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Article

# Short-term exposure to nitrogen dioxide and cardiopulmonary mortality among the oldest-old people: A nationwide time-stratified case-crossover study in China

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## ABSTRACT

Nitrogen dioxide ($NO_2$) is associated with various adverse human health outcomes. However, evidences on associations of ambient $NO_2$ with cardiopulmonary mortality among the oldest-old people (aged more than 80 years) are still limited. This study included 1,475,459 of the oldest-old deaths from cardiopulmonary diseases. The risk of cardiopulmonary mortality increased by 3.07% (95%confidence interval (CI): 2.80%, 3.35%) for each 10 μg/m³ increment in $NO_2$ concentration. The attributable fraction (AF) of $NO_2$ was 8.52% (95%CI: 7.79%, 9.24%) in all oldest-old cardiopulmonary deaths. If the World Health Organization (WHO)'s air quality guilds (AQG) standards of ambient 24-h $NO_2$ could be reached, the AF of $NO_2$ would decrease to 6.19% (95%CI: 5.66%, 6.72%) in all oldest-old cardiopulmonary deaths, avoiding 70 942 cardiopulmonary deaths across China in 2021. This study suggested substantial risks of cardiopulmonary mortality and corresponding mortality burden caused by short-term exposure to ambient $NO_2$ pollutant among the oldest-old people. A time-stratified case-crossover study linked to records of death from five provinces (Jilin, Tibet, Yunnan, Guangdong, and Zhejiang) in China during 2013–2018 was implemented to explore associations of short-term exposure to ambient $NO_2$ (lag0–4 days) with cardiopulmonary mortality among the oldest-old people. Data on daily average concentration of $NO_2$ was interpolated using random forest models at township-level of China. Conditional logistic regression models were utilized to estimate the effects of $NO_2$, excess risk (ER) and its 95% CI were reported. Mortality burdens, indicated by AF and attributable number (AN), caused by $NO_2$ were also estimated.

## KEYWORDS

nitrogen dioxide ($NO_2$), cardiopulmonary mortality, the oldest-old people, mortality burden

## 1 Introduction

The world is experiencing accelerated population aging, with the oldest-old people (aged 80 and above) as a particular concern due to their rapid growth in recent decades [1]. The



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number of the oldest-old people was 75 million worldwide in 2000, doubled to 151 million in 2020, and is projected to be more than 450 million in 2050 (https://population.un.org/wpp/Download/Standard/MostUsed/). The Global Burden of Disease (GBD) Study 2021 estimated an increase of 153% of years of life lost (YLLs) and 163% of mortality for the oldest-old people between 1990 and 2021, globally (https://vizhub.healthdata.org/gbd-results/). The World Health Organization (WHO) called on optimizing care on older people [2], and the United Nation (UN) General Assembly defined the period of 2021–2030 as the decade of healthy aging in 2020 (https://cdn.who.int/media/docs/default-source/decade-of-healthy-ageing/decade-proposal-final-apr2020-en.pdf), stressing the urgent need for global policymakers to focus on enhancing the health of older people. China has the world's largest number of older people, and this number will continuously grow with an unstoppable trend until 2050 [3].

The elderly are more susceptible to adverse environmental factors, which could lead to a worsening quality of life [4]. For example, Qian et al. found significant mortality risks caused by air pollution even below the air quality guidelines among the elderly [5]. Nitrogen dioxide ($NO_2$) is a gaseous air pollutant, mainly generated from fossil fuel combustion and motor vehicle exhausts [6], and is often considered to be the representative of transportation-related air pollutants. $NO_2$ has been linked to various adverse health events [6–10]. For example, long-term exposure to $NO_2$ increases risks of hypertension [7], and inhaling high level $NO_2$ could trigger a serious of respiratory symptoms and further cause pulmonary edema [9]. As a precursor to fine particulate matter ($PM_{2.5}$) and ozone ($O_3$), $NO_2$ contributes to the increase in other air pollutants, further intensifying overall air pollution [11]. Over the past decade, the emissions of $NO_2$ have continued to decline due to implementation of environmental regulations in China [12, 13]. Nevertheless, a large proportion of the China's population is still exposed to $NO_2$ levels exceeding the WHO guideline, which may bring unacceptable health burden to Chinese population [14].

Cardiovascular diseases (CVD) and respiratory diseases (RESP), two leading causes of mortality, accounting for nearly 35% of all deaths worldwide in 2021, with even higher proportions in middle and high-middle Socio-demographic Index (SDI) countries (https://vizhub.healthdata.org/gbd-results/, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). Some previous epidemiological studies have demonstrated the considerable associations of exposure to $NO_2$ with CVD and RESP mortality [15–17]. For example, Meng et al. found that short-term exposure to $NO_2$ was linked to an increased risk of total, CVD, and RESP mortality, with linear exposure-response curves and no thresholds [15]. However, there are still several issues in previous studies. First, evidences linking $NO_2$ to mortality in the oldest-old were limited. While some studies have examined the relationship between ambient $NO_2$ exposure and mortality risk in the elderly [5], they generally used traditional age categories (e.g., population aged more than 65 years), which did not allow for an analysis of variations among different age groups [18, 19]. We still don't know which age groups are the most vulnerable to ambient $NO_2$ pollutant. Second, although some previous epidemiological studies focused on the associations of $NO_2$ with mortality risk [15, 16], the mortality burden caused by ambient $NO_2$ pollution remains unknown. Third, there is lack of studies on the associations of $NO_2$ with cause-specific mortality. As a result, we are not clear which causes of mortality are more susceptible to ambient $NO_2$ pollution.

In this study, we conducted a time-stratified case-crossover study design based on individual information of deaths from five provinces in China to assess the associations between short-term exposure and $NO_2$ with cardiopulmonary mortality among the oldest-old people, and to estimate the mortality burden attributable to $NO_2$.

## 2 Results

### 2.1 General information of study population

This study included 1,475,459 deaths from cardiopulmonary diseases in the oldest-old people. Of the total study population, 786,326 (53.29%) were females; 1,025,584 (69.51%) died from CVD and 449,875 (30.49%) died from RESP; 607,323 people died at age 80–84 years with the highest proportion (41.16%) and 11,638 people died over 99 years old with the lowest proportion (0.79%) (Table 1). Compared with control days, case days had higher $NO_2$ concentration (28.56 ± 15.53 μg/m³ vs. 28.25 ± 13.08 μg/m³, $P < 0.001$), higher daily mean temperature (TM) (16.74 ± 9.36 ℃ vs. 16.73 ± 8.91 ℃, $P = 0.012$), and lower relative humidity (RH) (75.06% ± 13.00% vs. 75.13% ± 9.80%, $P < 0.001$) (Table S1 in the Electronic Supplementary Material (ESM)). Except daily maximum 8-h ozone (MDA8 $O_3$), $NO_2$ concentration was positively correlated with other three ambient air pollutants (correlation coefficients ($r$) between $NO_2$ and $PM_{2.5}$, carbon monoxide (CO), sulfur dioxide ($SO_2$) and MADA8 $O_3$ were 0.67, 0.37, 0.34, and −0.03, respectively), and negatively correlated with TM ($r = -0.23$) and RH ($r = -0.06$) (Table S2 in the ESM).

### 2.2 Associations of short-term exposures to $NO_2$ and mortality risk

Figure 1 illustrates the non-linear exposure-response curves

**Table 1** Basic information of study population

| Group | Case numbers (proportion) |
|---|---|
| **Total cardiopulmonary mortality** | 1,475,459 (100.00%) |
| **Sex** | |
| Males | 689,133 (46.71%) |
| Females | 786,326 (53.29%) |
| **Age at death (years)** | |
| 80–84 | 607,323 (41.16%) |
| 85–89 | 523,428 (35.48%) |
| 90–94 | 263,380 (17.85%) |
| 95–99 | 69,690 (4.72%) |
| ≥100 | 11,638 (0.79%) |
| **Causes of diseases** | |
| Cardiovascular diseases | 1,025,584 (69.51%) |
| Respiratory diseases | 449,875 (30.49%) |

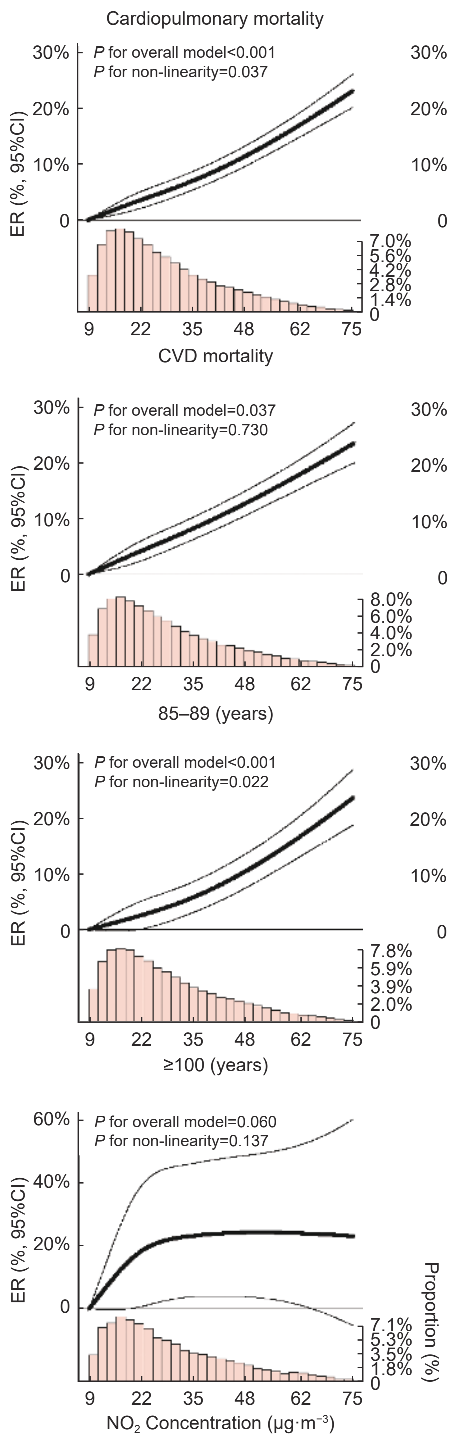


**Figure 1** Non-linear associations of short-term exposure to $NO_2$ (lag0–4) and cardiopulmonary mortality among the oldest-old people. Note: All models were adjusted for daily mean temperature (lag0–4) and daily mean relative humidity (lag0). When fitting the non-linear associations, $NO_2$ concentration below its 1st and above its 99th percentiles was removed from the models to avoid the influences from outliers.

between $NO_2$ (lag0–4 days) and risks of cardiopulmonary mortality. We found positive and monotonically increasing exposure–response relationships for total cardiopulmonary, cardiovascular, respiratory, sex-specific, and age-specific mortality. Although non-linearity with statistical significance were found in some groups (e.g., $P$ for non-linearity = 0.037 for total cardiopulmonary mortality), we didn't observe exact thresholds of $NO_2$ concentration that may reverse the positive results. In people over 100 years old, we observed the exposure-response curve become flat at $NO_2$ concentration greater than 30 μg/m$^3$. The non-linear exposure-response associations for subtypes of CVDs and RESPs could be found in Fig. S1 in the ESM.

Based on the linear assumption, Fig. 2A shows the positive associations of $NO_2$ with mortality. Each 10 μg/m$^3$ increment in $NO_2$ concentration was associated with 3.07% (95% confidence interval (CI): 2.80%, 3.35%) increase in risk of total cardiopulmonary mortality. Stratified analyses showed slightly greater excess risk (ER) in females (3.27%, 95%CI: 2.90%, 3.64%) than in males (2.85%, 95%CI: 2.45%, 3.25%,

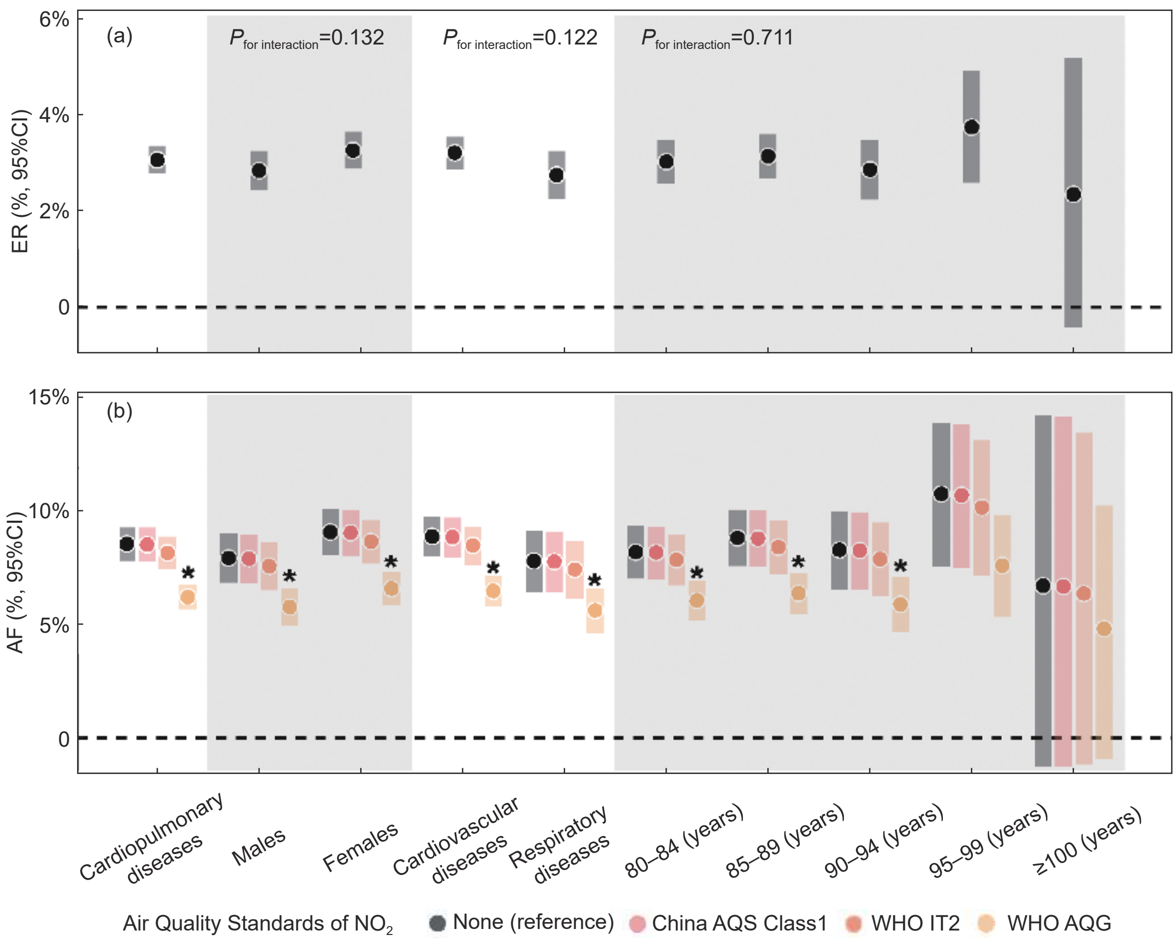


**Figure 2** Linear associations of $NO_2$ and cardiopulmonary mortality and corresponding mortality burden. Note: (A) showed the ERs of $NO_2$ for each 10 μg/m³ increase in $NO_2$ concentration. All models were adjusted for TM (lag0–4) and RH (lag0); (B) showed the AFs of $NO_2$ on cardiopulmonary mortality, "*" denoted appreciable differences of AFs between three standards and reference (without threshold). China AQS Class1 = the China's Air Quality Standards Class 1 of ambient 24-h $NO_2$ (80 μg/m³); WHO IT2 = the WHO Interim Targer-2 of ambient 24-h $NO_2$ (50 μg/m³); WHO AQG = the WHO's air quality guilds standards of ambient 24-h $NO_2$ (25 μg/m³)

$P_{for\ interaction}$ = 0.132), and on CVD mortality (3.22%, 95%CI: 2.89%, 3.55%) than on RESP mortality (2.75%, 95%CI: 2.27%, 3.24%, $P_{for\ interaction}$ = 0.122). The ERs were 3.02% (95%CI: 2.59%, 3.48%), 3.15% (95%CI: 2.69%, 3.60%), 2.87% (95%CI: 2.25%, 3.48%) and 3.75% (95%CI: 2.59%, 4.92%) for people aged 80–84, 85–89, 90–94, and 95–99 years, respectively. However, ambient $NO_2$ was not significantly associated with cardiopulmonary mortality for people over 100 years old (ER = 2.35%, 95%CI: –0.41%, 5.19%) (Table S3 in the ESM).

For CVD diseases, the strongest and the weakest associations were observed in other pulmonary heart diseases (the 10th Revision International Classification of Diseases (ICD-10): I27; ER = 6.13%, 95%CI: 2.79%, 9.59%) and heart failure (ICD-10: I50; ER = 1.83%, 95%CI: –2.42%, 6.26%) among all types of CVD, respectively. For RESP diseases, the strongest and the weakest associations were observed in emphysema (ICD-10: J43; ER = 6.66%, 95%CI: 3.25%, 10.19%) and pneumonia, organism unspecified (ICD-10: J18; ER = 1.89%, 95%CI: 0.74%, 3.04%), respectively (Table 2).

## 2.3 Mortality burden attributable to ambient $NO_2$ pollutant

Figure 2B shows the attributable fractions (AFs) of cardiopulmonary mortality caused by short-term exposure to $NO_2$. In the total cardiopulmonary mortality, 8.52% (95%CI: 7.79%, 9.24%) could be attributable to $NO_2$ exposure. The AFs were 7.90% (95%CI: 6.83%, 8.97%) and 9.04% (95%CI: 8.06%, 10.02%) for males and females, respectively. The AFs of mortality from CVD and RESP were 8.85% (95%CI: 7.98%, 9.71%) and 7.77% (95%CI: 6.45%, 9.09%), respectively. People aged 95–99 years had a greater AF (10.72%, 95%CI: 7.54%, 13.81%) compared to other age groups (Table S4 in the ESM). Moreover, $NO_2$ had the largest contribution on mortality from other pulmonary heart diseases (ICD-10: I27; AF = 13.76%, 95%CI: 6.54%, 20.57%) among all types of CVD diseases, and had contributed most on emphysema mortality (ICD-10: J43, AF = 14.55%, 95%CI:7.40%, 21.32%) among all types of RESP diseases (Table 2).

Lower AFs could be observed if the China and WHO's air quality standards of $NO_2$ could be reached. For example, for total cardiopulmonary mortality, the AFs were 8.49% (95%CI: 7.76%, 9.21%) under the China Air Quality Standard (AQS) Class1, 8.13% (95%CI: 7.44%, 8.82%) under the WHO Interim Targer-2 (IT2), and 6.19% (95% CI: 5.66%, 6.72%) under the WHO's air quality guilds (AQG), respectively. Similar results were observed in several subgroups (Fig. 2B, Table S4 in the ESM).

In 2021, short-term exposure to $NO_2$ may have caused 259,648 (95%CI: 237,401, 281,590) cardiopulmonary deaths in

**Table 2** Associations of $NO_2$ and mortality from specific diseases and corresponding mortality burden

| Specific Causes of Diseases (ICD-10) | ER (95%CI) | AF (95%CI) | | | |
|---|---|---|---|---|---|
| | | No Standard | China AQS Class 1 | WHO IT2 | WHO AQG |
| **CVDs** | | | | | |
| Other pulmonary heart diseases (I27) | 6.13% (2.79%, 9.59%) | 13.76% (6.54%, 20.57%) | 13.74% (6.53%, 20.54%) | 13.44% (6.40%, 20.05%) | 11.24% (5.35%, 16.79%) |
| Other cerebrovascular diseases (I67) | 4.36% (1.59%, 7.20%) | 10.36% (3.93%,16.48%) | 10.34% (3.92%, 16.44%) | 10.04% (3.81%, 15.95%) | 8.18% (3.10%, 13.01%) |
| Cerebral infarction (I63) | 3.99% (3.04%, 4.95%) | 10.80% (8.34%, 13.21%) | 10.77% (8.32%, 13.18%) | 10.33% (7.98%, 12.63%) | 7.90% (6.09%, 9.67%) |
| Stroke, not specified as hemorrhage or infarction (I64) | 3.95% (2.37%, 5.55%) | 11.72% (7.21%, 16.05%) | 11.69% (7.20%, 16.025) | 11.17% (6.88%, 15.29%) | 8.18% (5.02%, 11.23%) |
| Hypertensive heart disease (I11) | 3.42% (2.37%, 4.49%) | 10.04% (7.07%, 12.95%) | 10.02% (7.05%, 12.92%) | 9.57% (6.74%, 12.33%) | 7.03% (4.94%, 9.08%) |
| Intracerebral hemorrhage (I61) | 3.12% (2.04%, 4.21%) | 8.10% (5.38%, 10.77%) | 8.09% (5.38%, 10.75%) | 7.82% (5.20%, 10.39%) | 6.14% (4.08%, 8.16%) |
| Chronic ischemic heart disease (I25) | 2.97% (2.12%, 3.84%) | 8.59% (6.19%, 10.93%) | 8.55% (6.17%, 10.89%) | 8.15% (5.88%, 10.37%) | 6.08% (4.38%, 7.75%) |
| Acute myocardial infarction (I21) | 2.75% (1.84%, 3.66%) | 7.30% (4.96%, 9.59%) | 7.27% (4.95%, 9.56%) | 7.01% (4.77%, 9.21%) | 5.49% (3.73%, 7.22%) |
| Sequelae of cerebrovascular disease (I69) | 2.74% (1.67%, 3.82%) | 8.52% (5.28%, 11.66%) | 8.48% (5.26%, 11.61%) | 8.04% (4.99%, 11.01%) | 5.81% (3.60%, 7.98%) |
| Essential hypertension (I10) | 2.73% (−0.43%, 5.99%) | 6.81% (−1.13%, 14.31%) | 6.78% (−1.12%, 14.24%) | 6.53% (−1.09%, 13.69%) | 5.27% (−0.88%, 11.06%) |
| Heart failure (I50) | 1.83% (−2.42%, 6.26%) | 3.59% (−5.00%, 11.66%) | 3.58% (−5.00%, 11.65%) | 3.53% (−4.93%, 11.46%) | 3.15% (−4.41%, 10.22%) |
| Other CVDs | 2.14% (0.81%, 3.48%) | 5.59% (2.16%, 8.93%) | 5.57% (2.15%, 8.90%) | 5.35% (2.07%, 8.55%) | 4.21% (1.62%, 6.73%) |
| **RESPs** | | | | | |
| Emphysema (J43) | 6.66% (3.25%, 10.19%) | 14.55% (7.40%, 21.32%) | 14.51% (7.38%, 21.24%) | 14.08% (7.18%, 20.58%) | 11.83% (6.03%, 17.29%) |
| Simple and mucopurulent chronic bronchitis (J41) | 3.23% (−0.65%, 7.27%) | 6.95% (−1.48%, 14.87%) | 6.94% (−1.48%, 14.85%) | 6.80% (−1.45%, 14.52%) | 5.88% (−1.26%, 12.56%) |
| Other chronic obstructive pulmonary disease (J44) | 3.18% (2.35%, 4.02%) | 8.74% (6.54%, 10.91%) | 8.72% (6.52%, 10.88%) | 8.36% (6.25%, 10.43%) | 6.40% (4.79%, 8.00%) |
| Other respiratory disorders (J98) | 2.91% (0.72%, 5.15%) | 9.61% (2.46%, 16.36%) | 9.54% (2.44%, 16.24%) | 8.96% (2.30%, 15.23%) | 6.27% (1.60%, 10.72%) |
| Unspecified chronic bronchitis (J42) | 2.18% (0.82%, 3.57%) | 6.06% (2.33%, 9.69%) | 6.06% (2.33%, 9.68%) | 5.83% (2.24%, 9.31%) | 4.47% (1.72%, 7.15%) |
| Pneumonia, organism unspecified (J18) | 1.89% (0.74%, 3.04%) | 6.08% (2.45%, 9.62%) | 6.04% (2.43%, 9.56%) | 5.69% (2.29%, 8.99%) | 4.06% (1.63%, 6.44%) |
| Other RESPs | 2.77% (0.97%, 4.60%) | 7.53% (2.71%, 12.18%) | 7.51% (2.70%, 12.14%) | 7.19% (2.59%, 11.61%) | 5.50% (1.98%, 8.91%) |

Note: ERs were reported per 10 μg/m³ increase in $NO_2$ concentration. All models were adjusted for TM (lag0–4) and RH (lag0). In order to ensure statistical power, we only analyzed the associations between $NO_2$ and specific CVDs (and RESPs) with a sample size more than ten thousand, and those of with a sample size less than ten thousand were classified as "Other" ("Other CVDs" and "Other RESPs").

the oldest-old people across China. The $NO_2$-related mortality burden was greater in females (attributable number (AN) = 135,047, 95%CI: 120,312, 149,670) than in males (AN = 122,809, 95%CI: 106,108, 139,373), from CVD (AN = 204,914, 95%CI: 184,779, 224,914) than from RESP (AN = 56,851, 95%CI: 47,134, 66,469), and in people aged 85–89 years (100,270, 95%CI: 86,359, 114,051) than other age groups (Fig. 3, Table S7 in the ESM). In addition, lower $NO_2$-related mortality burden could be observed if the air pollution standards of $NO_2$ were reached. For example, under the WHO AQG standard, $NO_2$ may have caused 188,706 (95%CI: 172,513, 204,813) oldest-old cardiopulmonary deaths, avoiding 70,942 deaths across China in 2021 (Fig. 3, Table S5 in the ESM).

### 2.4 Sensitivity analyses

Results of sensitivity analyses indicted that changing the degrees of freedom (dfs) of TM and RH (dfs = 4, 5, and 6) did not considerably change the associations of $NO_2$ exposure with cardiopulmonary mortality (Table S6 in the ESM). The results of two-pollutant models also showed the stable and positive associations of $NO_2$ and morality, indicating the robustness of our results (Table S6 in the ESM).

## 3 Discussion

This nationwide study provides evidence of the associations between short-term exposure to ambient $NO_2$ and cardiopulmonary mortality among the oldest-old in China, as well as the mortality burden caused by $NO_2$. We found robust and positive effects of $NO_2$ pollution on overall cardiopulmonary mortality. The effects of $NO_2$ were greater in females, people aged 95–99 years old, and people died from several specific causes. We further found that 8.52% of the cardiopulmonary mortality could be contributable to short-term exposure to ambient $NO_2$ in the oldest-old Chinese people. To our knowledge, this is the first study that has examined the associations of short-term exposure to $NO_2$ with cardiopulmonary mortality and corresponding mortality burden among the old-oldest people. In the background of accelerating population ageing and subpar air quality worldwide, our findings suggest that urgent public health

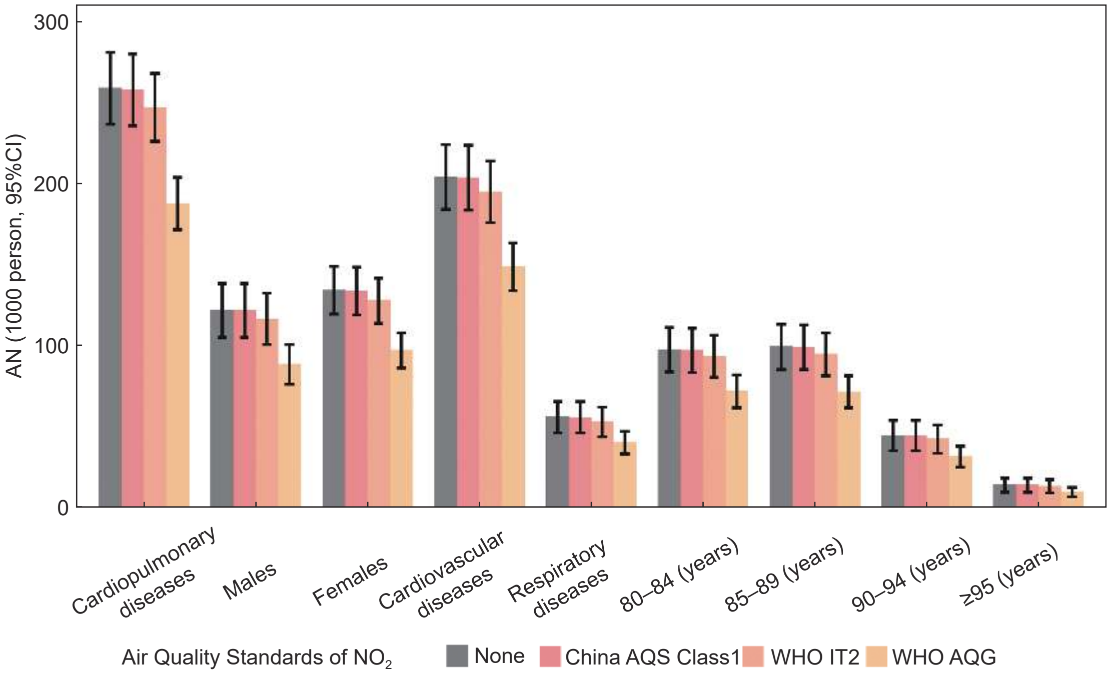


**Figure 3** Attributable number of cardiopulmonary deaths for the oldest-old people across China in 2021. Note: Because GBD 2021 did not provided the estimation of death numbers of CVD and RESP for 95–99 and 100+ (years) age groups (only 95+ was available), we aggregated these two age groups into "95+" group, and further estimated corresponding ER, AF, and AN in our supplementary analyses (Table S5 in the ESM).

strategies are needed to protect the oldest-old people's health.

Our results indicate an increased risk of cardiopulmonary mortality from ambient $NO_2$ pollution among the oldest-old, consistent with previous studies [10, 20, 21]. However, the associations observed were greater than those reported in many current studies [22–24]. For example, a study from South Africa found that short-term exposure to $NO_2$ was associated with RESP mortality among people aged over 65 years, with an increased risk of 0.7% for each 11 μg/m$^3$ increase in $NO_2$ concentration [24]. Goldberg et al. have estimated a 2.67% increase risk of CVD mortality for each 18 μg/m$^3$ increase in $NO_2$ concentration among people aged over 65 years [23]. Many previous studies usually estimated the associations of $NO_2$ with mortality risks in people aged over 60 or 65 years old, which may not capture the vulnerability of the oldest-old and could underestimate the effects of $NO_2$ pollution. By focusing on people over 80 years old, our findings suggested that the oldest-old people were more sensitive to $NO_2$ than younger population, which implied that more powerful protective measure should be considered for the oldest-old people to reduce their exposure to air pollution.

We further observed variations in the associations between $NO_2$ and cardiopulmonary mortality across different age groups. While similar effects of $NO_2$ on mortality were noted among groups aged 80–94 years, individuals aged 95–99 years showed the highest vulnerability, with the strongest $NO_2$-related mortality associations. A study from China also found that people over 90 years old faced higher risks of all-cause mortality from air pollution compared to younger age groups [25]. The impact of air pollution on human health tends to intensify with age increasing, which is due to the weakened physiological and metabolic processes in older people [26]. Weakened compensatory capacity leads to the accumulation of air pollutants in human body, imposing additional health burdens on the elderly [27]. Furthermore, older people are at greater risk of developing comorbidities, which may exacerbate the effects of adverse ambient air conditions on their health [28]. Of note, the association was not significant for people over 100 years in our results, which may cause by the lower statistical power because of a relatively small sample size in this group. Meanwhile, limited mobility in older people may reduce their exposure to outdoor air pollutants [29].

Stratified analyses by sex revealed slightly stronger effects of $NO_2$ in females compared to males, indicating that older women may be more sensitive to $NO_2$ exposure, which is consistent with numerous previous studies [16, 24, 30, 31]. However, the reasons for the sex difference in the effects of $NO_2$ remain unclear [31, 32]. Many researchers have attempted to explain the sex variations in air pollution through factors such as social behavior, biological structure, and sex steroid hormones [32–35]. For example, females generally have smaller airways than males of the same lung capacity, which makes it easier for extrinsic particles (e.g., PM2.5) to stay on the airway and trigger adverse health events. Due to the uncertainty and complexity of sex difference, researchers have advocated for that multiple stratifications analyses linked to sex-associated factors (e.g., occupation, fat, and housework) were needed to be performed to comprehensively illustrate the potential mechanisms [32], but it required a super large sample size.

We further found a slightly higher effect of $NO_2$ on CVD mortality than RESP mortality. Some previous studies have reported similar results [20, 36]. For example, a study by Eum et al. analyzed over 14 million death records in the United States, found a stronger association between long-term $NO_2$ exposure and mortality from CVD compared to RESP in older adults aged 65–120 years [20]. This difference may be attributed to individuals with respiratory conditions, such as asthma, being likely to alter their behavior to protect themselves from worsening air quality [37]. In addition, we estimated the associations of $NO_2$ on specific CVD and RESP mortality, revealing several significant associations that were consistent with previous researches [38–44]. For example, Liu et al. [40] conducted a time-stratified case-crossover study in China and reported that every 10 μg/m³ increase in $NO_2$ concentration was associated with a 1.46% (95%CI: 0.76%, 2.17%) increase in myocardial infarction mortality. There are some studies have demonstrated the associations between short-term exposure to $NO_2$ and mortality from ischemic heart disease [41], stroke [44], sequelae of cerebrovascular disease [43], cerebrovascular disease [43], pneumonia [38], and chronic obstructive pulmonary disease [42]. Given strong associations of air pollution and mortality from some specific diseases, individuals with these chronic diseases should be given more attention and protection to reduce the impact of adverse air conditions on their health.

In the context of simultaneous aging and severe air pollution in China, estimating the oldest-old people's mortality burden attributable to air pollution is necessary and meaningful. The WHO has estimated approximately 2 million deaths attributable to exposure to ambient particulate matter annually across China (https://www.who.int/hongkongchina/news/detail/02-05-2018-who-issues-latest-global-air-quality-report-some-progress-but-more-attention-needed-to-avoid-dangerously-high-levels-of-air-pollution/). The GBD 2021 has reported that approximately 900,000 deaths among the oldest-old population were attributable to exposure to outdoor air pollution (including particulate matter and $O_3$) across China in 2021 (https://vizhub.healthdata.org/gbd-results/). However, neither the WHO nor the GBD Study have reported estimates of $NO_2$-related deaths. Given the strong effects of $NO_2$ pollution on the health of the elderly, estimations of air pollution-related deaths from the WHO and GBD Study may be underestimated. In our study, we estimated that more than 259 thousand $NO_2$-related cardiopulmonary deaths occurred among the oldest-old people across China in 2021, indicating a considerable mortality burden caused by $NO_2$. Furthermore, we observed a significant decrease in $NO_2$-related deaths if the most stringent $NO_2$ standard could be achieved. Xu et al. [26] have pointed out that population aging will be the leading contributor to increases in $PM_{2.5}$-realted deaths from 2019 to 2035 in China. With China having the largest number of older adults and the fastest aging process [3], it is projected that China will have 395 million people over 65 years old by 2050 (https://population.un.org/wpp/Download/Standard/MostUsed/). The disease burdens caused by air pollution may escalate in the future across China. Given that the elderly are more vulnerable to adverse air conditions, severe population aging will amplify the effects of air pollution in the future. Our findings emphasized the importance of mitigation of air pollution and suggested that specific air quality standards may be required to better protect the elderly. Additionally, the government should improve healthcare services to address the increased health burden on older people due to the growing aging population in the future.

Air pollutants can penetrate through lung tissue and systemic circulation, subsequently causing blood vessel constriction, high blood pressure and plaque instability, leading to inflammation and oxidative stress, and resulting in cardiovascular and respiratory system damage [45]. Evidence from toxicology also suggests that inhaling $NO_2$ can promote the production of highly reactive protein and lipid oxidation products, resulting in onset of cardiovascular and cerebrovascular diseases [46]. Older people are generally more susceptible to air pollution due to their decreased ability of compensating environmental adverse effects, diminished immune reaction, and modified reaction to oxidative stress [47], frailty brings older people higher air pollution-related risks and finally causes a series of adverse health outcomes.

As far as we know, it is the first study focusing on the oldest-old population to estimate the effects of $NO_2$ on cardiopulmonary mortality in China. Our results provided new evidence for quantitatively assessing the associations between air pollution and mortality in the oldest-old people. We estimated the associations among several specific mortality, which helps to identify more susceptible older populations. Finally, we not only provided the associations of $NO_2$ and mortality, but also calculated the AFs and ANs, this contributes to further understanding the $NO_2$-induced mortality burden in the oldest-old people.

There are several limitations that need to be addressed in this study. First, relatively large sampling error may occur when analyzing the associations of $NO_2$ with cardiopulmonary mortality from several specific causes with small sample size. For example, we failed to find the statistically relationships of $NO_2$ and mortality from several specific diseases (e.g., heart failure). Second, the subjects were drawn from only five provinces (Tibet, Yunnan, Guangdong, Zhejiang, and Jilin) in China, which are located predominantly in the South, West, and Northeast regions, potentially affecting the representativeness of our findings. Third, even though people aged over 100 years may be virtually unaffected by outdoor air pollution because of their poor motility, we were unable to estimate the associations between indoor $NO_2$ exposure and mortality due to a lack of indoor air pollution data. Fourth, factors such as physical activity, diet, medicate, blood pressure were unable to obtain. However, these were important factors that may affect the health of older people [48–51]. For example, Kurata et al. suggested that higher protein intake is associated with reduced all-cause mortality risk in older people who aged over 85 years [48]. Paluch et.al found that increasing number of steps per day until 6000–8000 steps per day would decrease risks of all-cause mortality among old people [49]. Last, since this is a case-crossover study, some intrinsic biases could not be ignored. For example, autocorrelation occurs when the exposure levels are correlated among different time periods for each stratum, which may mislead estimates of standard errors [52]. Meanwhile, be analogous to any observational study, although the case-crossover design controls for time-invariant confounding factors, other unmeasured confounding is still possible [40]. In addition, the case-crossover design is usually used for estimating short-term associations of environmental exposures with acute events. However, our study included deaths from both acute and chronic cardiopulmonary diseases (CVD: ICD-10 I00–I99; RESP: ICD-10 J00–J99), which may magnify the harvesting effects [53]. Therefore, more researches introducing long lags of air pollution (e.g., long-term longitudinal studies) should be conducted to verify our results.

In this nationwide study from China, we observed strong and positive associations of short-term exposure to $NO_2$ with cardiopulmonary mortality among the oldest-old people. Controlling the emission of $NO_2$ in accordance with air pollution standards could alleviate the cardiopulmonary mortality burden and decrease corresponding deaths. Our findings highlight the risk of air pollution for the oldest-old people. Public policies and air pollution control measures should be developed to protect the oldest-old people in the context of severe aging.

## 4 Methods

### 4.1 Study settings and study population

This study enrolled the oldest-old deaths from mortality surveillance systems of five provinces (Jilin, Tibet, Yunnan, Guangdong, and Zhejiang) from January 1, 2013 to December 31, 2018 in China. We extracted key variables of each death from the surveillance systems including age at death, sex (male and female), death date, residential address of death at township level and causes of death (ICD-10). Township is the lowest administrative unit in China, detailed introduction of township could be found in supplementary file (Method 1.1 in the ESM). Next, we extracted records of deaths from cardiopulmonary diseases, in which cardiopulmonary diseases were identified as CVD (ICD-10: I00-I99) or RESP (ICD-10: J00-J99).

### 4.2 Study design

We conducted a time-stratified case-crossover study design to investigate the associations of short-term exposure to ambient $NO_2$ with cardiopulmonary mortality in the oldest-old people. Each record's death date was identified as the case day, and other days sharing the same year, month, and day of week with the case day were selected as the control days. With this study design, general confounders which were constant or less likely to change in the short term (e.g., age, sex, and family history), long-term trend, seasonality, and effect of day of week could be controlled for. Finally, 1,475,459 case days and 4,992,820 control days were enrolled in our study.

### 4.3 Data collection

Data on daily average concentration of ambient air pollutants, covering all monitoring stations in the five study provinces and study periods, including $NO_2$, $PM_{2.5}$, daily MDA8 $O_3$, $SO_2$, and CO were obtained from the Nation Urban Air Quality Real-time Publishing Platform (http://106.37.208.233:20035/). However, the monitoring station data were unable to cover residential townships of all death records because of the sparse air pollution monitoring stations in some regions. Therefore, we conducted random forest models to interpolate uncovered data, which has been described in detail elsewhere [36, 54]. Simply, some key predictors for concentration of air pollutants including daily TM, RH, land use, population density, road density, gross domestic product (GDP) per capital and the average concentration of air pollutants in the city where each monitoring station was located were included in the random forest models. Next, key predictors mentioned above were inputted to the established random forest models to predict concentration of air pollutants. To test the accuracy of the established models, we used 10-fold cross-validation to compare the prediction of air pollutants concentrations from the random forest models with the observed data from monitoring stations. The results showed that the cross-validation coefficient of determination (CV-$R^2$) of $NO_2$ was 83% and the root mean squared prediction error (RMSE) was 8.2 μg/$m^3$, which indicated good performance of model fitting (Table S7 in the ESM). Finally, the established random forest models were used to interpolate the daily air pollutants concentration for each death at township level.

Collection process of other data including TM, RH and variables as key predictors in the forest models could be found in Methods 1.2 in the ESM.

### 4.4 Statistical analysis

#### *4.4.1 Associations of short-term exposure to $NO_2$ with mortality risk*

We applied conditional logistic regression models to explore the associations of $NO_2$ concentration and cardiopulmonary mortality risk. Previous studies suggested that delayed effect of exposure to $NO_2$ on mortality could last for five days [55, 56]. Thus, we preliminarily analyzed the different lagged effects of $NO_2$ from lag0 (current day of death) to lag5 (five days ago of death). We also used the moving average concentration of $NO_2$ from two to six days (lag01–lag05) to explore the cumulative effects of $NO_2$ on mortality. The results indicated the strongest association of $NO_2$ exposure with mortality during lag04 days (Fig. S2 in the ESM). Therefore, we finally utilized the moving averages of $NO_2$ concentration from the current day to previous four days of deaths (lag0–4) to explore the associations. According to previous studies [36, 57], the same period TM (lag0–4) and current-day RH (lag0) were also considered as confounding factors in our analyses.

Both non-linear and linear associations of short-term exposure to $NO_2$ with mortality were estimated. Using a natural cubic spline (ns) function (df = 3) with two knots at equal percentile spaces (33.3th and 66.7th) of $NO_2$ ranges, we fitted the non-linear exposure-response relationships of $NO_2$ with mortality. Ambient TM and RH were adjusted for using the same *ns* functions in models. Likelihood ratio tests were used to test the non-linearity. Next, we fitted the linear associations by removing the *ns* functions of $NO_2$ from models. To examine the modifications of sex, age (80–84, 85–89, 90–94, 95–99, and ≥100 years) and causes of diseases (CVD and RESP), several stratified analyses were conducted by adding an interaction term in models, and likelihood ratio tests were used to test the differences of associations among subgroups. We reported the main results using ER and the corresponding 95%CI in this study. ER could be calculated by 100% × ($e^{\beta}$ − 1), in which $\beta$ denotes the coefficients from regression models.

#### *4.4.2 Mortality burden attributable to $NO_2$ exposure*

We used AF to quantify the mortality burden attributable to $NO_2$ exposure. We utilized the exposure-response relationships to calculate AF by following equation (1):

$$AF = \frac{\sum \left(P_i \times e^{\beta \times i}\right) - 1}{\sum \left(P_i \times e^{\beta \times i}\right)} \times 100\% \tag{1}$$

where $P_i$ is the proportion of death in concentration level $i$ of $NO_2$ (be accurate to one decimal place), and $\beta$ denotes the linear coefficient of $NO_2$ from regression model. Here, we also calculated AFs by assuming that the air pollution standards of $NO_2$ would be reached. Three standards were selected in this study: the China's Class 1 standards of ambient 24-h $NO_2$ (80 μg/m³); the WHO IT2 of ambient 24-h $NO_2$ (50 μg/m³); and the WHO's AQG standards of ambient 24-h $NO_2$ (25 μg/m³). The $NO_2$ concentration level that exceeded the threshold of standard would be reassigned to the threshold. Furthermore, to examine the potential benefit of controlling air pollution, we used Monte Carlo method to compare the AFs under three standards with the AFs without standards (Method 1.3 in the ESM).

Based on AFs and data from GBD 2021 (https://vizhub.healthdata.org/gbd-results/), we further calculated AN of cardiopulmonary mortality caused by exposure to $NO_2$ across China in 2021, using the following equation (2):

$$\mathrm{AN} = \mathrm{AF} \times D \tag{2}$$

where $D$ was number of deaths from cardiopulmonary disease across China in 2021, which was estimated by GBD 2021 (Table S8 in the ESM). We also calculated ANs under different assumptions of air pollution standards.

#### 4.4.3 Sensitivity analyses

To examine the robustness of our results, we implemented several sensitivity analyses: (1) changing the dfs in ns functions for TM and RH in models; (2) conducting two-pollutant models by adjustment for ambient CO, $SO_2$ and MDA8 $O_3$, respectively ($PM_{2.5}$ was not considered because of the high correlation between $NO_2$).

We did all statistical analyses using R (version 4.3.1, R Core Team 2023), *survival* package was used to perform conditional logistic regression models. A two-sided $P$ value less than 0.05 referred statistical significance.

## Author contributions

Wenjun Ma and Tao Liu designed the project and interpreted the results. Qijiong Zhu and Cuiling Wu performed the statistical analysis and took the lead in drafting the manuscript. Siwen Yu, Zhiqing Chen, Shangfeng Yang, Min Yu, Guoxia Bai, Ruilin Meng, Biao Huang, Weiwei Gong, Yanfang Guo, Haoming Zhang, Ruying Hu, Zhulin Hou, Yize Xiao, Mingfang Qin, Jianpeng Xiao and Lifeng Lin collected the raw data for this study. Guanhao He and Jianxiong Hu contributed to the interpretation of the results.

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## Conflict of interests

The authors declare no competing interests.

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