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Acute effects of ambient nitrogen oxides and interactions with temperature on cardiovascular mortality in Shenzhen, China

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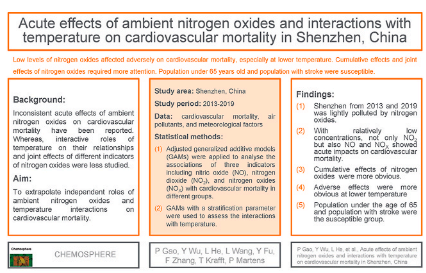
HIGHLIGHTS

- Shenzhen was lightly polluted by nitrogen oxides from 2013 to 2019.
- Low levels of nitrogen oxides affected adversely on cardiovascular mortality.
- Cumulative effects of nitrogen oxides were most significant.
- The adverse effects of nitrogen oxides were more obvious at lower temperature.
- Joint effects were shown when different types of nitrogen oxides were combined.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Though inconsistent, acute effects of ambient nitrogen oxides on cardiovascular mortality have been reported. Whereas, interactive roles of temperature on their relationships and joint effects of different indicators of nitrogen oxides were less studied. This study aimed to extrapolate the independent roles of ambient nitrogen oxides and temperature interactions on cardiovascular mortality.

Methods: Data on mortality, air pollutants, and meteorological factors in Shenzhen from 2013 to 2019 were collected. Three indicators including nitric oxide (NO), nitrogen dioxide (NO_2), and nitrogen oxides (NO_X) were studied. Adjusted generalized additive models (GAMs) were applied to analyse their associations with cardiovascular mortality in different groups.

Results: The average daily concentrations of NO, NO_2, and NO_X were 11.7 μg/m^3, 30.7 μg/m^3, and 53.2 μg/m^3, respectively. Significant associations were shown with each indicator. Cumulative effects of nitrogen oxides were more obvious than distributed lag effects. Males, population under 65 years old, and population with stroke-related condition were more susceptible to nitrogen oxides. Adverse effects of nitrogen oxides were more

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significant at low temperature. Impacts of NO_2 on cardiovascular mortality, and NO on stroke mortality were the most robust in the multi-pollutant models, whereas variations were shown in the other relationships.

Conclusions: Low levels of nitrogen oxides showed acute and adverse impacts and the interactive roles of temperature on cardiovascular mortality. Cumulative effects were most significant and joint effects of nitrogen oxides required more attention. Population under 65 years old and population with stroke-related health condition were susceptible, especially days at lower temperature.

1. Introduction

Copious research about the effects of air pollution on mortality has been conducted for years (Anderson, 2009), and it is suggested that air pollution plays an increasingly considerable role on mortality due to different causes (Cohen et al., 2017). Besides, climatic factors, temperature in particular, were indicated to be involved in mortality associated with air pollution (Burkart et al., 2013; Scortichini et al., 2018; Chen et al., 2018a). Cardiovascular diseases (CVDs) rank first in the causes of death globally (World Health Organization) and have been widely suggested to be associated with air pollution (Franklin et al., 2015) and temperature (Moghadamnia et al., 2017).

Oxides of nitrogen are among the major ambient pollutants, mainly emitted from the power station, motor vehicles, and other industrial combustion processes. The primarily emitted product is nitric monoxide (NO), which will be oxidised by air ozone and become nitrogen dioxide (NO_2). Nitrogen oxides (NO_X) is a collective expression of NO and NO_2 as they can be transformed into each other in the atmosphere.

Previous research has been conducted to study the short-term health impacts of nitrogen oxides on cardiovascular morbidity and mortality. NO_2 is the most studied indicator of nitrogen oxides. NO_2 was suggested to be associated with a higher risk of cardiovascular hospital admission (Mills et al., 2015) and mortality in different cities (Samoli, 2006; Bravo et al., 2016). In addition to the mortality due to total CVDs, cause-specific cardiovascular mortality was also reported to be significantly associated with NO_2. NO_2 was found to be positively related to deaths caused by ischemic heart disease (IHD) (Jerrett et al., 2013) and stroke (Chen et al., 2013).

Moreover, the lag effects of NO_2 on mortality due to CVDs were found. Positive associations were reported between the 2-day average of NO_2 and deaths caused by overall CVDs (Bravo et al., 2016; Chen et al., 2018b), hypertension (Chen et al., 2018b), coronary heart disease (Chen et al., 2018b), and stroke (Chen et al., 2018b; Hong et al., 2002). However, some studies did not reveal any relationships between nitrogen oxides and deaths due to CVDs (Luo et al., 2020; Anderson, 2001; Atkinson et al., 2016).

The interaction of temperature on cardiovascular mortality associated with air pollutants was mostly reported in research about particulate matters (PM) and ozone. The risks of cardiovascular mortality with the increment of PM increased when the temperature was higher (Chen et al., 2017). It was estimated that temperature enhanced the impacts of ozone on deaths caused by CVDs (Ren et al., 2009). Nevertheless, whether temperature could modify the health effects of nitrogen oxides was less extrapolated.

Overall, the conclusions obtained from previous research were inconsistent. The main focus of previous research was on the health effects of NO_2, with less discussion on NO and NO_X, or the possible joint effects among them. Moreover, the possible modification of temperature on effects related to nitrogen oxides was not understood well by now. Therefore, further and comprehensive studies are still in need to recognize their roles and interplay with temperature on human health.

This study aimed to evaluate the independent health impacts of nitrogen oxides and interactions with temperature on mortality due to overall and specific CVDs in different sex and age groups. To our best knowledge, it was the first study that did not only consider lag effects but also joint effects of ambient nitrogen oxides.

2. Materials and methods

2.1. Study area

This research was conducted in Shenzhen, a coastal city in southern China. The climate in Shenzhen is subtropical monsoon, and therefore, its weather is warm and humid (Shenzhen Government Onlin, 2021). By 2019, the population in Shenzhen has reached over 13.4 million (Shenzhen Government Onlin, 2021). It is the most crowded city in China. Shenzhen is now involved in the Greater Bay Area, embracing more chances of economic development and facing more challenges towards environmental protection at the same time. Studies on the effects of current nitrogen oxides on population health could provide a reference for the further steps of Shenzhen. Furthermore, Shenzhen is one of the first-stage cities which complies with the new national standard of air quality GB3095-2012. Since 1 January 2013, monitoring data of the real-time hourly concentration of six air pollutants in Shenzhen have been released to the public. With these rich and high-quality data, it is possible to explore the independent health impacts of nitrogen oxides with relatively low levels.

2.2. Mortality data

Death records, including sex, age, primary death cause and the corresponding *International Classification of Diseases*, *10*th *version* (*ICD-10*) codes, in Shenzhen from 2013 to 2019 were collected. The data were separated into several groups to investigate the effects of environmental exposure on mortality rates due to CVDs (*ICD-10* codes, I00–I99), hypertensive diseases (HBP) (*ICD-10* codes, I10–I15), IHD (*ICD-10* codes, I20–I25), and stroke (STR) (*ICD-10* codes, I60–I69).

2.3. Air pollutants and meteorological factors

The daily records of air pollutants from 2013 to 2019 were collected from Shenzhen Environmental Monitoring Centre and China National Environmental Monitoring Centre (CNEMC). The locations of monitoring sites were set according to the government-suggested technical guidelines. They were not around any traffic intersections or major sources of industrial pollution and were sufficiently far away from any other emission sources. The distribution of the monitoring sites in Shenzhen was shown in Appendix Fig. A. Therefore, the collected data could represent the situation of air quality in Shenzhen.

The monitored indices included NO, NO_2, NO_X, daily 1-h mean of ozone (O_3-1 h), sulphur dioxide (SO_2), carbon monoxide (CO), particulate matter with an aerodynamic diameter less than 10 μm (PM_{10}). The daily levels of air pollutants were calculated based on the available hourly data from 11 state-controlled monitoring stations covering the Shenzhen area. Only when 75% or more of hourly concentrations of air pollutants from each station in each day would the data from this station be included. The whole dataset from one monitoring station with more than 25% data missing during the whole study period would be excluded.

The daily average values of meteorological factors from 2013 to 2019, including temperature (Tem), relative humidity (Hum), precipitation (Pre), barometric pressure (BP), wind speed (WS), and sunshine duration (SSD), were obtained from a weather monitoring station of Meteorological Bureau of Shenzhen Municipality. The monitoring procedure followed the international standards of the World Meteorological Organization (WMO).

2.4. Statistical analyses

The statistical analyses aimed to evaluate the relationship between the number of daily mortality and the concentrations of nitrogen oxides including NO, NO_2, and NO_X. The procedure included imputing missing values, correlation analysis, and modelling. To evaluate the direct effects of nitrogen oxides, PM_{10}, O_3, SO_2, and CO(Chen et al., 2018b) were included as confounders since joint effects between them and nitrogen oxides have been reported.

Missing values in air pollutants (Wijesekara et al., 2020) and meteorological factors (Afrifa-Yamoah et al., 2020) were imputed using Kalman Smoothing on Structural Time Series method with the "imputeTS" package in R 4.0.2. There were no missing values of temperature, relative humidity, or barometric pressure. There was one day missing each for NO_2, O_3-1 h, SO_2, CO, PM_{10}, precipitation, and sunshine duration. Data of 95 days for NO, 93 days for NO_X, and 214 days for wind speed were missing. Spearman correlation was then applied to describe the associations between ambient nitrogen oxides and meteorological factors.

To better understand the effects of nitrogen oxides in different groups of the population, the mortality data were stratified by sex and age. The daily number of deaths were summarized by death cause, sex, and age. Death which was under 65 years old was categorized into the young group, otherwise, the death was coded into the senior group. Interactions between nitrogen oxides and temperature on cardiovascular mortality were assessed by stratifying temperature using its median value. Days with temperature not higher than median values were expressed as "low", otherwise as "high". Days that were not stratified by median values were expressed as "NS".

Generalized additive models (GAMs) with penalized splines were applied to assess the risk of cardiovascular mortalities attributable to ambient nitrogen oxides. GAMs have less restrictions on the types of the relationships between the response and independent variables. It offered a flexible modelling tool by including non-linear and non-monotonic links between variables and mortalities (Wood, 2017).

The analysis used GAMs with log link and Poisson error since death was considered to be a rare event and the daily mortality followed a Poisson distribution. The analysis included two steps: 1) to build up the best basic model for each death cause which excluded nitrogen oxides, 2) to develop the main model for each death cause which included nitrogen oxides.

The basic models consisted of the smoothed spline functions of death date, meteorological factors, and other possible confounding air pollutants including PM_{10}, O_3, SO_2, and CO. The day of week (DOW) was involved in the basic models as a dummy variable.

Assuming a linear relationship between nitrogen oxides and the logarithmic mortalities of CVDs, nitrogen oxides were introduced into basic models to assess their associations with cardiovascular mortalities. Akaike's Information Criterion (AIC) was used to evaluate the fitness of the model. The model with a smaller AIC value was considered to be more preferred. Briefly, the following log-linear GAMs were fitted to obtain the estimated log-relative rate β in Shenzhen:

$$Log[E(Yt)] = \alpha + \sum_{i=1}^{q} \beta i(Xi) + \sum_{j=1}^{p} fj(Zj, df) + Wt(DOW)$$

Here E(Yt) represents the expected number of mortality at day t; β represents the log-relative rate of mortality associated with a unit increase of nitrogen oxides; *Xi* indicates the concentrations of pollutants at day t; $\sum_{j=1}^{p} fj(Zj, df)$ is the non-parametric spline function of death date, meteorological factors, and other air pollutants; $Wt(DOW)$ is the dummy variable for the day of the week. We initialized the degree of freedom (df) as 9 df /year for death date, and 3 df for all the other confounders.

The lag effects of each indicator of nitrogen oxides on cardiovascular mortalities were also examined. Our previous work suggested that the effects of confounding air pollutants were stable with a 3-day lag (Wang et al., 2017; Wu et al., 2016; Zhang et al., 2016). Therefore, this study selected 3 days to analyse the lag effects. For the models of lag effects, nitrogen oxides with different lag (L) structures of single-day lag (also distributed lag, from L0 to L3, L0 corresponds to concentration on the current-day, and L1 corresponds to concentration on the previous day) and multi-day lag (also moving average lag; L01 to L03, L03 corresponds to the four-day moving average of the pollutant concentration of the current day and previous three days). The current-day data of weather variables and other confounding pollutants were used in the lag models.

The interactions of nitrogen oxides and temperature on cardiovascular mortality were examined using GAMs with a stratification parameter. The effects of nitrogen oxides on the current day and aforementioned lag effects were included, respectively. The model was as following:

$$Log[E(Yt)] = \alpha + \beta_1(X) + \beta_2(Tem_k) + \beta_3(X : Tem_k) + \sum_{j=1}^{p} fj(Zj, df) + Wt(DOW)$$

β_1 indicates the effects of nitrogen oxides; *X* indicates the concentrations of nitrogen oxides; β_2 indicates the effects of temperature; Tem_k is the level of temperature on the current day; β_3 indicates the interactive effects of nitrogen oxides and temperature. $\sum_{j=1}^{p} fj(Zj, df)$ is the non-parametric spline function of death date, meteorological factors, and other air pollutants. $Wt(DOW)$ is the dummy variable for the day of the week. The effects of nitrogen oxides on days with high temperature were derived from $\beta_1 + \beta_3$. The confidence intervals were obtained using the method for interaction terms (Figueiras et al., 1998).

The joint effects of nitrogen oxides on deaths caused by CVDs were evaluated using multi-pollutant models. Two-pollutant models included every two of the three kinds of nitrogen oxides, while the three-pollutant model included all of them were introduced in the basic models.

All the analyses were conducted using the 'mgcv' package in R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). The results were presented as the relative risk (RR) of mortality number per 10 μg/m^3 increase of nitrogen oxides (RR = $e^{\beta \times \Delta c}$, where Δc is 10 μg/m^3 of nitrogen oxides).

3. Results

3.1. Descriptive statistics

The mean and percentiles of air pollutants and meteorological factors during the study period were displayed in Table 1. From 2013 to 2019, the daily concentrations of NO, NO_2, and NO_X were on averages of 11.7 μg/m^3, 30.7 μg/m^3, and 53.2 μg/m^3 in Shenzhen, respectively. The mean value of NO in days at low temperature was lower while the means of NO_2, and NO_X in days at high temperature were lower. The temperature in Shenzhen from 2013 to 2019 was 23.5 °C on averagely and with

Table 1
Summary of ambient nitrogen oxides, meteorological factors, and daily cardiovascular deaths.

	Tem		Mean	Standard deviation	Minimum	25%	Median	75%	Maximum
NO (μg/m3)	NS		11.7	13.1	1	4	7	13	133
	Low		11.1	12.1	2	4	7	13	133
	High		12.3	14	1	4.6	7	13	87
NO_2 (μg/m3)	NS		30.7	12.2	7	22	28	36	111
	Low		34.4	13.7	10	25	32	41	111
	High		26.9	9	7	21	25	32	69
NO_X (μg/m3)	NS		53.2	29.6	8	34	46	63	290
	Low		57.1	32.6	8	36	50	68	290
	High		49.1	25.5	11	33	43	57	193
Tem (°C)	NS		23.5	5.4	3.5	19.5	24.8	28.1	33
	Low		19.1	3.9	3.5	16.6	19.6	22.4	24.8
	High		28	1.6	24.9	26.7	28.1	29.4	33
Hum (%)	NS		75.6	13.1	19	69.5	78	84.5	100
	Low		72.2	15.2	19	64.3	75	83.3	100
	High		79	9.3	38.8	73.5	79.8	85.3	99.5
Pre (mm)	NS		5.3	15.9	0	0	0	1.3	187.8
	Low		2.9	11.8	0	0	0	0.1	187.8
	High		7.8	19	0	0	0	5.4	173.5
BP (hPa)	NS		1005.5	6.5	983.1	1000.7	1005.5	1010.4	1027.2
	Low		1010.3	4.3	994.4	1007.4	1010.3	1013.3	1027.2
	High		1000.5	4.2	983.1	997.8	1000.7	1003.1	1012.8
WS (m/s)	NS		2	0.7	0.4	1.4	1.8	2.3	6.1
	Low		2	0.7	0.6	1.5	2	2.4	5.9
	High		1.9	0.7	0.4	1.4	1.8	2.2	6.1
SSD (h)	NS		5.2	3.8	0	1.4	5.5	8.7	12.5
	Low		4.2	3.7	0	0.3	3.6	7.9	10.7
	High		6.3	3.6	0	3.3	6.9	9.5	12.5
Daily cardiovascular deaths									
Total	NS	CVD	9.9	5.4	0	5	9	14	33
		HBP	0.9	1	0	0	1	1	6
		IHD	4	3	0	2	3	6	17
		STR	3.6	2.4	0	2	3	5	14
	Low	CVD	10.7	5.8	0	6	10	15	33
		HBP	1	1	0	0	1	2	6
		IHD	4.2	3.1	0	2	4	6	17
		STR	3.9	2.6	0	2	4	5.25	14
	High	CVD	9	4.8	0	5	9	13	24
		HBP	0.8	0.9	0	0	1	1	5
		IHD	3.7	2.7	0	1	3	6	13
		STR	3.2	2.1	0	2	3	5	11
Female	NS	CVD	3.7	2.5	0	2	3	5	16
		HBP	0.4	0.6	0	0	0	1	5
		IHD	1.4	1.5	0	0	1	2	8
		STR	1.4	1.3	0	0	1	2	7
	Low	CVD	4	2.7	0	2	4	6	16
		HBP	0.4	0.6	0	0	0	1	5
		IHD	1.5	1.5	0	0	1	2	8
		STR	1.5	1.4	0	0	1	2	7
	High	CVD	3.3	2.3	0	2	3	5	12
		HBP	0.3	0.5	0	0	0	1	3
		IHD	1.3	1.3	0	0	1	2	8
		STR	1.3	1.2	0	0	1	2	6
Male	NS	CVD	6.2	3.7	0	3	6	9	24
		HBP	0.5	0.7	0	0	0	1	4
		IHD	2.5	2.1	0	1	2	4	11
		STR	2.2	1.7	0	1	2	3	10
	Low	CVD	6.7	3.9	0	4	6	9	24
		HBP	0.6	0.8	0	0	0	1	4
		IHD	2.7	2.2	0	1	2	4	11
		STR	2.4	1.8	0	1	2	3	10
	High	CVD	5.7	3.4	0	3	5	8	17
		HBP	0.5	0.7	0	0	0	1	4
		IHD	2.4	2	0	1	2	4	10
		STR	2	1.5	0	1	2	3	8
Senior	NS	CVD	5.9	3.8	0	3	5	8	24
		HBP	0.5	0.8	0	0	0	1	5
		IHD	2.5	2.1	0	1	2	4	15
		STR	2.3	1.9	0	1	2	3	11
	Low	CVD	6.5	4	0	3	6	9	24
		HBP	0.6	0.8	0	0	0	1	5
		IHD	2.8	2.2	0	1	2	4	15
		STR	2.5	2	0	1	2	4	11
	High	CVD	5.3	3.4	0	3	5	8	19
		HBP	0.5	0.7	0	0	0	1	5

(continued on next page)

Table 1 (*continued*)

	Tem		Mean	Standard deviation	Minimum	25%	Median	75%	Maximum
		IHD	2.3	1.9	0	1	2	3	11
		STR	2.1	1.7	0	1	2	3	10
Young	NS	CVD	3.9	2.5	0	2	4	5	17
		HBP	0.3	0.6	0	0	0	1	4
		IHD	1.4	1.5	0	0	1	2	10
		STR	1.3	1.1	0	0	1	2	6
	Low	CVD	4.2	2.6	0	2	4	6	17
		HBP	0.4	0.6	0	0	0	1	4
		IHD	1.5	1.5	0	0	1	2	10
		STR	1.4	1.2	0	0	1	2	6
	High	CVD	3.7	2.3	0	2	3	5	14
		HBP	0.3	0.5	0	0	0	0	3
		IHD	1.4	1.4	0	0	1	2	7
		STR	1.1	1	0	0	1	2	6

Table 2
Summary of death counts due to each cardiovascular death cause in different groups (%CVD).

Death cause	Tem	Total	Female	Male	Senior	Young
CVD	NS	25,204 (100)	9380 (37.22)	15,824 (62.78)	15,161 (60.15)	10,043 (39.85)
	Low	13,820 (54.83)	5179 (20.55)	8641 (34.28)	8441 (33.49)	5379 (21.34)
	High	11,384 (45.17)	4201 (16.67)	7183 (28.50)	6720 (26.66)	4664 (18.50)
HBP	NS	2263 (8.98)	901 (3.57)	1362 (5.40)	1382 (5.48)	881 (3.50)
	Low	1306 (5.18)	517 (2.05)	789 (3.13)	788 (3.13)	518 (2.06)
	High	957 (3.80)	384 (1.52)	573 (2.27)	594 (2.36)	363 (1.44)
IHD	NS	10,097 (40.06)	3640 (14.44)	6457 (25.62)	6446 (25.58)	3651 (14.49)
	Low	5479 (21.74)	1999 (7.93)	3480 (13.81)	3583 (14.22)	1896 (7.52)
	High	4618 (18.32)	1641 (6.51)	2977 (11.81)	2863 (11.36)	1755 (6.96)
STR	NS	9106 (36.13)	3573 (14.18)	5533 (21.95)	5911 (23.45)	3195 (12.68)
	Low	5037 (19.98)	1986 (7.88)	3051 (12.10)	3283 (13.03)	1754 (6.96)
	High	4069 (16.14)	1587 (6.30)	2482 (9.85)	2628 (10.43)	1441 (5.72)

a median value of 24.8 °C. The average temperatures in days with low temperature and days with high temperature were 19.1 °C and 28.0 °C respectively.

In total, during the study period, averagely there were 9.9 deaths due to cardiovascular causes, with a maximum of 33 per day. IHD accounted for the majority of cardiovascular death, with an average of and a maximum of 17 per day. IHD, stroke, and hypertensive diseases were the following major causes of daily mortality in the total population and in different groups.

Table 2 summarized the mortality number due to each cardiovascular death cause in different subgroups. In total, there were 25,204 deaths due to cardiovascular causes, among which 37.22% were female and 60.15% were senior. Among the cardiovascular deaths, ischemic heart disease and stroke were the main specific causes. Despite the different causes of death, mortality counts in the male group, senior group, and in days with low temperature were higher than those in the female group, young group, and in days with high temperature, respectively.

Table 3 showed the correlation coefficients between nitrogen oxides and meteorological factors. Most of the correlations were found to be statistically significant. Three kinds of nitrogen oxides were positively related to each other. NO was noticed to be positively associated with temperature, relative humidity, and precipitation, whereas negatively correlated with barometric pressure and wind speed. NO_2 was found to be negatively associated with all studied meteorological factors except barometric pressure. NO_X was shown to be positively related to relative humidity, barometric pressure, while negatively associated with temperature and wind speed.

3.2. Effects of nitrogen oxides on cardiovascular mortalities

The health influence of NO, NO_2, and NO_X on death caused by CVDs was assessed using single-pollutant models and multi-pollutant models. The results about effects obtained from single-pollutant models of each pollutant were presented in several tables, respectively. Most of the significant effects were positive and were mostly found when the temperature was not stratified and in days at low temperature, while the rest were negative effects and were mostly found in days at high temperature. In general, despite different indicators and different lag windows of nitrogen oxides, overall CVDs and stroke were the most affected death causes and people under 65 years old was the most susceptible population.

Table 3
Spearman correlation between ambient nitrogen oxides and meteorological factors.

	NO	NO_2	NO_X	Tem	Hum	Pre	BP	WS	SSD
NO	1								
NO_2	0.396**	1							
NO_X	0.781**	0.556**	1						
Tem	0.039*	−0.307**	−0.118**	1					
Hum	0.219**	−0.110**	0.068**	0.211**	1				
Pre	0.091**	−0.079**	−0.038	0.104**	0.611**	1			
BP	−0.095**	0.257**	0.086**	−0.850**	−0.471**	−0.349**	1		
WS	−0.224**	−0.254**	−0.319**	−0.149**	−0.174**	−0.089**	0.130**	1	
SSD	0.003	−0.079**	−0.021	0.398**	−0.486**	−0.471**	−0.106**	0.030	1

Note: *, $p < 0.05$; **, $p < 0.01$.

Table 4
The effects of current-day nitrogen oxides on cardiovascular mortality in Shenzhen (single-pollutant model, RR (95%CI)).

	Death cause	Tem	Total	Female	Male	Senior	Young
NO	CVD	Low	1.016 (1.001, 1.031)*	1.020 (0.997, 1.044)	1.018 (0.999, 1.037)	1.017 (0.999, 1.036)	1.028 (1.005, 1.052)*
	HBP	Low	1.005 (0.955, 1.058)	1.040 (0.965, 1.121)	0.995 (0.931, 1.063)	0.974 (0.908, 1.043)	1.074 (1.002, 1.150)*
	STR	NS	1.029 (1.010, 1.050)**	1.026 (0.995, 1.058)	1.027 (1.004, 1.050)*	1.025 (1.001, 1.050)*	1.029 (0.998, 1.061)
		Low	1.041 (1.017, 1.066)***	1.024 (0.986, 1.064)	1.047 (1.017, 1.078)**	1.033 (1.004, 1.063)*	1.043 (1.002, 1.086)*
NO_2	CVD	NS	1.021 (1.001, 1.042)*	1.023 (0.991, 1.055)	1.016 (0.992, 1.041)	1.009 (0.985, 1.035)	1.045 (1.014, 1.076)**
		Low	1.026 (1.004, 1.048)*	1.028 (0.995, 1.063)	1.018 (0.993, 1.045)	1.014 (0.988, 1.041)	1.049 (1.017, 1.083)**
	STR	NS	1.031 (0.998, 1.065)	1.025 (0.974, 1.079)	1.035 (0.994, 1.077)	0.999 (0.960, 1.040)	1.059 (1.006, 1.115)*
		Low	1.030 (0.996, 1.066)	1.029 (0.976, 1.086)	1.032 (0.988, 1.077)	0.991 (0.950, 1.033)	1.071 (1.014, 1.131)*
NO_X	CVD	NS	1.002 (0.996, 1.008)	1.006 (0.997, 1.016)	1.002 (0.994, 1.009)	1.000 (0.992, 1.007)	1.009 (1.001, 1.018)*
		Low	1.005 (0.999, 1.012)	1.008 (0.998, 1.018)	1.005 (0.998, 1.013)	1.005 (0.997, 1.013)	1.013 (1.003, 1.023)**
		High	0.988 (0.977, 0.999)*	0.999 (0.982, 1.017)	0.987 (0.975, 1.000)*	0.984 (0.971, 0.997)*	1.002 (0.988, 1.015)
	STR	NS	1.009 (1.000, 1.019)	1.006 (0.991, 1.021)	1.012 (1.000, 1.023)*	1.004 (0.992, 1.015)	1.016 (1.001, 1.032)*
		Low	1.011 (1.000, 1.021)*	1.005 (0.988, 1.021)	1.015 (1.002, 1.028)*	1.004 (0.991, 1.017)	1.019 (1.002, 1.037)*

Note: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.00$.

3.2.1. *Effects of current-day nitrogen oxides and interactions with temperature*

Table 4 showed the significant effects of current-day nitrogen oxides and their interactions with stratified temperature on the deaths due to CVDs. Among the three indicators of nitrogen oxides, the effects of NO and NO_X were more obvious than those of NO_2 on the cardiovascular mortality.

The concentration of NO on the current day was found to be only positively related to the deaths due to stroke in the total population, the males, and the senior. These positive relationships remained in the days with low temperature and disappeared in the days with high temperature. In addition, some positive effects of NO showed up only in the days with low temperature, such as effects on CVD deaths in total, and deaths caused by CVDs and hypertensive diseases under 65 years old.

There were positive associations found between the level of NO_2 on the current day, CVD-caused deaths in the total population and the young, and the stroke mortality in the young. These associations remained in days with low temperature and turned into insignificant at high temperature.

With increasing NO_X on the current day, higher risks were noticed in the male and the young, which remained at low temperature while

Table 5
The lag effects of nitrogen oxides on cardiovascular mortality stratified by temperature (single-pollutant model, RR (95%CI)).

	Lag	Death cause	Tem	Total	Female	Male	Senior	Young
NO	L1	CVD	Low	1.015 (1.001, 1.029)*	1.013 (0.991, 1.036)	1.018 (1.001, 1.036)*	1.018 (1.001, 1.036)*	1.023 (1.001, 1.045)*
			High	0.981 (0.959, 1.004)	1.024 (0.991, 1.058)	0.976 (0.953, 0.999)*	0.985 (0.962, 1.009)	1.000 (0.976, 1.025)
		STR	NS	1.032 (1.013, 1.051)***	1.028 (0.998, 1.058)	1.030 (1.008, 1.053)**	1.028 (1.006, 1.052)*	1.033 (1.004, 1.064)*
			Low	1.043 (1.021, 1.066)***	1.024 (0.988, 1.062)	1.052 (1.024, 1.080)***	1.036 (1.008, 1.064)*	1.051 (1.013, 1.090)**
	L2	CVD	NS	1.000 (0.988, 1.012)	1.010 (0.992, 1.029)	1.002 (0.988, 1.016)	0.994 (0.980, 1.008)	1.021 (1.005, 1.038)*
			Low	1.010 (0.996, 1.024)	1.011 (0.989, 1.034)	1.013 (0.996, 1.030)	0.998 (0.980, 1.016)	1.039 (1.019, 1.061)***
		IHD	Low	1.015 (0.994, 1.036)	1.022 (0.988, 1.057)	1.020 (0.994, 1.046)	1.000 (0.974, 1.027)	1.043 (1.010, 1.078)*
		STR	Low	1.011 (0.988, 1.034)	1.000 (0.964, 1.038)	1.016 (0.988, 1.045)	0.993 (0.965, 1.022)	1.038 (1.000, 1.077)*
	L3	CVD	Low	1.002 (0.988, 1.016)	1.018 (0.995, 1.040)	0.998 (0.981, 1.016)	0.997 (0.979, 1.015)	1.023 (1.001, 1.044)*
NO_2	L1	CVD	NS	1.015 (1.000, 1.030)	1.025 (1.002, 1.050)*	1.011 (0.993, 1.030)	1.008 (0.990, 1.027)	1.033 (1.010, 1.056)**
			Low	1.028 (1.011, 1.045)***	1.030 (1.004, 1.057)*	1.024 (1.003, 1.045)*	1.021 (1.000, 1.042)*	1.043 (1.017, 1.069)***
		HBP	NS	1.031 (0.986, 1.078)	1.073 (1.002, 1.150)*	1.014 (0.957, 1.073)	1.016 (0.960, 1.075)	1.076 (1.003, 1.155)*
		STR	Low	1.040 (1.013, 1.068)**	1.038 (0.995, 1.082)	1.045 (1.011, 1.080)**	1.027 (0.993, 1.062)	1.056 (1.011, 1.102)*
	L2	CVD	NS	1.012 (0.998, 1.026)	1.022 (1.000, 1.044)	1.009 (0.992, 1.026)	1.002 (0.985, 1.020)	1.035 (1.014, 1.056)**
			Low	1.022 (1.006, 1.038)**	1.024 (0.999, 1.050)	1.018 (0.999, 1.038)	1.005 (0.986, 1.025)	1.051 (1.027, 1.076)***
		IHD	NS	1.020 (0.998, 1.041)	1.050 (1.014, 1.087)**	1.005 (0.978, 1.032)	1.006 (0.980, 1.033)	1.042 (1.006, 1.079)*
			Low	1.027 (1.002, 1.052)*	1.052 (1.011, 1.095)*	1.017 (0.987, 1.048)	1.013 (0.983, 1.044)	1.054 (1.012, 1.097)*
		STR	NS	1.014 (0.993, 1.037)	1.010 (0.975, 1.046)	1.019 (0.991, 1.048)	1.003 (0.976, 1.032)	1.038 (1.002, 1.075)*
			Low	1.025 (0.999, 1.051)	1.017 (0.976, 1.059)	1.029 (0.997, 1.062)	1.006 (0.975, 1.039)	1.059 (1.018, 1.102)**
	L3	CVD	NS	1.006 (0.992, 1.019)	1.009 (0.988, 1.031)	1.005 (0.989, 1.022)	0.988 (0.971, 1.005)	1.040 (1.019, 1.061)***
			Low	1.005 (0.990, 1.022)	1.015 (0.990, 1.041)	1.000 (0.981, 1.020)	0.980 (0.960, 0.999)*	1.051 (1.027, 1.076)***
		IHD	Low	1.009 (0.984, 1.034)	1.017 (0.976, 1.059)	1.012 (0.981, 1.043)	0.989 (0.959, 1.020)	1.049 (1.007, 1.093)*
		STR	NS	0.999 (0.977, 1.021)	1.000 (0.965, 1.035)	1.002 (0.974, 1.030)	0.972 (0.945, 0.999)*	1.053 (1.017, 1.091)**
			Low	1.000 (0.975, 1.027)	0.999 (0.958, 1.041)	1.006 (0.974, 1.039)	0.966 (0.935, 0.998)*	1.068 (1.026, 1.111)**
NO_X	L1	CVD	NS	1.003 (0.998, 1.008)	1.008 (1.000, 1.016)	1.003 (0.996, 1.009)	1.003 (0.996, 1.009)	1.008 (1.001, 1.016)*
			Low	1.008 (1.002, 1.014)**	1.008 (0.999, 1.017)	1.009 (1.002, 1.016)*	1.008 (1.001, 1.015)*	1.013 (1.005, 1.022)**
			High	0.987 (0.977, 0.998)*	1.005 (0.989, 1.022)	0.982 (0.971, 0.995)**	0.986 (0.974, 0.998)*	0.998 (0.985, 1.011)
		HBP	Low	1.015 (0.996, 1.034)	1.026 (0.997, 1.055)	1.012 (0.988, 1.036)	1.008 (0.984, 1.033)	1.029 (1.002, 1.057)*
		STR	NS	1.011 (1.003, 1.020)**	1.008 (0.995, 1.021)	1.014 (1.004, 1.024)**	1.009 (0.999, 1.019)	1.016 (1.002, 1.029)*
			Low	1.016 (1.006, 1.025)***	1.008 (0.993, 1.023)	1.021 (1.009, 1.032)***	1.011 (1.000, 1.023)	1.022 (1.007, 1.037)**
	L2	CVD	NS	1.002 (0.997, 1.007)	1.004 (0.996, 1.012)	1.002 (0.996, 1.009)	0.998 (0.992, 1.004)	1.012 (1.005, 1.019)***
			Low	1.006 (1.000, 1.011)*	1.006 (0.997, 1.015)	1.007 (1.000, 1.013)	1.000 (0.993, 1.007)	1.018 (1.010, 1.027)***
		IHD	NS	1.005 (0.997, 1.012)	1.011 (0.999, 1.023)	1.004 (0.995, 1.013)	1.000 (0.990, 1.009)	1.013 (1.001, 1.025)*
			Low	1.007 (0.999, 1.016)	1.012 (0.999, 1.026)	1.007 (0.997, 1.018)	1.000 (0.990, 1.011)	1.020 (1.006, 1.033)**
		STR	Low	1.005 (0.996, 1.014)	0.997 (0.982, 1.012)	1.010 (0.999, 1.022)	0.998 (0.987, 1.010)	1.019 (1.004, 1.034)*
	L3	CVD	NS	0.999 (0.994, 1.004)	1.004 (0.996, 1.012)	0.998 (0.992, 1.004)	0.995 (0.989, 1.001)	1.009 (1.002, 1.016)*
			Low	1.001 (0.995, 1.007)	1.006 (0.998, 1.015)	0.999 (0.992, 1.006)	0.996 (0.989, 1.003)	1.013 (1.004, 1.021)**
		IHD	Low	1.005 (0.996, 1.013)	1.010 (0.996, 1.024)	1.006 (0.995, 1.016)	1.000 (0.990, 1.011)	1.014 (1.001, 1.028)*
		STR	High	0.991 (0.975, 1.006)	1.010 (0.986, 1.035)	0.981 (0.964, 0.999)*	0.993 (0.974, 1.013)	0.992 (0.969, 1.015)

Note: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

became insignificant at high temperature. Additionally, the current-day concentration of NO_X was found to be positively associated with stroke deaths in the total population in days at low temperature. In days at high temperature, negative effects of current-day NO_X were shown in CVD-caused deaths of the total population, males, and the senior.

3.2.2. Lag effects of nitrogen oxides and their interactions with temperature

Table 5 showed distributed lag effects with statistical significance of nitrogen oxides and the interactions with temperature on mortality due to CVDs. Overall, the 1-day distributed lag effects of nitrogen oxides were most obvious. NO_2 was found to affect the cardiovascular mortality the most. Most of the significant associations were positive, while the majority of the negative associations were found in NO_X at high temperature.

When the temperature was not stratified, NO on L1 was found to be positively associated with the mortality due to stroke in each population except for the female. These associations remained at low temperature and became insignificant at high temperature. Higher risks were further observed at low temperature between one-day lagged NO and CVD-caused deaths in these population groups. Regarding NO on L2, statistical relationships were only identified in deaths under 65 years old. A higher risk of dying from CVDs was revealed when not stratifying temperature and at low temperature. The risk of IHD and stroke death increased only in the days with low temperature. The increment of NO on L3 was only noticed to be positively associated with CVD-caused deaths in the young group at low temperature.

Table 6
The cumulative effects of nitrogen oxides on cardiovascular mortality stratified by temperature (single-pollutant model, RR (95%CI)).

	Lag	Death cause	Tem	Total	Female	Male	Senior	Young
NO	L01	CVD	NS	1.007 (0.992, 1.022)	1.025 (1.002, 1.047)*	1.007 (0.990, 1.024)	1.009 (0.992, 1.026)	1.016 (0.997, 1.036)
			Low	1.022 (1.005, 1.040)*	1.024 (0.997, 1.052)	1.026 (1.004, 1.048)*	1.026 (1.004, 1.048)*	1.037 (1.010, 1.064)**
			High	0.975 (0.950, 1.001)	1.025 (0.989, 1.063)	0.973 (0.948, 0.998)*	0.982 (0.957, 1.008)	1.000 (0.974, 1.027)
		HBP	Low	1.017 (0.958, 1.080)	1.055 (0.965, 1.153)	1.023 (0.948, 1.103)	0.988 (0.912, 1.069)	1.099 (1.013, 1.192)*
		STR	NS	1.042 (1.019, 1.065)***	1.036 (1.001, 1.073)*	1.037 (1.011, 1.064)**	1.036 (1.009, 1.064)**	1.041 (1.006, 1.077)*
			Low	1.062 (1.034, 1.092)***	1.035 (0.990, 1.082)	1.072 (1.037, 1.109)***	1.050 (1.015, 1.086)**	1.070 (1.021, 1.121)**
	L02	CVD	NS	1.006 (0.989, 1.023)	1.025 (1.001, 1.050)*	1.007 (0.989, 1.025)	1.004 (0.986, 1.022)	1.023 (1.002, 1.044)*
			Low	1.025 (1.005, 1.045)*	1.027 (0.997, 1.059)	1.030 (1.006, 1.054)*	1.020 (0.996, 1.045)	1.055 (1.025, 1.086)***
			High	0.970 (0.943, 0.998)*	1.021 (0.983, 1.060)	0.974 (0.948, 1.000)*	0.982 (0.956, 1.008)	1.000 (0.973, 1.027)
		HBP	Low	1.011 (0.945, 1.082)	1.075 (0.974, 1.187)	1.008 (0.927, 1.097)	0.973 (0.890, 1.063)	1.113 (1.017, 1.217)*
		STR	NS	1.035 (1.011, 1.059)**	1.031 (0.993, 1.070)	1.030 (1.003, 1.058)*	1.025 (0.996, 1.055)	1.042 (1.005, 1.081)*
			Low	1.058 (1.026, 1.091)***	1.029 (0.979, 1.082)	1.069 (1.030, 1.110)***	1.038 (0.999, 1.078)	1.081 (1.028, 1.138)**
	L03	CVD	NS	1.002 (0.984, 1.020)	1.029 (1.003, 1.055)*	1.002 (0.983, 1.022)	1.000 (0.980, 1.019)	1.025 (1.003, 1.047)*
			Low	1.024 (1.002, 1.046)*	1.035 (1.001, 1.071)*	1.026 (0.999, 1.053)	1.017 (0.990, 1.044)	1.062 (1.029, 1.096)***
			High	0.967 (0.938, 0.996)*	1.020 (0.981, 1.060)	0.974 (0.948, 1.001)	0.979 (0.953, 1.007)	1.001 (0.974, 1.029)
		HBP	Low	1.013 (0.940, 1.091)	1.098 (0.987, 1.222)	0.998 (0.910, 1.095)	0.968 (0.878, 1.067)	1.126 (1.021, 1.243)*
		STR	NS	1.027 (1.001, 1.053)*	1.033 (0.992, 1.075)	1.019 (0.991, 1.049)	1.016 (0.985, 1.048)	1.040 (1.001, 1.081)*
			Low	1.054 (1.018, 1.090)**	1.032 (0.977, 1.090)	1.060 (1.017, 1.105)**	1.028 (0.985, 1.072)	1.088 (1.029, 1.151)**
NO_2	L01	CVD	NS	1.026 (1.005, 1.047)*	1.036 (1.003, 1.070)*	1.019 (0.994, 1.045)	1.012 (0.987, 1.038)	1.056 (1.024, 1.089)***
			Low	1.038 (1.015, 1.062)***	1.042 (1.007, 1.079)*	1.028 (1.001, 1.056)*	1.024 (0.996, 1.052)	1.065 (1.030, 1.101)***
		HBP	NS	1.038 (0.975, 1.105)	1.064 (0.967, 1.171)	1.022 (0.944, 1.106)	1.000 (0.926, 1.081)	1.114 (1.010, 1.229)*
		STR	NS	1.037 (1.004, 1.072)*	1.034 (0.981, 1.089)	1.046 (1.004, 1.090)*	1.011 (0.970, 1.054)	1.065 (1.010, 1.124)*
			Low	1.049 (1.013, 1.087)**	1.047 (0.990, 1.107)	1.055 (1.009, 1.102)*	1.016 (0.972, 1.062)	1.086 (1.026, 1.150)**
	L02	CVD	NS	1.028 (1.006, 1.050)*	1.042 (1.009, 1.077)*	1.020 (0.995, 1.047)	1.011 (0.985, 1.037)	1.067 (1.034, 1.101)***
			Low	1.045 (1.021, 1.069)***	1.049 (1.012, 1.088)**	1.033 (1.005, 1.063)*	1.022 (0.994, 1.052)	1.083 (1.046, 1.120)***
		HBP	NS	1.029 (0.966, 1.096)	1.061 (0.963, 1.170)	1.010 (0.932, 1.095)	0.996 (0.920, 1.077)	1.107 (1.003, 1.223)*
		IHD	NS	1.032 (0.999, 1.066)	1.075 (1.020, 1.132)**	1.009 (0.969, 1.051)	1.011 (0.971, 1.052)	1.064 (1.008, 1.122)*
			Low	1.045 (1.009, 1.083)*	1.076 (1.016, 1.140)*	1.032 (0.987, 1.078)	1.030 (0.986, 1.076)	1.072 (1.010, 1.137)*
		STR	NS	1.037 (1.003, 1.073)*	1.031 (0.978, 1.087)	1.047 (1.004, 1.092)*	1.011 (0.969, 1.054)	1.076 (1.020, 1.136)**
			Low	1.054 (1.016, 1.093)**	1.047 (0.987, 1.110)	1.059 (1.012, 1.108)*	1.016 (0.970, 1.065)	1.105 (1.042, 1.172)***
	L03	CVD	NS	1.027 (1.004, 1.051)*	1.041 (1.006, 1.078)*	1.020 (0.993, 1.048)	1.001 (0.974, 1.028)	1.081 (1.047, 1.117)***
			Low	1.043 (1.017, 1.070)**	1.051 (1.011, 1.092)*	1.030 (0.999, 1.061)	1.008 (0.978, 1.039)	1.100 (1.061, 1.140)***
		IHD	NS	1.036 (1.002, 1.072)*	1.076 (1.019, 1.137)**	1.016 (0.974, 1.060)	1.011 (0.970, 1.055)	1.076 (1.017, 1.138)*
			Low	1.045 (1.006, 1.085)*	1.075 (1.011, 1.143)*	1.034 (0.987, 1.083)	1.021 (0.974, 1.070)	1.089 (1.023, 1.159)**
		STR	NS	1.030 (0.994, 1.067)	1.026 (0.970, 1.085)	1.039 (0.995, 1.086)	0.990 (0.947, 1.035)	1.098 (1.038, 1.161)**
			Low	1.046 (1.005, 1.087)*	1.040 (0.977, 1.107)	1.051 (1.002, 1.103)*	0.993 (0.945, 1.044)	1.130 (1.062, 1.202)***
NO_X	L01	CVD	NS	1.004 (0.997, 1.010)	1.010 (1.000, 1.020)	1.003 (0.995, 1.011)	1.002 (0.994, 1.009)	1.011 (1.002, 1.021)*
			Low	1.009 (1.002, 1.017)*	1.011 (1.000, 1.023)*	1.010 (1.001, 1.019)*	1.009 (1.000, 1.017)	1.018 (1.007, 1.029)**
			High	0.984 (0.972, 0.997)*	1.004 (0.985, 1.023)	0.981 (0.968, 0.995)**	0.981 (0.967, 0.995)**	1.000 (0.986, 1.015)
		HBP	Low	1.014 (0.990, 1.038)	1.029 (0.994, 1.066)	1.006 (0.977, 1.037)	1.000 (0.971, 1.031)	1.038 (1.005, 1.073)*
		STR	NS	1.014 (1.004, 1.025)**	1.009 (0.993, 1.026)	1.018 (1.005, 1.030)**	1.009 (0.996, 1.021)	1.021 (1.005, 1.038)*
			Low	1.018 (1.007, 1.030)**	1.008 (0.990, 1.027)	1.024 (1.010, 1.039)***	1.011 (0.997, 1.025)	1.028 (1.009, 1.048)**
	L02	CVD	NS	1.004 (0.997, 1.011)	1.010 (0.999, 1.020)	1.004 (0.995, 1.012)	1.000 (0.992, 1.008)	1.015 (1.006, 1.025)**
			Low	1.011 (1.003, 1.019)**	1.012 (1.000, 1.024)	1.012 (1.002, 1.021)*	1.007 (0.997, 1.016)	1.025 (1.013, 1.036)***
			High	0.983 (0.969, 0.996)*	1.001 (0.982, 1.022)	0.982 (0.968, 0.996)*	0.982 (0.968, 0.997)*	1.000 (0.985, 1.015)
		HBP	Low	1.015 (0.989, 1.041)	1.037 (0.999, 1.076)	1.004 (0.972, 1.036)	0.999 (0.968, 1.032)	1.042 (1.006, 1.079)*
		IHD	Low	1.011 (1.000, 1.023)	1.019 (1.000, 1.037)*	1.011 (0.996, 1.025)	1.006 (0.992, 1.020)	1.021 (1.002, 1.040)*
		STR	NS	1.012 (1.001, 1.023)*	1.005 (0.988, 1.022)	1.017 (1.004, 1.030)*	1.005 (0.992, 1.019)	1.024 (1.006, 1.041)**
			Low	1.017 (1.005, 1.030)**	1.005 (0.985, 1.025)	1.025 (1.010, 1.040)**	1.007 (0.992, 1.023)	1.033 (1.013, 1.054)**
	L03	CVD	NS	1.003 (0.995, 1.010)	1.010 (0.999, 1.022)	1.002 (0.993, 1.011)	0.997 (0.989, 1.006)	1.017 (1.007, 1.027)**
			Low	1.010 (1.001, 1.018)*	1.014 (1.001, 1.027)*	1.010 (1.000, 1.020)	1.004 (0.994, 1.014)	1.027 (1.015, 1.040)***
			High	0.982 (0.968, 0.997)*	1.000 (0.979, 1.021)	0.983 (0.969, 0.998)*	0.982 (0.967, 0.997)*	1.001 (0.985, 1.016)
		HBP	Low	1.015 (0.987, 1.043)	1.042 (1.002, 1.084)*	0.998 (0.964, 1.033)	0.997 (0.963, 1.031)	1.044 (1.006, 1.083)*
		IHD	NS	1.017 (1.000, 1.033)*	1.015 (0.998, 1.033)	1.007 (0.994, 1.020)	1.001 (0.988, 1.014)	1.015 (0.999, 1.033)
			Low	1.012 (1.000, 1.025)*	1.021 (1.001, 1.042)*	1.012 (0.997, 1.027)	1.005 (0.990, 1.021)	1.025 (1.005, 1.045)*
		STR	NS	1.008 (0.997, 1.020)	1.005 (0.987, 1.024)	1.011 (0.998, 1.025)	1.001 (0.987, 1.015)	1.023 (1.005, 1.042)*
			Low	1.014 (1.001, 1.028)*	1.004 (0.983, 1.026)	1.020 (1.004, 1.036)*	1.002 (0.986, 1.019)	1.035 (1.013, 1.057)**

Note: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

The concentration of NO_2 on L1 was positively associated with CVD-caused deaths in the female and the young without stratifying temperature, and in each population group at low temperature. The positive relationships with mortality due to hypertensive diseases became insignificant after the temperature was stratified. The risk of stroke mortality increased in the total population, male group, and young group in the days with low temperature. The increment of NO_2 on L2 was related to higher risks of IHD mortality in females and every studied mortality except for mortality due to hypertensive diseases in the young. Higher risks remained at low temperature and disappeared at high temperature. Besides, in the days with low temperature, positive associations were also in CVD-caused and IHD mortality in the total population. NO_2 on L3 was positively related to deaths due to CVDs and stroke in the young, while negatively related to stroke mortality in the senior. These relationships were stable in days with low temperature. At low temperature, the risk of IHD mortality in the young turned to increase and the risk of CVD-caused mortality in the senior decreased.

The concentration of NO_X on L1 was identified to be positively associated with mortality due to CVDs only in the young at unstratified temperature, whereas in each group except the female at low temperature. However, at high temperature, some of these associations were significantly negative. There was also a positive association observed in mortality due to hypertensive diseases in the young group. At unstratified and low temperature, NO_X on L2 was positively related to CVD-caused and IHD mortality in the population under 65 years old. At low temperature, more increasing risks were discovered in deaths caused by CVDs in the total population, and stroke mortality in the young group. NO_X on L3 was positively related with CVD-caused deaths when the temperature was not stratified and with deaths caused by CVD and IHD at low temperature only in the young. Nevertheless, the risk of stroke mortality was found to decrease in the male group.

3.2.3. Cumulative effects of nitrogen oxides and their interactions with temperature

The significantly cumulative effects of nitrogen oxides and interactions with temperature on cardiovascular deaths were presented in Table 6. The 1-day moving-average lag effects of NO influenced the cardiovascular mortality most. For NO_2 and NO_X, the most influential lag windows were 2 days and 3 days, respectively. Similar with the distributed lag effects, most of the impacts were positive and the majority of the negative effects were found in NO_X at high temperature. Whereas, on the whole, the cumulative effects of nitrogen oxides were more obvious than their distributed lag effects.

NO with L01 was identified to be positively associated with CVD-caused deaths in the female and stroke mortality in each group. The associations in females became insignificant after stratifying the temperature. Instead of the female group, the effects on mortality due to CVDs and stroke in the rest of the groups showed up at low temperature. A higher risk of mortality caused by hypertensive diseases was revealed in the young at low temperature. Reverse effects were observed in mortality due to CVDs in males at high temperature.

The increment of NO with L02 was associated with higher risks of CVD-caused deaths and stroke-caused deaths in the study population. These relationships were stable at low temperature except for the female group. Insignificant associations between NO with L02 and CVD-caused mortality in total and the male polarized after stratifying the temperature. NO with L02 was positively related to mortality due to hypertensive diseases in the young at low temperature.

Regarding NO with L03, it was identified to be constantly associated with higher risks of mortality due to CVDs and stroke in the study population at unstratified and low temperature. More positive associations were observed in mortality due to CVDs stroke and hypertensive diseases at low temperature. Further, there was a negative association in total deaths caused by CVDs at high temperature.

NO_2 with L01 was related to higher risks of mortality due to CVDs and stroke in some population groups. These relationships remained at low temperature rather than at high temperature. However, the noted associations in mortality due to hypertensive diseases in the young disappeared after temperature stratification. NO_2 of L01 increased the risk of deaths caused by CVDs in the male at low temperature.

Increasing NO_2 of L02 was found to be associated with higher risks of deaths caused by overall CVDs, IHD, and stroke in different population groups at unstratified and low temperature. The positive relationship in mortality due to hypertensive diseases in the young became insignificant after stratifying the temperature. Significantly higher risks of CVD-caused deaths in male and IHD-caused deaths in the total population were further observed only at low temperature.

There were constantly positive associations between NO_2 of L03 and CVD-caused mortality, IHD-caused mortality, and stroke-caused mortality at unstratified temperature and at low temperature. More increasing risks of stroke mortality in the total and male group were uncovered at low temperature.

Elevated NO_X of L01 was statistically related with higher risks of mortality due to CVDs, stroke at unstratified and low temperature. Positive effects were also observed only at low temperature in deaths caused by CVDs in the total population, female group, and male group, and deaths caused by hypertensive diseases in the young. Nevertheless, negative effects on CVD-caused mortality in the total population, male group, and senior group were found in days with high temperature.

Most of the relationships found with NO_X of L01 continued when NO_X of L02 was involved in the models instead, no matter considering the interactions with temperature or not. Instead of the association between NO_X of L01 and CVD-caused deaths in females at low temperature, IHD-caused deaths in the female and the young were positively affected by NO_X of L02 in days with low temperature.

Higher risks of mortality due to CVDs, IHD, and stroke were noticed when the NO_X level of L03 increased without stratifying the temperature and at low temperature. In addition, only in days with low temperature, more positive associations were uncovered in deaths caused by overall CVDs and each specific cardiovascular cause. Constant with NO_X of L01 and L02, the risks of CVD-caused mortality in the total population, male group, and senior group still decreased with increasing NO_X of L03 in days with high temperature.

3.2.4. Joint effects

The comparison of the results obtained from single pollutant models, 2-pollutant models and a 3-pollutant model using the concentrations of pollutants on the current day was shown in Fig. 1. The RRs of mortalities due to hypertensive diseases and IHD with increasing nitrogen oxides were not shown in this figure since there were no significant relationships found. In general, with different combinations of nitrogen oxides indicators, varied reactions on the associations between nitrogen oxides and cardiovascular mortalities were observed. Rather than NO_2, the positive relationships with NO turned out to be more stable. Moreover, they showed the potential to be strengthened with the existence of NO_2 and NO_X.

The joint effects of nitrogen oxides on cardiovascular mortality were presented in Fig. 1(a). The existence of the other two pollutants did not affect the associations between total cardiovascular deaths, NO, and NO_X. The effects of NO_2 varied when other two kinds of nitrogen oxides were involved. The positive association between NO_2 and total cardiovascular mortality disappeared when NO was considered, but it showed up again when NO_X joined as well. The effect of NO on the cardiovascular deaths among females became significant when considering it together with NO_2 and NO_X, whereas the influence of NO_2 and NO_X was not affected by the others. No joint effects of nitrogen oxides on the male deaths due to CVDs were observed. The positive relationships between NO and cardiovascular deaths in the senior group were noticed in the three-pollutant model. In the meanwhile, in the three-pollutant model, the risk of cardiovascular deaths among the senior was positively associated with NO_2 concentration, while negatively with NO_X. The effects of NO_2 on cardiovascular deaths under the age of 65 were consistently

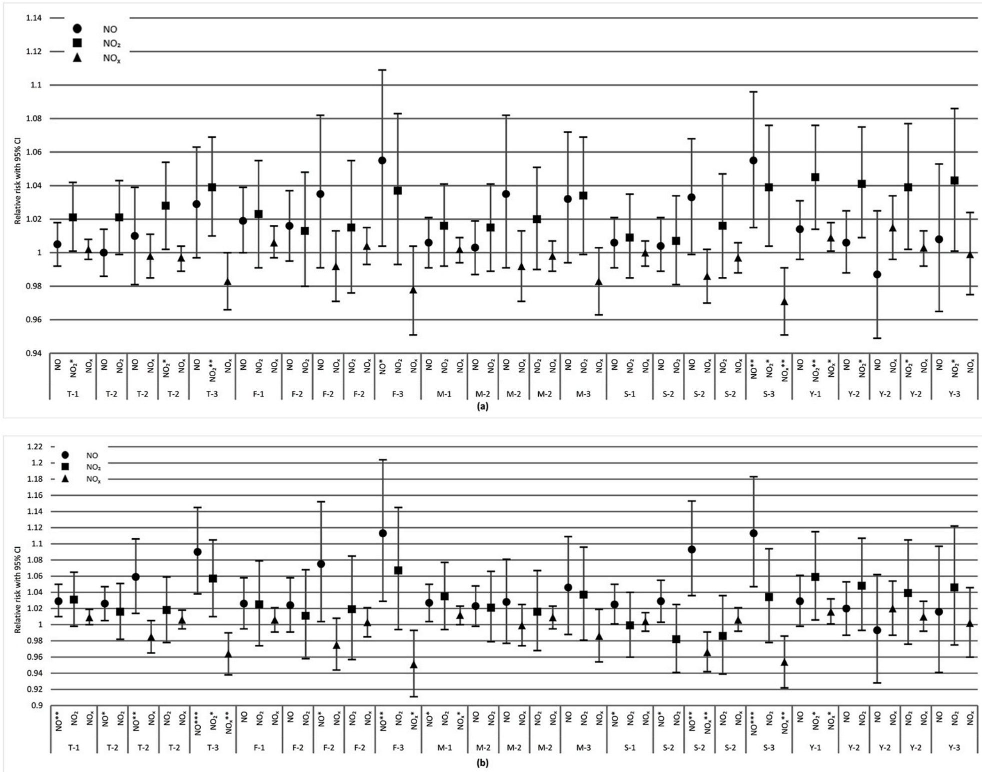

Fig. 1. Joint effects of nitrogen oxides on cardiovascular mortality (a) and stroke mortality (b) (multi-pollutant models). Note: T-1, single-pollutant model in the total population; T-2, 2-pollutant models in the total population; T-3, 3-pollutant model in the total population; Likewise, F represents the models in the female group; M, the male group; S, the senior group; Y, the young group; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

positive in different models, whereas the effects of NO_X disappeared when combing the other types of nitrogen oxides.

The results obtained from different types of models on deaths caused by stroke were shown in Fig. 1(b). The effects of NO on total stroke mortality were stable with the existence of NO_2 and NO_X. The total deaths caused by stroke turned to be positively associated with NO_2, and negatively associated with NO_X in the three-pollutant model. NO_2 consistently have no effects on stroke-caused deaths in females, while the effects of NO became significant when combining NO_X. Further, a negative association was found between NO_X and stroke mortality in the female in the three-pollutant model. The impacts of NO and NO_X on deaths caused by stroke in males disappeared in multi-pollutant model. Increasing NO was statistically related to stroke mortality in the senior group despite different models, while increasing NO_2 consistently had no impacts. The influence of NO_X on stroke deaths above the age of 65 became significantly negative when NO was involved in the same model. The effects of NO_2 and NO_X on the stroke deaths under 65 years old turned to be insignificant in the multi-pollutant models.

4. Discussion

This study demonstrated the acute impacts of three indicators of ambient nitrogen oxides on the overall and cause-specific cardiovascular mortality. Possible confounders including various meteorological factors and other air pollutants were taken into consideration to evaluate the independent effects of nitrogen oxides. The temperature was stratified to discuss the interactions with exposure to air nitrogen oxides. The studied population was separated by sex and age to identify the susceptible groups.

The daily average of NO_2 from 2013 to 2019 was 30.7 $\mu g/m^3$, which generally met the national standard of 80 $\mu g/m^3$ for daily NO_2 concentration (GB3095-2012). Though there are no specific standards for NO and NO_X, it is possible to conclude that the air pollution of nitrogen oxides in Shenzhen from 2013 to 2019 was light. Shenzhen has been taking great efforts to protect the environment. Various local laws and regulations covering different fields on environmental protection were promoted and implemented. Shenzhen has the most comprehensive local standards for atmospheric environmental protection in China. It is the first city in which all the buses are new energy automobile in the world. Further, by industrial reform and technological research and development, the installed power capacity using clean energy in Shenzhen is the largest in China. The actions of environmental protection in Shenzhen could be a reference for other regions where share the similar weather condition. As one of the most developed cities in China, Shenzhen could also be a valuable example of balancing between economic growth and environmental protection for regions experiencing rapid development.

Impacts of ambient nitrogen oxides on the deaths caused by CVDs were revealed in our study. Stroke was the most sensitive death cause to the exposure of nitrogen oxides. For sex stratification, males were more vulnerable than females. This finding was supported by other research (Duan et al., 2019), whereas studies reported higher risks in females (Chen et al., 2018b; Hong et al., 2002) and no modifying effects of sex (Chen et al., 2012). People under 65 years old were suggested to be a more susceptible population, which was similar to what was found by a study in Iran (Khajavi et al., 2019). However, other investigations suggested the elderly above 65 years old to be more sensitive to NO_2 exposure (Chen et al., 2010, 2012; Kan et al., 2008).

NO_2 was the main risk factor, while NO and NO_X had relatively fewer effects on cardiovascular mortality in this research. The vast majority of found associations were positive. However, nitrogen oxides, mainly NO_2, have been widely studied and the findings were inconsistent. A systematic review including time-series studies of NO_2 on mortality before May 2011 found positive relationships between NO_2 and daily death counts of CVDs, IHD, and stroke (Mills et al., 2015), whereas another meta-analysis involving NO_2 of research before November 2017 summarized no significant associations between NO_2 and cardiovascular deaths (Orellano et al., 2020).

Moreover, results obtained from individual investigations varied. Some of the previous studies suggested nitrogen oxides to be associated with increased risks of mortalities due to total (Jerrett et al., 2013; Kan et al., 2008; Tao et al., 2012) and specific CVDs such as IHD and stroke (Jerrett et al., 2013) in previous studies, which was in accordance with our results. On the contrary, there were other groups of researcher noticing different results. Some reported no associations between NO_2 (Anderson, 2001; Perez et al., 2015; Yap et al., 2019), NO_X (Atkinson et al., 2016) and cardiovascular deaths. Negative associations were identified between NO_X and CVD-caused mortality, NO_2 and stroke mortality, NO_X and stroke mortality in our research, while such effects were reported only between NO_2 and total mortality in a Swedish study (Olstrup et al., 2019).

For NO and NO_X, the concentrations with one day lag had the most significant effects on stroke mortality in our studied population. No more evidence on the lag effects of NO or NO_X was found in other research. One-day lag level of NO_2 affected deaths caused by total CVDs the most. NO_2 with two-day lag and three-day lag affected IHD mortality and stroke mortality the most, respectively. There were significant associations between NO_2 at one-day lag and CVD-caused deaths reported in other research (Chen et al., 2010; Tsai et al., 2010). However, varying from what we found, no distributed lag effects of NO_2 on stroke mortality were reported in a study conducted in Taiwan (Tsai et al., 2010).

The cumulative effects of nitrogen oxides were the most obvious in this research. Higher risks of cardiovascular mortality were noticed when L01, L02, and L03 of NO_2 increased in our study. Similar results were obtained from an investigation in Beijing, China (Li et al., 2019). There was another investigation with a larger study scale in China reporting that one to three-day moving averages of NO_2 were associated with IHD mortality (Li et al., 2015). Nevertheless, the lag windows for NO_2 affecting CVD-caused death varied from study to study. Research in Shenzhen from 2013 to 2017 identified stable and significant associations with the increment of NO_2 at L02 and L04 in all sex and age group (Duan et al., 2019). In Anshan, China, only was NO_2 with 2-day moving average (L01) showed to be positively associated with daily deaths caused by CVDs (Chen et al., 2010). 10-day moving average of NO_2 was found to be associated with circulatory deaths in Sao Paulo, Brazil (Costa et al., 2017).

Our findings indicated that temperature modified the effects of nitrogen oxides on cardiovascular mortality. The low temperature was shown to generally strengthen the adverse effects. This conclusion is in agreement with studies in Shenzhen from 2013 to 2017 (Duan et al., 2019) and Iran (Khajavi et al., 2019). The high temperature was observed to lower the risk of cardiovascular mortality associated with ambient nitrogen oxides. The most stable associations were identified between NO_X and CVD-caused deaths in total, the male and the senior. However, a multi-centre investigation in China (Luo et al., 2017) and a meta-analysis (Song et al., 2017) did not detect the modification of temperature on the effects related to NO_2. Furthermore, there were few studies involving NO or NO_X when considering temperature modification, which made it difficult to compare with other studies.

The inconsistent conclusions on individual indicators of nitrogen oxides may result from several reasons. The first would be that the situations varied from region to region including the concentrations of air pollutants, the socio-demographics, climate condition, and other environmental factors. Then the research settings may affect the results. Different from our research without any particular selection of population group, there were investigations focusing on deaths of specific age groups (Khajavi et al., 2019; Chiusolo et al., 2011; Fischer et al., 2003). The socioeconomic status was involved as well in some studies (Bravo et al., 2016; Luo et al., 2016).

Another possible reason is that the confounders, including meteorological factors and other air pollutants, varied in different research. The most considered meteorological factors were temperature, relative humidity, and precipitation. In this study, barometric pressure, wind speed and sunshine duration were counted in, which are associated with the level of air pollution (Chen et al., 2008; Zhang, 2019).

Regarding confounders of other air pollutants, many previous studies took several of PM, ozone, SO_2, and CO into consideration. However, the changes of effects also occurred when combining three indicators of nitrogen oxides with each other in our investigation. To our best knowledge, similar research is so sparse that it is difficult to compare our findings with others'. Thus, the joint effects of nitrogen oxides themselves need further discussion. What we found indicated that the monitoring of NO and NO_X is necessary, and NO_2 could not completely represent the other two, even though they are highly correlated.

Generally, the positive associations of ambient nitrogen oxides on cardiovascular mortality could probably be explained by several biological pathways. Though unstable, the exposure to air NO was positively related with exhaled NO (Van Amsterdam et al., 1999; Adamkiewicz, 2004), which is a biomarker for pulmonary inflammation partly resulting in cardiovascular effects. Animal experiments indicated that NO_2 inhalation could affect cardiac health through oxidative stress, endothelial dysfunction as well as inflammation (Li et al., 2011). It was reported in an investigation of the human population that NO_2 was robustly associated with thrombin generation, which contributed to IHD development (Strak et al., 2013). The modification of lower temperature may take into effects through elevated blood pressure (Aksari et al., 2014), and higher levels of cholesterol (Hadaegh, 2006). Moreover, the concentrations of inflammatory biomarkers were found to be negatively associated with temperature (Schneider et al., 2008), which may further strengthen the adverse effects of nitrogen oxides through heavier inflammation. Regarding the negative effects of NO_X, the low exposure at high temperature may activate the self-regulation of cardiovascular system.

Overall, the ambient nitrogen oxides with relatively low concentrations could affect cardiovascular mortality, and low temperature may worsen the adverse effects. Further measures are still in need even for cities that share the similar situation of Shenzhen. Due to the inconsistency of relative research, comparable research concerning the independent roles of nitrogen oxides on cardiovascular deaths is urged to better support the local policies regarding health and the environment.

There were limitations worth noting in this study. First, the demographic and socioeconomic characteristics, the baseline of cardiovascular condition of the studied population was not considered due to the nature of the research design. Second, seasonal variations of the effects of nitrogen oxides have been demonstrated by other studies (Luo et al., 2020; Amini et al., 2019; Sunyer et al., 1996), yet the seasonal changes in this study needed to be further analysed.

5. Conclusions

This study underlined the adverse and cumulative effects of ambient nitrogen oxides with relatively low concentrations and the interactive roles of temperature on cardiovascular mortality. Although Shenzhen has great achievements in reducing air pollution, further efforts are still in need to lower the concentrations of air nitrogen oxides. Joint effects among NO, NO_2, and NO_X reminded the necessities to monitor and study all three indicators of ambient nitrogen oxides. Population under the age of 65 and those with health condition related to stroke required more attention in days with higher nitrogen oxides, especially days at lower temperature. Our findings provided insights for the regions with similar levels of nitrogen oxides and climate conditions. From the perspective of public health, more efforts are demanding to reduce the levels of ambient nitrogen oxides, especially in the background of climate change.

Credit author statement

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Declaration of competing interest

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

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Appendix A. Supplementary data

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