produced by the European Center for Medium-Range Weather Forecasts (https://climate.copernicus.eu/climate-reanalysis), and then calculated county-specific average temperatures for 162 included counties to estimate participants' time-varying exposures at annual scales. Third, as an alternative method for selecting covariates [39], directed acyclic graph (DAG) was adopted was to determine minimal sufficient adjustment sets for estimating the total effect of nitrogen dioxide on adult mortality (Fig. S1). Finally, our DAG-based Cox model was stratified by sex and age and adjusted for educational attainment, household income, and urbanicity.

2.3.3 Attributable deaths due to NO_2 exposure

In line with the methodological strategy widely adopted in prior modelling studies [40, 41], we quantified spatiotemporal changes in NO_2-attributable deaths in China between 2010 and 2018. Based on the dose-response function estimated by the RCS smoother with 3 knots, we first derived HR estimates at a range of annual NO_2 concentrations with an interval of 0.1 μg/m³ through referring to a counterfactual exposure of 6.9 μg/m³ (the lowest county-average level in our cohort) [41]. For a given county (i) in China, attributable deaths (AD_i) due to NO_2 exposure were then calculated via multiplying total observed deaths (TD_i) in a specific year (e.g., 2010 and 2018) by population attributable fraction (PAF_i) estimated through the formula (HR−1)/HR×100%.[42] Total deaths attributable to ambient NO_2 in China and its provincial

regions could be finally yielded by summing up county-specific AD estimates for a given year. More details for AD calculation and relevant data sources could be found in the supplementary material, as documented in our prior publication[38].

3. Results

Table 1 describes the baseline characteristics of 30,843 study participants involved in this cohort. During a total of 224020.2 person-years' follow-up (median 8.1 year), 1662 all-cause deaths were identified from 2011 to 2018. Participants were aged 45.6 ± 16.3 years (range: 16–110 years), and 48.5% were men. 8-year mean NO_2 concentrations for 162 CFPS counties varied greatly from 10.3 μg/m^3 to 41.0 μg/m^3, exhibiting an overall decline of 3.7 μg/m^3 from 2010 (22.8 [range: 7.8–43.9] μg/m^3) to 2018 (19.1 [6.2–39.2] μg/m^3) in annual mean concentration (Table 2). The included study locations covered a wide span of latitudes across mainland China (Fig. 1), with a substantial temperature range of -2.0–24.2°C in 2010 (Table 2).

Table 1
Baseline characteristics of study participants included in the cohort.

Variables	Entire cohort	Quartiles* of NO$_2$ concentration, µg/m^3			
		Q1 (10.3–17.1)	Q2 (17.3–22.2)	Q3 (22.4–27.0)	Q4 (27.1–41.0)
Population					
Persons, n	30843	8096	7779	7618	7350
Death, n	1662	487	421	411	343
Total person-years	224020.2	59177.9	56880	55921.7	52040.6
Median year of follow-up	8.1	8.1	8.1	8.1	8.1
Demographic characteristics					
Men, %	48.5	48.8	48.8	48.4	48.1
Age (y), mean ± SD	45.6 ± 16.3	45.5 ± 16.0	45.1 ± 16.1	45.7 ± 16.2	46.3 ± 16.8
Han Ethnicity, %	91.7	81.8	92.1	95.1	98.7
Educational attainment, %					
Illiteracy	24.1	27.6	29.1	23.8	15.4
Primary to middle school	53.3	56.1	52.4	52.8	51.7
High school or above	22.5	16.3	18.4	23.4	32.9
Urban, %	43.7	33.5	33.5	47.2	62.3
Married, %	80.5	79.6	80.4	81.3	80.7
Employment, %	50.6	53.9	48.0	47.6	52.6
Lifestyle factors					
Smokers, %	36.7	36.2	39.7	36.1	35.0
Alcohol drinking, %	20.7	22.8	20.4	20.0	19.5
Regular physical activity, %	26.8	17.9	23.8	29.8	36.7
Sleep duration at night, %					
<6 h	28.9	28.2	29.7	30.6	27.1

*Quartiles were calculated based on average NO$_2$ concentrations for 162 CFPS counties through 2010 to 2018. NO$_2$, nitrogen dioxide; SD, standard deviation; BMI, body-mass index.

Variables	Entire cohort	Quartiles* of NO_2 concentration, µg/m³			
		Q1 (10.3–17.1)	Q2 (17.3–22.2)	Q3 (22.4–27.0)	Q4 (27.1–41.0)
6−8 h	63.2	64.8	61.6	62.0	64.4
≥8 h	7.9	7.0	8.7	7.4	8.5
Health status					
BMI (kg/m²), mean ± SD	21.5 ± 5.2	20.8 ± 5.2	21.2 ± 5.3	21.7 ± 5.4	22.6 ± 4.6
<18.5, %	10.9	14.8	11.5	9.6	7.3
18.5−24, %	62.0	64.8	64.4	61.0	57.5
≥24, %	27.1	20.4	24.1	29.4	35.2
Prevalence of chronic diseases, %	14.8	13.6	15.3	14.3	16.0
Depressive symptoms, %	3.6	3.6	4.7	3.7	2.4
Household characteristics					
Annual household income, %					
<15000 RMB	28.8	32.9	34.4	27.3	20.1
15000−40000 RMB	42.8	44.1	43.1	44.5	39.5
≥40000 RMB	28.3	23.0	22.5	28.3	40.5
Air pollution from cooking solid fuel, %	50.7	62.3	67.1	44.7	26.8

*Quartiles were calculated based on average NO_2 concentrations for 162 CFPS counties through 2010 to 2018. NO_2, nitrogen dioxide; SD, standard deviation; BMI, body-mass index.

Table 2

Summary statistics of environmental exposures for 162 CFPS counties between years 2010 and 2018.

Environmental exposures	Mean	SD	Min	Percentiles			Max
				P_{25}	P_{50}	P_{75}	
Year = 2010							
NO_2, µg/m^3	22.8	7.8	8.9	16.4	21.6	27.5	43.9
$PM_{2.5}$, µg/m^3	59.0	24.7	14.4	37.4	53.6	79.7	115.4
O_3, µg/m^3	89.4	8.6	69.4	83.4	88.5	95.3	113.4
Average temperature,°C	13.5	5.2	-2.0	9.5	14.4	16.4	24.2
Year = 2018							
NO_2, µg/m^3	19.1	6.2	6.9	14.6	18.1	22.6	39.2
$PM_{2.5}$, µg/m^3	38.6	13.3	14.6	29.2	35.3	47.5	77.9
O_3, µg/m^3	89.8	8.9	69.3	83.0	89.7	95.8	109.7
Average temperature, °C	14.0	5.0	-0.9	10.1	15.0	17.1	23.9
Abbreviations:							
SD, standard deviation; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; O_3, ozone.							

Figure 2 depicts the concentration-response curve for long-term association between annual NO_2 exposure and all-cause death risk. We identified an approximately linear NO_2-mortality relation (p = 0.273 for nonlinearity) across a broad concentration range of 6.9−57.4 µg/m^3, with slightly steeper slopes at high concentrations (> 25 µg/m^3). A look-up table of concentration – response function derived from our study was available in the supplementary material (Table S2). Per 10-µg/m^3 increase in annual exposure to NO_2 was associated with an all-cause death risk of 1.127 (95% CI: 1.042−1.219, p < 0.003). Sensitivity analyses largely supported the robustness of our findings on NO_2-mortality association (Table S3). Two-pollutant models additionally introducing $PM_{2.5}$ or O_3 estimated corresponding HRs of 1.158 (1.043− 1.286) and 1.144 (1.052−1.244), and temperature-adjusted analysis gave a more comparable HR estimate of 1.121 (1.025−1.225). Our DAG-based analysis associated a slightly lower risk of 1.081 (1.007−1.159) compared to the fully adjusted model.

Figure 3 summarizes estimates of subgroup analyses for NO_2-mortality associations, stratified by demographic and behavioral characteristics. Only men suffered from increased risk of death (HR = 1.219

[1.101–1.340] for a 10-μg/m^3 rise) associated with NO$_2$ exposure, and we identified a significant effect modification by sex (p = 0.024). Younger participants, particularly groups aged less than 45 years, were at higher risks when exposed to outdoor NO$_2$ pollution. NO$_2$-mortality associations were observed among smokers and alcohol drinkers only, corresponding to an estimated HR of 1.200 [1.075–1.339] and 1.263 [1.087–1.468] associated with a 10-μg/m^3 increase in annual NO$_2$ exposure, both suggesting a marginal significance for effect differences between stratum. Highly similar risks of mortality were estimated for regular exercisers (1.160 [1.004–1.341]) and non-exercisers (1.117 [1.017–1.227]) related to ambient NO$_2$ exposure.

Figure 4 & Fig. S2 illustrate county-specific estimates of NO$_2$-attributable deaths across China for years 2018 and 2010. In 2018, a total of 1.65 million deaths could be attributed to ambient NO$_2$ exposure (national average 17.3 μg/m^3) in China, representing a decrease of 4.3% compared with the estimate of 1.72 million in 2010 (20.5 μg/m^3). NO$_2$-attributable mortality burden varied substantially between regions, and top leading regions were mainly focused in densely populated metropolitan areas including North China Plain region, Yangtze River Delta, Wuhan metropolitan region, the Sichuan Basin, and the Pearl River Delta. Great disparities across counties were also seen in temporal changes in NO$_2$-attributable deaths in China through 2010 to 2018 (Fig. S3). The most majority of counties experienced a significant decline in NO$_2$-related deaths during the 8-year period, wherein the reduction in NO$_2$ concentration offset the effects of population growth. However, great increases were seen in the Pearl River Delta, Southern Jiangsu, and some top megacities such as Beijing, Shanghai, Chengdu, and Wuhan. Provincial estimates of NO$_2$-attributable deaths for years 2010 and 2018 could be found in Table S4.

4. Discussion

To the best of our knowledge, this is the first national perspective cohort study investigating mortality effects of long-term exposure to ambient NO$_2$ in China. By involving 30,000 + adult participants ages 16–110 years, our study provided robust longitudinal evidence for raised death risk associated with NO$_2$ exposure in Chinese general population. Stratified analyses revealed potential heterogeneities in NO$_2$-mortality associations between subpopulations, suggesting significantly greater vulnerability among men.

In accordance with the up-to-date evidence synthesized from epidemiologic studies, our cohort study identified a significantly positive association between NO$_2$ exposure and all-cause mortality. Several toxicological mechanisms may possibly interpret NO$_2$-induced hazards. Exposure to ambient NO$_2$ could promote a systemic vascular oxidative stress reaction[43, 44], and cause endothelial dysfunction, monocyte activation, and certain pro-atherosclerotic changes in lipoproteins, thereby initiating plaque formation, exacerbating disease, and increasing mortality[43]. For a 10-ppb rise in NO$_2$ exposure, a recent meta-analysis of 28 cohorts estimated a pooled risk of 1.06 (95% CI: 1.04–1.08) in all-cause mortality, whereas substantial heterogeneities existed across studies (HRs ranging between 0.95–1.91). By

enrolling a national cohort of 30,843 adults in mainland China, this study associated an excessive death risk of 27.8% (8.8–50.2%) with a 10-ppb increase in annual NO_2 exposure. However, two prior Chinese investigations reported an insignificant or opposite NO_2-mortality association in Hong Kong elderly[13] and northern residents[14]. Sources of huge heterogeneity between existing studies still remain not well clarified, but could possibly be related to great diversity in exposure assessment methods (e.g., fixed monitor, land use regression, and satellite-based retrievals), study demographics (e.g., age structure, locations, and NO_2 exposure levels), methodological strategies (e.g., sample size, confounding adjustment, and statistical analysis)[10].

Using time series data from 398 cities in 22 low to high income countries/regions, Meng and colleagues[8] provided strong evidence for the linear associations between short-term NO_2 exposure and daily total, cardiovascular, and respiratory mortality. In terms of long-term assessments, most international studies failed to investigate the dose-response curve and reported estimates by assuming a linear relation[11]. Our study did not identify evidence (p = 0.273) for the nonlinear effect of NO_2 exposure on all-cause death at a concentration range of 6.9–57.4 µg/m^3. The Dutch Environmental Longitudinal Study (DUELS)[45] reported a consistent finding (p = 0.37 for nonlinearity) in associations of NO_2 with non-accidental deaths, but found a strongly superlinear relation (p < 0.005) with deaths due to circulatory diseases. Owing to limited longitudinal evidence available for C-R associations between NO_2 and mortality outcomes, the state-of-art global burden of disease (GBD) studies only provided comparative estimates of deaths attributable to ambient $PM_{2.5}$ and ozone, irrespective of the potential contribution from NO_2[46]. Using a counterfactual analytic framework adopted by GBD, we attributed 1.65 million deaths to NO_2 exposure in China for the year 2018 only, accounting for 112% of GBD 2019 estimate (1.47 million) due to ambient $PM_{2.5}$ and ozone for Chinese population[46]. NO_2-mortality cohort studies focusing on C-R analyses are thus warranted across the world, particularly in developing countries, so as to facilitate more comprehensive GBD estimation of disease burden attributable to ambient air pollution.

Our study observed an elevated death risk associated with NO_2 among adult men only, showing a significant effect modification by sex. This finding could be partially explained by great differences in biological heredity between sex and intensity of work-related exposures to outdoor air pollution. Stronger NO_2-mortality associations were also estimated for men in two European cohorts[47], while DUELS[45] reported significantly greater vulnerability among women when assessing mortality causes of respiratory disease and lung cancer. We found a tendency for higher NO_2-related HR in younger age groups (16–59 years), which was in agreement with evidence of effect modification by age as highlighted in two large cohorts (over 1 million participants) in Rome[47] and Netherlands[45] for nonaccidental deaths. As demonstrated in our stratified analyses by behavioral factors, only ever/current smokers and alcohol drinkers were at greater death risks induced by NO_2 exposure, whereas no clear evidence for modifying effects was identified in our study population. In addition, we estimated highly comparable NO_2-associated hazards between those having and not having regular physical activity. Combined effects of

air pollution and physical activity on mortality raised great research interest but remained not yet fully understood[48]. In several existing large cohorts of US women[48] (n = 104,990), middle-aged Danish adults[49] (n = 52,061), and Hong Kong elderly[50] (n = 66,820), no significant interactions between NO_2/$PM_{2.5}$ exposure and physical activity were reported in associations with total and cardiovascular mortality.

This study has several strengths. First, this cohort investigation provided the first nationwide epidemiologic evidence for long-term association between NO_2 exposure and adult mortality in mainland China. Second, exposure assessment in our analysis was based on high-resolution NO_2 prediction models, through taking advantages of satellite retrieved estimates and machine learning methods. This novel advance in methodology could largely reduce exposure errors as compared to the majority of prior cohort studies relying on measurements from fixed-site monitors or estimates derived from geospatial statistical methods and chemistry transport models[10]. Additionally, our analyses took into account a rich set of confounders including individual lifestyles and provided robust NO_2-mortality evidence by including high-resolution $PM_{2.5}$/O_3 for additional adjustment.

Some limitations of our analyses should also be noted. First, participants' NO_2 exposures were assessed at the county level rather than assigned based on residential addresses, which may result in some inevitable exposure misclassifications. Second, high-quality NO_2 estimates at finer spatial-temporal scales were still of wide lack globally and regionally[51], which has hampered the comparative analyses using various exposure datasets. Third, owing to data unavailability, we failed to account for residential mobility of study participants in CFPS follow-up surveys during 2012–2018. Finally, cause-specific analyses for NO_2-mortality associations were not performed due to a relative high proportion of indeterminable causes of death in the CFPS database. This limitation may introduce some difficulty in direct comparison of estimates of NO_2-attributable deaths between our calculation based on all-cause deaths and assessments through summing up cause-specific contributions[38].

5. Conclusions

In summary, this study associated elevated risk of adult mortality with long-term exposure to ambient NO_2, utilizing an 8-year nationwide cohort in mainland China. Our dose-response analysis highlighted an approximately linear NO_2-mortality curve, which provided a valuable opportunity to quantify mortality burden attributable to NO_2 exposure in Chinese general population. Future population-based cohorts should well take advantages of high-quality exposure datasets, so as to enhance the understanding of NO_2-induced health risks and promote the comprehensive assessment of regional and global disease burden due to ambient NO_2.

Declarations

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.

Author Contributions

Yunquan Zhang: Conceptualization, Formal analysis, Methodology, Software, Validation, Visualization, Data curation, Resources, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition, Project administration; **Jing Wei**: Methodology, Data curation, Resources; **Yu Zhan**: Methodology, Data curation, Resources; **Zhiming Yang**: Methodology, Data curation, Resources, Writing - review & editing; **Riyang Liu**: Methodology, Data curation, Resources; **Yuanyuan Zhang**: Methodology, Data curation, Writing - review & editing; **Linjiong Liu**: Methodology, Data curation, Writing - review & editing; **Zongwei Ma**: Methodology, Data curation, Resources.

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