Is the short-term lethal effect of NO₂ ignored? Focus on the relationship between short-term exposure to NO₂ and tumor death in Shenyang, China

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Abstract

Although related studies have shown that the short-term exposure of NO₂ is associated with all-cause and respiratory mortality, there is still no clear evidence for the effect of NO₂ on tumor death. This study aimed to understand whether the lethal effect of NO₂ air pollution was underestimated in China. We comprehensively estimated the association between mortality and NO₂ concentration and also the population susceptibility differences for whole tumors(C00-D48), lung cancer(C34), gastric cancer(C16), liver cancer(C22), colorectal cancer(C18-C20), breast cancer(C50), thyroid cancer(C73), prostate cancer(C61), bladder cancer(C67) and leukemia (C90.1, C91-C95) in a typical old industrial city in the northeast of China. The generalized linear model showed that the increase of NO₂ concentration was positively correlated with an increase of 0.95% (95% confidence interval, 0.33-1.57%), 1.86% (0.79-2.95%), 2.33% (0.38-4.32%), 2.55% (0.68-4.45%), 16.3% (4.01-30.04%), 11.29% (5.9-16.94%), respectively, in the mortality of whole tumors, lung cancer, liver cancer, colorectal cancer, thyroid cancer, and leukemia in the city of Shenyang. Population susceptibility differences were also significant for the short-term effects of NO₂ on tumor mortality. Young and old persons suffering from leukemia were at more death risk from increased concentration of NO₂ and most of this risk of death can be observed on lag0. However, young adults aged 15 to 65 with all tumors and thyroid cancer, were more susceptible to their effects. Women with total tumors, colorectal cancer, were more vulnerable to die from NO₂ air pollution, and significant risk effects can be observed in lag0-lag6 and lag0/lag4/lag5, respectively. Since WHO has recommended a short-term (24-hour) nitrogen dioxide AQGs level of 25 µg/m³, which is more stringent than that of 80 µg/m³ in the Ambient Air Quality Standard of China. We suggest that the local government should seriously consider guiding legislation and policies of air pollution based on the new WHO Global Air Quality Guidelines, to protect public health with an adequate margin of safety.

Introduction

A report by World Health Organization (WHO) showed that, in 2012, poor air quality was responsible for the loss of seven million lives around the world, with more than one-third of those deaths occurring in the fast-developing nations of Asia. Being the largest developing country, China has been facing some of the worst air quality in recent decades mainly due to its rapid economic development (Li et al. 2015). In 2015, outdoor air pollution was estimated to contribute annually to 4.2 million premature deaths, with 1.1 million premature deaths in China alone (Cohen et al. 2017). Nitrogen dioxide mainly comes from the release of high-temperature combustion processes, such as motor vehicle exhaust and imperfect combustion of coal caused by the boiler. Shenyang is a representative industrial city in northern China. Its winter lasts from November to March every year, accompanied by heating. Our previous studies have also shown that air pollution in northern China, Shenyang, was associated with increased mortality, mainly due to the equipment of heating system (Liu et al. 2019; Xue et al. 2018).

Many epidemiological studies have found that exposure to air pollutants not only has a risk effect on lung cancer but also many other systemic tumors of the human, such as urinary system tumors, colorectal cancer, and childhood leukemia (Filippini et al. 2019; Turner et al. 2017; Zare Sakhvidi et al. 2020). Also, some studies indicated that there were some significant correlations between long-term exposure of NO₂ and lung cancer, nasopharyngeal carcinoma and other respiratory tumors, as well as breast cancer, and cystadenocarcinoma (Bai et al. 2020, Ribeiro et al. 2019, Turner et al. 2019a, Yorifuji and Kashima. 2020). And it can also be found that the correlation between NO₂ exposure and incidence/mortality of tumor was more significant, and the effect seemed to be more stable and long-lasting than that of other pollutants, compared with other particulates and gaseous pollutants. However, the evidence that short-term exposure to ambient NO₂ could lead to tumor death is still inconclusive. Since burning coal for heating in winter will lead to the increased concentration of ambient NO₂. We suspected that the short-term exposure effect of nitrogen dioxide may be more serious in Shenyang based on the previous studies. Although some studies focused on the short-term effects of air pollutants in China (Chen et al. 2012a, Chen et al. 2012b), due to the geographical and demographic differences (Lin et al. 2017), the evidence from other cities in China may not be suitable enough to apply to Shenyang city. Here, we provided a critical appraisal of the effect of exposure to NO₂ on tumor death.

Materials And Methods

Data Collection

The mortalities of tumors in Shenyang urban area from 2013 to 2018 were obtained from the death registration system of Shenyang Center for Disease Control and Prevention (the causes of death were registered in the system according to the Tenth edition of the international classification of diseases, ICD-10). The daily death data of all tumors (C00-D48), lung cancer (C34), gastric cancer (C16), liver cancer (C22), colorectal cancer (C18-C20), breast cancer (C50), thyroid cancer (C73), prostate cancer (C61), bladder cancer (C67) and leukemia (C90.1, C91-C95) were screened out from death registration system. Data was stratified according to age and gender.

The daily average concentration of six pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂, CO, and O₃) in Shenyang were obtained from 13 air quality monitoring stations of the national environmental monitoring center in Shenyang. Meteorological data (including daily average temperature, wind speed, humidity, and air pressure) was downloaded from the website of the Chinese National Meteorological Administration.

Data Analysis

The number of tumor deaths, pollutant concentration, and meteorological data were statistically described to understand the changing trend of tumor mortality and pollutant distribution characteristics, separately. The Spearman correlation coefficients of air pollutants were calculated to detect the relationship among air pollutants, and the deviance of daily death toll was measured to verify the distribution characteristics.

The generalized linear model was established by using well-sorted data. In the model, the degree of freedom of spline function controlling covariates in the model referred to previous literature and uses the Akaike information criterion (AIC criterion), to obtain the best-fit model. According to other similar articles, took 7 days as a period to observe the lag effect of NO₂ short-term exposure. Firstly, a single pollutant model was established to observe the effects of single-day Lag (denoted by Lag1, Lag2.....Lagk) both and cumulative Lag (denoted by Lag01, Lag02.....Lag0k), and then the stability of NO₂-induced impact on tumor disease risk effect was compared according to the results of two-pollutant models and three-pollutant models. Finally, the above methods were also used to analyze the threshold and lag effect of NO₂ in the analysis of stratified populations, based on gender and age. There were three age groups: < 15 years old: children; 15-65 years old: middle-aged and young/adults; > 65 years old: old population. The different cancer types, including lung cancer, gastric cancer, liver cancer, colorectal cancer, breast cancer, thyroid cancer, prostate cancer, bladder cancer, and leukemia, were also analyzed separately.

All statistical analyses were implemented by R(4.0.2) software. A p-value less than 0.05 is considered statistically significant.

Results

Data Description

Table 1 shows the distribution of air pollutants, meteorological data, and the number of cancer deaths during 2013-2018. In the study period, the daily average concentrations of PM_{2.5}, PM₁₀, SO₂, NO₂, O₃ and CO were 59.07μg/m³, 99.66μg/m³, 51.28μg/m³, 41.38μg/m³, 68.65μg/m³ and 1.03mg/m³ respectively, and the maximum concentrations were 848μg/m³, 912μg/m³, 379μg/m³, 125μg/m³, 286μg/m³ and 4.93 mg/m³ respectively. According to the National Ambient Air Quality Standard (GB3095-2012), the 24h average secondary concentration limit of NO₂ is 80 μg/m³. During the study period, only in a few days, the NO₂ concentration exceeded the standard (total of 55 days, including 8 days in 2013, 23 days in 2014, 16 days in 2015, 2 days in 2016, 6 days in 2017, and no day in 2018), and mainly occurred in January, February, November, and December, that is, the winter in the north.

However, the new WHO Global Air Quality Guidelines (AQGs) from 2021, identify the levels of a 24-hour average concentration of NO₂ as 25μg/m³. It could be observed that there was a wide gap in the qualified rate between China and WHO standards. Importantly, in more than 84% of the days during the study period, people in Shenyang lived in areas where concentrations exceed 2021 WHO AQG level. Table2 summarized the number of does not exceed the air quality standards from 2013 to 2018 according to the standards of WHO and China.

It can be observed that in Table1 there were significant differences in temperature among all the observed meteorological factors in Shenyang. From 2013 to 2018, the highest temperature in Shenyang urban area was 32.4°C, while the lowest temperature was -22.8°C. This also indicates the differences in climate between the north and south of China. Among all kinds of tumors, the average daily death toll of all tumors, lung cancer, gastric cancer, liver cancer, colorectal cancer, bladder cancer, leukemia, breast cancer, prostate cancer, and thyroid cancer were 23.23, 7.79, 1.76, 2.30, 2.59, 0.11, 0.46, 0.85, 0.29 and 0.06 respectively, and the average daily death of lung cancer was much higher than that of others.

Table3 shows both total and tiered data about the number of deaths caused by tumors and other nine tumors in each year during the five years. During 2013-2018, the number of deaths of tumors was 8229, 8392, 8456, 8661, 8610, and 8545 respectively. In addition, in Table3, a few children died of cancer. The change in the number of tumor deaths is shown in Figure 1. From this picture, it is easy to see that during the study period, the death toll of the whole tumors, lung cancer, liver cancer, colorectal cancer, pancreatic cancer, breast cancer, bladder cancer, and leukemia increased. The death toll of gastric cancer decreased. The number of deaths from thyroid cancer remained basically unchanged after fluctuations. Table4 shows the Spearman correlation coefficients between pollutants and meteorological data. NO₂ was significantly correlated with other air pollutants. It had the strongest correlation with PM_{2.5} (r=0.7), and a significant negative correlation with ozone, with a correlation coefficient of -0.46. The correlations between NO₂ and meteorological factors were also significant. The correlation coefficient between NO₂ and temperature is negative, which means that NO₂ concentration will increase with the decrease of temperature.

Single-pollutant model

According to the established single-pollutant model (Fig. 2), it could be observed that the increase of NO₂ concentration was related to the death toll of the whole tumors, lung cancer, liver cancer, colorectal cancer, leukemia, and thyroid cancer.

The effect of NO₂ on tumor death reached peak values on Lag1. The mortality of all tumors increased by 0.95% (95% CI: 0.33-1.57%) for per 10μg/m³ increment in daily average concentration. The maximum effect on lung cancer death also occurred on Lag1, with a 1.86% (95%CI: 0.79-2.95%) increase per 10μg/m³. The significant effect for liver cancer was observed only on Lag4 with an increment of 2.33% (95% CI: 0.38 - 4.32%). As for colorectal cancer, the maximum effect of 2.55% (95% CI: 0.68-4.45%) appeared on Lag0 for every 10μg/m³ increment of the 24-hour average

concentration of NO₂. The strongest effect on thyroid cancer death occurred on Lag2, with 16.3% (95% CI: 4.01-30.04%) mortality increased. The maximum effect on leukemia death only occurred on Lag0 by 11.29% (95% CI: 5.9-16.94%) mortality increased.

For the cumulative lag effect, in the whole tumors and lung cancer death population, statistically significant effect values could be observed on lag01 to lag07, and reach the maximum in lag03 (RR=1.01; 95% CI: 1.00-1.02) and lag07 (RR=1.03, 95% CI: 1.01-1.05) respectively; On lag05 to lag07, NO₂ had a significant effect on the death of liver cancer. Significant risk effects were observed on Lag01 and Lag04 to Lag07 for colorectal cancer death toll; In the death population of thyroid cancer, significant risk effects could be observed in Lag01 to Lag05, and reach the maximum on Lag03 (RR=1.25; 95% CI: 1.06-1.48). A significant risk effect of NO₂ could be observed on Lag01 to Lag03 in leukemia deaths.

Multi-pollutant model

As shown in Fig. 3, the risk effects of NO₂ on the tumors death were very robust in the multi-pollutant models, except for breast and prostate cancer, although the respective RR values varied slightly.

The risk effect of NO₂ mostly persisted from lag0 to lag5 in all tumor deaths; In lung cancer, the danger effect was concentrated on lag1-lag3; For colorectal cancer, the hazard effect focused on lag5; For leukemia, the danger effect was observed almost exclusively on lag0. While NO₂ showed incoherent harmful effects for liver and thyroid cancer, for liver cancer the harmful effects were mostly observed on lag0, lag2, lag4, and lag6; For thyroid cancer, the hazard effects were more frequently found on lag0, lag2, and Lag3.

Heterogeneity by sex and age group

AGE

<15-year-old

NO₂ contributed to a harmful effect on children who died of all-cause tumors or leukemia. As shown in the Fig. 4, among the children with all tumors, the effect value on Lag1 reached the maximum in the single-pollutant model(the death rate of all tumors increased by 16.37% (95% CI: 1.91-32.88%) in every 10µg/m³ increase in daily NO₂ average concentration); Moreover, in the two-pollutant model composed of SO₂, CO and O₃ and some three-pollutant models (+PM₁₀+CO+SO₂+CO+SO₂+O₃+CO+O₃), significant RR(relative risk) was observed on Lag1. In children with leukemia, NO₂ had significant harmful effects on Lag4 in the single-pollutant model and some multi-pollutant models (+CO+O₃+PM_{2.5}+CO+PM₁₀+CO+CO+O₃).

15-65-year-old

In all tumors, liver cancer, thyroid cancer, and leukemia, NO₂ not only showed independent hazard effects but also remained significant and stable in most multi-pollutant models, as shown in Fig. 5. There were also great differences in the time and persistence of NO₂ harmful effects. For all tumors, lung cancer, and leukemia, the risk effect of NO₂ was mostly observed on lag0 and Lag1, while for other malignant tumors, it was mostly observed after lag2. In addition, for young and middle-aged patients with all tumors, liver cancer, and thyroid cancer, the risk effect of NO₂ lasted for a long time, about 3-4 days.

>65-year-old

It could be observed from the Fig. 6 that the significant and lasting independent harmful effect of NO₂ could be observed only in elderly patients with lung cancer, and this harmful effect could last for three days from lag0. After the adjustment of multi-pollutant models, the significant and stable risk effect of NO₂ could be observed in all cancers, lung cancer, colorectal cancer, thyroid cancer, bladder cancer, and leukemia in the elderly. For all tumors and lung cancer, the harmful effect of NO₂ lasted a long time. For colorectal cancer, thyroid cancer, bladder cancer, and leukemia, the harm of NO₂ could only take 1 day, on lag5, Lag1, and lag0 respectively.

GENDER

MALE

In Fig. 7, it can be seen that the independent harmful effect of NO₂ was very significant in male patients with lung cancer, which lasted for three days from lag0. In the multi-pollutant models, only stable risk effects for male patients with lung cancer and leukemia could be found. Among them, for lung cancer, the duration of risk effect was mostly 2 days, while for leukemia, the harmful effect could be observed only on lag0.

FEMALE

For female cancer patients, the independent risk effect of NO₂ could be observed in the whole tumors, colorectal cancer, thyroid cancer, and leukemia. For all tumors, liver cancer, colorectal cancer, and leukemia, the risk effect of NO₂ could be observed in almost all multi-pollutant models.

As shown in Fig. 9, the duration of NO₂ harmful effect on female tumor patients was very different. For the whole tumors, lasting and significant harmful effects could be observed almost from lag0 to lag6. For liver cancer, significant relative risks almost appeared on lag6. The effect of NO₂ on colorectal cancer was mostly concentrated on lag0, lag4, and lag5. For leukemia, the effect of NO₂ could continue from lag0 to lag2 and mostly focused on lag0 and lag2. Besides, it could be found that the effect of NO₂ concentrated on Lag3 for lung cancer and lag0 for thyroid cancer.

Discussion

In the present study, all people who died from the tumor in the old industrial city of Northeast China were analyzed. We sought to comprehensively estimate the impacts of NO₂ on the mortality of cancers. Ambient NO₂ exposure may increase the risk of tumor death. And the harmful impacts were almost still significant after controlling for the other pollutants in our two-pollutant models or multi-pollutant models. Sex and age are effect modifiers of the association between NO₂ exposure and daily cancer mortality risk.

The results from our study were consistent with several prior studies. A meta-analysis showed that all-cancer mortality significantly correlated with long-term exposure to NO₂ (RR: 1.06, 95% CI: 1.02-1.10) (Kim et al. 2018). Similarly, a study that studied the relationship between childhood cancer risk and acute air pollution in Tehran, Iran, observed a positive association between NO₂ exposure and childhood cancer incidence (Seifi et al. 2019). Another study in Great Britain also confirmed that exposure to NO₂ increased the risk of childhood cancer (Knox. 2005). In our study, NO₂ also showed a strong risk for middle-aged and elderly cancer patients. Besides, the risk effect of NO₂ on male cancer patients was not significant. On the contrary, for female patients, the risk effect of NO₂ on death was significant and lasted for a long time

China is a big country in coal consumption, especially in the north of China with prolonged heating times (Xing et al. 2019). Since the respiratory tract is the first organ that contacts and affected ambient air pollutants. The correlation between NO₂ exposure and mortality from respiratory diseases, especially lung cancer is well-established. A Japanese study showed that there was a statistically significant association between NO₂ and lung cancer death (HR = 1.20, 95% CI: 1.03-1.40) (Yorifuji et al. 2013). In addition, a cohort study of 70000 people in California observed a statistically significant positive correlation between NO₂ and lung cancer death (Jerrett et al. 2013). Besides, a meta-analysis reported that there was a positive correlation between traffic-related NO₂ and lung cancer mortality (Hamra et al. 2015). The results of our study were consistent with those yielded by the above studies. It was found that there was a significant correlation between the death of lung cancer patients and an increased level of NO₂ concentration. We found that males were more vulnerable to the NO₂ exposure than females on lung cancer mortality, and the delayed effects for 3days (lag0-2) were observed for male lung cancer patients. The lag patterns were similar in the elderly, however, for the young and middle-aged adults, only effect estimates for lag2 were significant. In the analysis of different age groups in our study, we observed the significant risk effect of NO₂ on the death of elderly patients with lung cancer; In different genders, NO₂ has a risk effect on both male and female lung cancer patients, but the effect on male patients is mostly on Lag1 and for women is mostly on Lag3

Epidemiologic studies suggest air pollutants as a risk factor in liver cancer. In a study with six European cohorts, it was estimated per a 10µg/m³ increase in NO₂ concentrations was associated with a 17% (95% CI: 2%-35%) increase in liver cancer incidence in the fully adjusted model (So et al. 2021). However, the relationship between NO₂ and liver cancer was still inconclusive. A cohort study conducted in Danish and Austria did not demonstrate a significant association between the increase of NO₂ concentration and the high incidence rate of liver cancer (Pedersen et al. 2017). In our present study, although it could be found that liver cancer death is related to NO₂ concentration, Moreover, the association was varying across age groups. The significant relationship was only observed in the young and middle-aged population and the strongest effect of NO₂ was observed at 4 and 5 lag days. Associations between NO₂ and mortality of liver cancer were intensified, in two-pollutant models, with PM_{2.5} or other gaseous pollutants such as CO or O₃. The effect of NO₂ pollution on liver cancer death requires further investigation and confirmation. In our study, we found that NO₂ had a significant risk effect on the death of young and middle-aged patients with liver cancer; It also had a significant risk of liver cancer in men and women, which occurred on lag4 and lag6 respectively.

In a cancer prevention study - CPS - II in the United States, it was found that there was a significant positive correlation between NO₂ exposure and the mortality of stomach cancer, colorectal cancer, breast cancer, and bladder cancer. However, no association between NO₂ and gastric cancer death had been found in our study. There was a positive but weak association between NO₂ exposure and colorectal cancer mortality, and the HR was 1.06 (95% CI: 1.02-1.10, per 6.5 ppb) (Turner et al. 2017). In our study, we also found a significant association between colorectal cancer death and NO₂ exposure. In the analysis of different age groups, we found that NO₂ had a significant harmful effect on elderly patients with colon cancer, and it concentrated on lag5; For people of different genders, NO₂ was only harmful to female patients with colorectal cancer, and mostly appears on lag0, lag4, and lag5.

A study in South Korea found that NO₂ was significantly associated with breast cancer incidence, a district with 10 ppb higher NO₂ concentration suffered from higher OR of breast cancer incidence by 1.14 (95% CI: 1.12-1.16) in the single-pollutant model, and NO₂ remained associated with the breast cancer incidence rate when additionally adjusted with the other three pollutants in multi-pollutant models (Hwang et al. 2020). A Canadian

study also found that the incidence of breast cancer is associated with long-term exposure to NO₂ (Hystad et al. 2015). However, we did not observe any significant association between NO₂ exposure and the mortality of breast cancer.

The association between NO₂ exposure and bladder cancer was observed in 15 European cohort studies and a study of bladder cancer in Spain, but with no statistical significance (Pedersen et al. 2018; Turner et al. 2019a). Another research in Canadian found that, for each increase of 5 parts per billion of NO₂, the adjusted OR was 1.44 (95% CI: 1.21-1.73) (Parent et al. 2013). In our study, we found an increase of 10µg/m³ in NO₂ average concentration corresponded to an increase of 5.4% in bladder cancer mortality in the elderly. In our analysis of bladder cancer, NO₂ only had a significant risk effect on elderly patients with bladder cancer in different age groups.

In addition, in our study, we also found a significant association between NO₂ and leukemia death. The association between NO₂ and leukemia mortality was evident on the day of the event (lag0) for children but for adults, it was present for up to two days (lag2) before the event. Also, the effects of NO₂ on leukemia mortality appeared immediately for males and lasted for 2 days for females. Prior epidemiological studies on the relationship between air pollutants and leukemia mostly focused on children, and relatively few focused on adults. A meta-analysis found that, for all children with leukemia, NO₂ exposure caused an OR of 1.21 (95% CI: 0.97-1.52), and for acute lymphoblastic leukemia was 1.21 (95% CI: 1.04-1.41) (Filippini et al. 2015). But the association between NO₂ and childhood leukemia was found to be not significant in another meta-analysis of the relationship between traffic pollutants and childhood leukemia (Gong et al. 2019). In an epidemiological study of adult leukemia, it was found that the odds ratio for acute myeloid leukemia was 1.31(95% CI:1.02-1.68) per 10mg/m³ increase in NO₂ (Raaschou-Nielsen et al. 2016). Our study also found a significant risk effect of NO₂ on death in leukemia patients. The risk effect of NO₂ on the death of leukemia children concentrated on lag4, while for young adults and elderly, the risk effect of NO₂ concentrated on the day of pollution; In male and female leukemia patients, NO₂ showed a significant risk effect. For men, the risk effect concentrated on lag0, but for women, this significant risk effect could still be observed not only on lag0, Lag1, lag2, and lag5.

No association between NO₂ and gastric cancer death has been found in our study, and no difference has been observed among patients in different age or gender groups. Few relevant studies found a significant association between them. The research on this aspect needs further in-depth discussion. Indeed, a total of 2163 days of NO₂ concentration data were obtained during our study period. Only on 55 days, the 24-hour average NO₂ concentration exceeded the level of 80µg/m³ according to the Chinese air quality standard. However, following WHO AQG2021, the number of days that exceeded the standard was 1832. The gap between these two numbers is surprising. And from the results, we could find a significant association between NO₂ and cancer patient death. This led us to suggest that, under the current policy, the survival of cancer patients would be affected even if the concentration of NO₂ drop to the so-called healthy levels. So, this study not only reminded us of the existence of the short-term lethal effect of NO₂ but also might have implications for local governments to make policies for NO₂ pollutant controls.

Limitations

Due to the accumulation of air pollutants, it was difficult to avoid that the short-term exposure effect we studied was not affected by the long-term cumulative effect. In addition, due to the strong linear relationship among air pollutants, although multi-pollutant models with strong collinearity have been removed, it was still difficult to completely remove the influence of collinearity in the results.

Conclusions

In this study, we found the significant associations of ambient NO₂ concentration with the increase of mortality in patients with all tumors, lung cancer, liver cancer, colorectal cancer, thyroid cancer, and leukemia in Shenyang. Short-term exposure to NO₂ may induce a significantly increased risk of death in children with all tumors and leukemia. The higher risk of death in the patients with tumors and thyroid cancer in the young and middle-aged population should also be especially concerned due to the significant and stable correlation with the concentration of NO₂; In the elderly, NO₂ showed the significant risk for all tumors, lung cancer, colorectal cancer, bladder cancer, and leukemia. The mortality of male patients with lung cancer and leukemia was significantly correlated with the concentration of NO₂, while for females, the death of all patients with tumor, liver cancer, colorectal cancer, and leukemia were significantly positively correlated with the increased short-term exposure of NO₂. However, more researches are needed to better understand potential age and gender differences.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Please contact the author for data requests.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Authors` contributions

Cheng Yang: Investigation, Visualization, Writing –Original draft, Writing – Reviewing and Editing. Xiaoxia Xue: Investigation, Visualization. Shuai Liu: Investigation, Writing – Reviewing and Editing. Xinyue Ma: Investigation, Writing – Reviewing and Editing. Lin Xiong: Investigation, Writing – Reviewing and Editing. Baosen Zhou: Investigation, Visualization. Xuelian Li: Investigation, Visualization, Supervision, Project administration.

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Tables

Table1 Air pollution, meteorological measurements mortality in Shenyang, 2013–2018

	Mean±SD	IQR	MIN	quartile			MAX
				Q1	Q2	Q3	
PM _{2.5} (μg/Ⓜ)	59.07±49.87	46	4	29	44	75	848
PM ₁₀ (μg/Ⓜ)	99.66±65.51	65	8	58	84	123	912
SO ₂ (μg/Ⓜ)	51.28±56.19	48	3	16	29	64	379
NO ₂ (μg/Ⓜ)	41.38±16.65	22	10	29	38	51	125
O ₃ (μg/Ⓜ)	68.65±41.51	52	0	38	62	90	286
CO(μg/Ⓜ)	1.03±0.51	0.53	0.3	0.7	0.9	1.23	4.93
temperature(°C)	8.93±13.30	24	-22.8	-2.8	10.9	21.2	32.4
humidity(%)	61.49±16.34	24	13	50	63	74	100
wind speed(0.1m/s)	21.71±9.59	13	2	14	20	27	64
atmospheric pressure(hPa)	1010.34±9.63	15.975	980.8	1002.13	1010.3	1018.1	1037.4
all tumors	23.23±4.91	6.5	6	20	23	26.5	43
lung cancer	7.79±2.81	4	0	6	8	10	20
gastric cancer	1.76±1.35	2	0	1	2	3	7
liver cancer	2.30±1.53	2	0	1	2	3	9
colorectal cancer	2.59±1.61	3	0	1	2	4	10
bladder cancer	0.44±0.67	1	0	0	0	1	5
breast cancer	0.85±0.94	1	0	0	1	1	5
prostate cancer	0.29±0.53	1	0	0	0	1	3
thyroid cancer	0.06±0.25	0	0	0	0	0	2
leukemia	0.46±0.70	1	0	0	0	1	4

SD standard deviation, IQR interquartile range, MIN minimum, Q quartile, MAX maximum, PM_{2.5} particulate matter<2.5μm in diameter, PM₁₀ particulate matter<10μm in diameter

Table2 Summary of the number of days does not exceed the NO₂ concentration air quality standards of WHO and China in Shenyang from 2013 to 2018

	2013	2014	2015	2016	2017	2018
WHO	69(20.41%)*	21(5.77%)	29(7.95%)	73(19.95%)	51(13.97%)	88(24.11%)
China	330(97.63%)	341(93.68%)	349(95.62%)	364(99.45%)	359(98.36%)	365(100%)

* % as a percentage of annual days

Table3 Annual deaths caused by all tumors and other nine specific tumors in Shenyang,2013-2018

		all tumors	lung cancer	gastric cancer	liver cancer	colorectal cancer	breast cancer	thyroid cancer	prostate cancer	bladder cancer	leukemia
2013	total	8229	2627	646	735	871	270	19	94	172	159
	male	4854	1641	420	533	481	6	6	94	134	78
	female	3375	986	226	202	390	264	13	—	38	81
	<15	13	0	0	0	0	0	0	0	0	6
	15-65	3019	801	193	376	265	148	7	7	23	74
	>65	5197	1826	453	359	606	122	12	87	149	79
2014	total	8392	2965	634	896	890	275	19	114	161	193
	male	4898	1794	449	642	490	4	8	114	117	102
	female	3494	1171	185	254	400	271	11	—	44	91
	<15	17	1	0	1	0	0	0	0	0	9
	15-65	3160	925	242	431	262	161	6	10	23	92
	>65	5215	2039	392	464	628	114	13	104	138	92
2015	total	8456	2923	698	821	970	324	18	102	144	157
	male	4871	1831	466	555	518	1	7	102	105	86
	female	3585	1092	232	266	452	323	11	—	39	71
	<15	17	0	0	0	0	0	0	0	0	3
	15-65	3108	897	238	406	273	192	6	12	26	69
	>65	5331	2026	460	415	697	132	12	90	118	85
2016	total	8661	2929	643	833	1040	320	24	107	153	170
	male	5108	1861	439	576	581	4	11	107	113	104
	female	3553	1068	204	257	459	316	13	—	40	66
	<15	18	0	0	0	0	0	0	0	0	6
	15-65	3176	891	227	437	290	187	10	13	22	81
	>65	5467	2038	416	396	750	133	14	94	131	83
2017	total	8610	2833	639	913	947	344	33	100	165	163
	male	5020	1794	439	612	522	2	16	100	119	99
	female	3590	1039	200	301	425	342	17	—	46	64
	<15	15	0	0	1	0	0	0	0	0	3
	15-65	3158	865	220	451	280	193	8	10	20	76
	>65	5437	1968	419	461	667	151	25	90	145	84
2018	total	8545	2797	594	849	958	319	19	109	178	163
	male	4990	1766	398	579	561	3	10	109	120	91
	female	3555	1031	196	270	397	316	9	—	58	72
	<15	20	0	0	1	1	0	0	0	0	9
	15-65	2992	818	187	380	277	191	7	10	16	72
	>65	5533	1979	407	468	680	128	12	99	162	82

Table4 Spearman's rank correlation coefficients between pollutants and weather variables

	PM _{2.5}	PM ₁₀	SO ₂	NO ₂	CO	O ₃	Temperature	Wind speed	Humidity	Barometric pressure
PM _{2.5}	1.000									
PM ₁₀	0.920***	1.000								
SO ₂	0.696***	0.677***	1.000							
NO ₂	0.701***	0.647***	0.644***	1.000						
CO	0.808***	0.733***	0.661***	0.659***	1.000					
O ₃	-0.285***	-0.247***	-0.508***	-0.459***	-0.248***	1.000				
Temperature	-0.378***	-0.353***	-0.695***	-0.392***	-0.275***	0.652***	1.000			
Wind speed	-0.164***	-0.041	-0.104***	-0.465***	-0.269***	0.245***	0.049*	1.000		
Humidity	0.075**	-0.092***	-0.143***	0.047*	0.240***	-0.107***	0.279***	-0.386***	1.000	
Barometric pressure	0.379***	0.331***	0.647***	0.423***	0.272***	-0.588***	-0.853***	-0.139***	-0.272***	1.000

(*p<0.05,**p<0.01,***p<0.001)

Figures

Figure 1

Long term trend of cancer deaths in Shenyang from 2013 to 2018

Figure 2

Estimation of the effect of NO₂ on tumor mortality by single-pollutant model

(Measurement for every 10µg/m³ increment of NO₂, * the results were statistically significant, RR relative risk, CI confidence interval)

Figure 3

Multi-pollutant models for the relationship between cancer deaths and air pollutants

(+ components of multi-pollutant models, Two kinds of particles were not included in the three-pollutant model at the same time to avoid collinearity interference considering that the strong correlation between $PM_{2.5}$ and PM_{10} ($r=0.918$).)

Figure 4

Relative risks of NO₂ on whole tumor deaths and leukemia on Lag1 and Lag4, respectively

(Measurement for every 10µg/m³ increment of NO₂, * the results were statistically significant)

Figure 5

Lag days in which NO₂ has a significant effect on the death of tumor patients aged 15-65 years were observed in the pollutant models

(+ components of multi-pollutant models)

Figure 6

Lag days observed in the pollutant models that NO_2 has a significant effect on the death of tumor patients older than 65 years old (+ components of multi-pollutant models)

Figure 7

Lag days observed in the pollutant models that NO_2 has a significant effect on the death of male tumor patients

(+ components of multi-pollutant models)

Figure 8

Lag days observed in the pollutant models that NO₂ has a significant effect on the death of female tumor patients

(+ components of multi-pollutant models)