

Preplanned Studies

Associations of Ambient NO₂ with Daily Hospitalization, Hospitalization Expenditure and Length of Hospital Stay of Cause-Specific Respiratory Diseases — Shanxi, China, 2017–2019

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Summary

What is already known about this topic?

Numerous epidemiological studies have documented the association between ambient nitrogen dioxide (NO₂) and mortality and morbidity of respiratory diseases, however, research on the effect of NO₂ on the length of hospital stay (LOS) and hospitalization expenditure is limited.

What is added by this report?

This study collected the respiratory hospitalization, hospital expenditure, and LOS for respiratory diseases from 2017–2019 in Shanxi, China, and comprehensively evaluated the association between ambient NO₂ exposure and respiratory hospitalization, expenditure, and LOS.

What are the implications for public health practice?

This study provides evidence on the association between ambient NO₂ and respiratory burden, suggesting that continuously reducing the NO₂ concentrations could prevent respiratory disease-associated hospital admissions and decrease the relative burden in Shanxi Province and other similar regions.

Nitrogen dioxide (NO₂) has been widely associated with respiratory morbidity and mortality. However, its association with hospitalization expenditure and length of hospital stay (LOS) is scarcely analyzed. Thus, we analyzed this association in Shanxi Province, which has famously high fuel combustion with residential and industrial regions centralized in basins and valleys, making it difficult for air pollutants to disperse (1). Daily air pollution exposures were estimated for each case using an inverse distance approach and then averaged for each city. City-specific associations of NO₂ with hospital admission, hospitalization expenditure, and LOS were assessed by general additive models. The overall effects were then pooled through a random-effects meta-analysis. The potentially

avoidable values and population attributable fraction (PAF) for total respiratory disease, asthma and chronic obstructive pulmonary disease (COPD) were assessed by reducing the concentration to the standards of the World Health Organization (WHO) (25 µg/m³) and Chinese government (40 µg/m³). Significant associations between NO₂ and respiratory hospitalization, hospital cost, and LOS were observed. We estimated 198.73 million CNY [95% confidence interval (CI): 119.07–278.40] in hospital costs, and 272.00 thousand days (95% CI: 179.22–364.79) of LOS could be potentially avoided under the WHO's standards for Shanxi during 2017–2019. This study provides evidence for the association between NO₂ exposure and respiratory burden, suggesting that continually diminishing ambient NO₂ could effectively reduce respiratory burden.

This study collected hospital admission data for respiratory diseases from all the secondary and tertiary hospitals in Shanxi Province from February 2017 to November 2019. The information included general characteristics, residential address, date of admission and discharge, the principal diagnosis (based on the International Classification of Diseases, ICD-10), and hospital expenditures. The hospital expenditures included fees for drugs, clinical examinations, nursing care, and clinical operations. The LOS was calculated based on the admission date, and the LOS for each case was summed and regarded as the value for that day. We included the participants who had resided in Shanxi Province and excluded cases with missing information and those who had only received emergency or outpatient treatment and were then discharged.

Daily ambient air pollutant concentrations of NO₂, fine particulate matter, sulfur dioxide, and ozone at all state-controlled air quality monitoring stations in Shanxi from 2017 to 2019 were also obtained. Individual level exposure was assessed using reverse distance weighting (IDW) by geocoding patient

addresses and monitoring station locations and averaging an individual's daily exposure for each city (1–2).

The daily mean temperature and relative humidity were extracted from ERA5-L and reanalysis data (3). A bilinear interpolation approach was used to estimate the daily meteorological exposure for each participant, and then average the exposure for each city.

The city-specific and overall associations between NO₂ and hospitalization, hospital cost, and LOS for respiratory diseases, COPD, and asthma were assessed using a two-stage statistical approach based on the time-series model. At the first stage, a generalized additive model (GAM) with a quasi-Poisson was built to explore the effect of NO₂ on daily hospital admissions for each city. Considering the normal distribution of LOS and cost, the GAM with a Gaussian link was applied to examine the association between NO₂ and those two indicators. Time trend was controlled by a penalty smoothing spline function of 6 degrees of freedom (df) per year. Daily mean temperature and relative humidity were adjusted using the same spline function with 6 df and 3 df. Public holidays and days of the week (DOW) were treated as categorical variables.

Considering the lag effect, the associations on single lag days of 0 to 5 and moving average days of 01 to 03 were also examined. Further, a random-effect meta-analysis based on the associations of all 11 cities was applied to obtain the overall effects of NO₂.

At the second stage, this study estimated the attributable value and PAF of respiratory hospitalization, cost, and LOS for overall respiratory disease, asthma, and COPD to elucidate the potential benefits by controlling NO₂ concentration to a certain level. The recommended concentrations by the WHO (25 µg/m³) and Chinese government (40 µg/m³) were used as reference concentrations. The formula and sensitivity analysis can be found in the Supplementary Materials (available in <http://weekly.chinacdc.cn>).

This analysis included 666,189 hospital admissions due to respiratory diseases, corresponding to a total of 5.54 million days of LOS and 4.58 billion CNY in hospital expenditures.

Figure 1 illustrates the positive effects of NO₂ on daily hospitalizations, hospital expenditures, and LOS across different lag days and moving average days at the provincial level. The effect was highest in lag03, every 10 µg/m³ increment in NO₂ was associated with a 2.14% (95% CI: 1.39–2.89) increase in respiratory

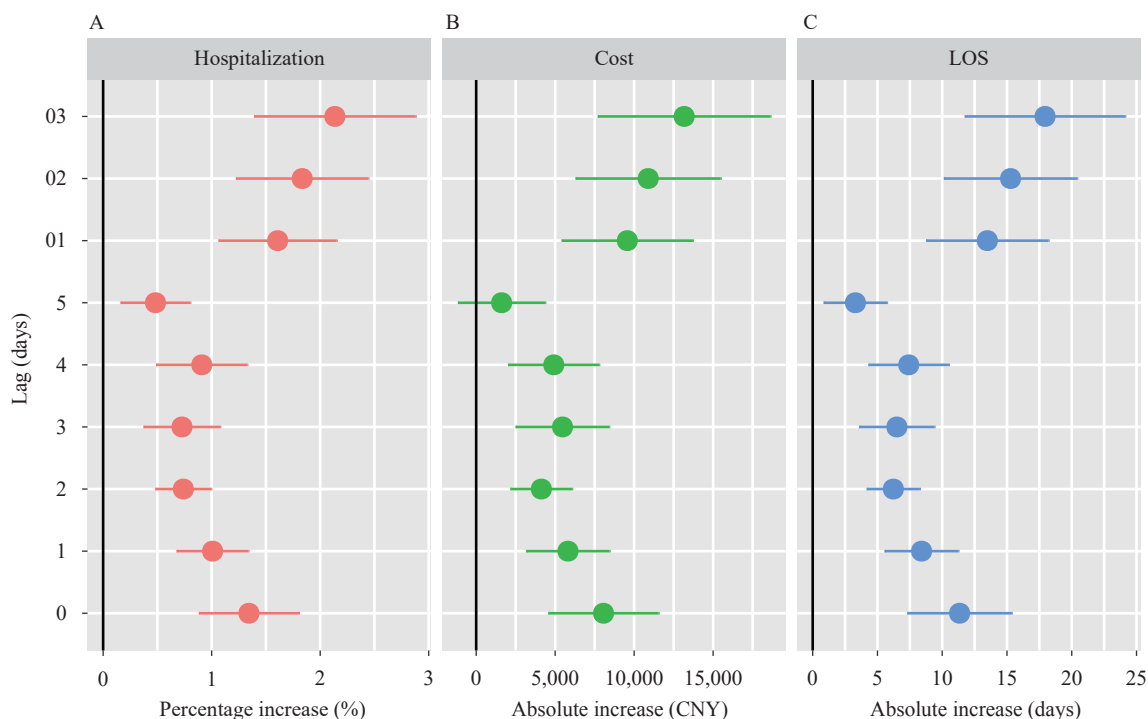


FIGURE 1. The provincial overall association of daily NO₂ (10 µg/m³) with (A) hospital admission, (B) hospitalization expenditure, and (C) length of hospital stay (days) at different lag days including single lag days (lag0–5) and moving average days (lag01–03) from 2017 to 2019.

Abbreviation: CNY=Chinese Yuan; LOS=length of hospital stay.

hospitalization, 13,167.36 CNY (95% CI: 7,697.29–18,637.43) in hospital expenditures, and 17.94 days (95% CI: 11.74–24.14) increase of LOS. Supplementary Tables S1–S3 (available in <https://weekly.chinacdc.cn>) displayed the city-specific attributable values which vary across different cities.

The potentially avoidable value and PAF by meeting different air quality standards are shown in Table 1. Under the WHO's standards, about 18.10 thousand (95% CI: 11.78–24.54) hospital admissions, 198.73 million CNY (95% CI: 119.07–278.40) hospital costs, and 272.00 thousand days (95% CI: 179.22–364.79) of LOS could be avoided.

The potentially avoidable cost and LOS per capita based on the two standards are demonstrated in Table 2. About 298.31 CNY (95% CI: 178.73–471.90) in hospital costs and 0.41 days (95% CI: 0.27–0.55) of LOS could be avoided for each respiratory case under the standards of WHO.

Supplementary Table S4 (available in <https://weekly.chinacdc.cn>) delineates the overall attributable burden of COPD and asthma due to NO₂. About 5.69 million CNY (95% CI: 0.72–10.65) for asthma and 50.66 million (95% CI: 25.06–776.26) for COPD could be prevented by decreasing ambient NO₂ concentrations to 25 µg/m³, corresponding to PAFs of 5.40% (95% CI: 0.69%–10.11%) and 4.79% (95% CI: 2.37%–7.22%).

DISCUSSION

This analysis firstly demonstrated that higher NO₂

exposure was associated with increased respiratory hospitalization, higher hospital cost, and longer LOS. Furthermore, the results indicate that numbers of respiratory hospitalization, hospital costs, and length of hospital stay could be potentially saved by reducing the NO₂ concentrations. These findings provided ample evidence for formulating air pollution control policies, suggesting that continuously reducing NO₂ concentrations can decrease the burdens of respiratory diseases in Shanxi Province and other similar regions with high NO₂ pollution.

Our results indicate an adverse effect of ambient NO₂ on hospital burden due to respiratory diseases, which is in line with previous studies. For example, one study found an association between life expectancy of people living with respiratory diseases and air pollution (4). Furthermore, in Pennsylvania, the regions with more serious air pollution were found to have a higher hospital expenditure for respiratory diseases (5).

The potentially avoidable values and PAFs for cause-specific respiratory diseases in our analysis were also aligned with previous studies. For example, Guo et al. estimated that the asthma-induced economic cost attributed to NO₂ was 17.15 million dollars per year for Shanghai, China (6). Notably, the similar PAFs suggested that ambient NO₂ had an adverse effect on both chronic and allergic respiratory diseases.

Several mechanisms could help explain the observed adverse effect of NO₂ on the respiratory system. In one clinical trial, NO₂ caused mild airway inflammation in healthy subjects, which affected blood cells and

TABLE 1. Potentially avoidable values and population attributable fraction of hospital admission, hospitalization expenditure and hospital stay due to respiratory disease by reducing ambient NO₂ concentration to the recommended concentration by WHO (25 µg/m³) and Chinese government (40 µg/m³), 2017–2019.

Variable	Potential avoidable value (95% CI)		PAF (% , 95% CI)	
	25 µg/m ³	40 µg/m ³	25 µg/m ³	40 µg/m ³
Hospitalizations (thousand)	18.10 (11.78–24.54)	7.06 (4.60–9.55)	2.72 (1.77–3.68)	1.06 (0.69–1.43)
Hospitalization expenditure (million CNY)	198.73 (119.07–278.40)	72.81 (43.62–101.99)	4.34 (2.60–6.08)	1.59 (0.95–2.23)
Hospital stay (thousand days)	272.00 (179.22–364.79)	99.65 (65.66–133.64)	4.91 (3.23–6.58)	1.80 (1.18–2.41)

Abbreviation: WHO=World Health Organization; PAF=population attributable fraction; CI=confidence interval; CNY=Chinese Yuan.

TABLE 2. The potentially avoidable hospitalization expenditure and length of hospital stay for each respiratory case by controlling daily NO₂ concentrations to criteria of WHO (25 µg/m³) and Chinese government (40 µg/m³), 2017–2019.

Variable	Potentially avoidable values for each case (95% CI)	
	25 µg/m ³	40 µg/m ³
Hospitalization expenditure (CNY)	298.31 (178.73–471.90)	109.29 (65.48–153.10)
Hospital stay (days)	0.41 (0.27–0.55)	0.15 (0.10–0.20)

Abbreviation: WHO=World Health Organization; CI=confidence interval; CNY=Chinese Yuan.

increased susceptibility to respiratory virus infections in airway epithelial cells (7). Moreover, exposure to higher ambient NO₂ was confirmed to be associated with lung function, which could trigger or aggravate COPD (8).

Limitations should be considered. First, this was an ecological study and it is difficult to make a causal inference on the association between ambient NO₂ exposure and respiratory burden. Second, this study only included cases from secondary and tertiary hospitals in Shanxi Province but excluded those from primary hospitals and patients without hospital admission, which may create a representativeness issue and lead to an underestimate of the respiratory burden in Shanxi Province.

In conclusion, this study elaborated on the association between ambient NO₂ exposure and respiratory hospitalization, hospital cost, and hospital stay. The findings in this analysis identified that government's continued implementation of NO₂ concentration control can potentially reduce hospital admissions, saving a considerable amount of hospital expenditure for people in regions with high NO₂ pollution.

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SUPPLEMENTARY METHODS

Formulas and Models

$$\text{Attributable value} = \sum_{i=0}^n (\text{baseline hospital admission}) \times [\exp(\beta \times \Delta C_i) - 1]$$

$$\text{Attributable hospital expenditure (or length of hospital stay)} = \sum_{i=0}^n (\beta \times \Delta C_i)$$

$$\text{Population attributable fraction} = \frac{\text{attributable value}}{\text{overall number}} \times 100\%$$

$$\text{Attributable value for each case} = \frac{\text{attributable value}}{\text{cases number}} \times 100\%$$

where i is the observation days with a higher NO_2 concentration than the recommended concentration offered by the WHO or Chinese government. C_i is the difference between the daily NO_2 concentration and the reference concentration on day i .

SUPPLEMENTARY TABLE S1. The estimated avoidable number of hospital admissions for respiratory diseases in 11 cities in Shanxi, China, 2017–2019.

City	Overall (in thousand)	25 $\mu\text{g}/\text{m}^3$		40 $\mu\text{g}/\text{m}^3$	
		Avoidable value (in thousand) (95% CI)	Population attributable fraction (%; 95% CI)	Avoidable value (in thousand) (95% CI)	Population attributable fraction (%; 95% CI)
Datong	85.72	3.28 (2.06 to 4.53)	3.82 (2.40 to 5.29)	0.71 (0.45 to 0.97)	0.82 (0.52 to 1.13)
Jincheng	55.53	1.73 (1.07 to 2.41)	3.12 (1.93 to 4.33)	0.68 (0.42 to 0.95)	1.23 (0.76 to 1.71)
Jinzhong	90.42	2.24 (0.52 to 4.02)	2.48 (0.58 to 4.45)	0.97 (0.23 to 1.73)	1.07 (0.25 to 1.91)
Linfen	73.08	3.32 (2.28 to 4.40)	4.55 (3.12 to 6.02)	1.43 (0.98 to 1.88)	1.95 (1.35 to 2.58)
Lyuliang	64.97	3.19 (1.77 to 4.66)	4.91 (2.72 to 7.17)	0.95 (0.53 to 1.38)	1.46 (0.81 to 2.12)
Shuozhou	28.31	0.29 (0.11 to 0.47)	1.01 (0.38 to 1.65)	0.07 (0.03 to 0.11)	0.25 (0.09 to 0.40)
Taiyuan	74.04	2.14 (0.68 to 3.65)	2.89 (0.92 to 4.93)	1.15 (0.37 to 1.95)	1.55 (0.49 to 2.63)
Xinzhou	36.64	0.42 (−0.04 to 0.90)	1.15 (−0.12 to 2.45)	0.14 (−0.01 to 0.29)	0.37 (−0.04 to 0.79)
Yangquan	32.60	0.26 (0.01 to 0.50)	0.79 (0.04 to 1.54)	0.11 (0.10 to 0.22)	0.35 (0.02 to 0.68)
Yuncheng	47.20	0.92 (0.53 to 1.34)	1.96 (1.11 to 2.83)	0.43 (0.24 to 0.62)	0.91 (0.52 to 1.31)
Changzhi	77.67	1.90 (0.58 to 3.26)	2.44 (0.74 to 4.20)	0.59 (0.18 to 1.01)	0.76 (0.23 to 1.30)

Abbreviation: CI=confidence interval.

SUPPLEMENTARY TABLE S2. The estimated avoidable hospital cost for respiratory diseases in 11 cities in Shanxi, China, 2017–2019.

City	Overall (million CNY)	25 $\mu\text{g}/\text{m}^3$		40 $\mu\text{g}/\text{m}^3$	
		Avoidable value (million CNY, 95% CI)	Population attributable fraction (%; 95% CI)	Avoidable value (million CNY, 95% CI)	Population attributable fraction (%; 95% CI)
Datong	683.11	26.40 (12.07 to 40.74)	3.87 (1.77 to 5.96)	5.22 (2.39 to 8.05)	0.76 (0.35 to 1.18)
Jincheng	314.07	16.98 (5.94 to 28.02)	5.41 (1.89 to 8.92)	6.27 (2.20 to 10.35)	2.00 (0.70 to 3.30)
Jinzhong	546.70	23.18 (−0.17 to 46.53)	4.24 (−0.03 to 8.51)	8.95 (−0.06 to 17.97)	1.64 (−0.01 to 3.29)
Linfen	479.07	36.35 (21.96 to 50.73)	7.59 (4.58 to 10.59)	13.66 (8.25 to 19.07)	2.85 (1.72 to 3.98)
Lyuliang	405.99	35.98 (16.35 to 55.62)	8.86 (4.03 to 13.70)	11.72 (5.32 to 18.11)	2.89 (1.31 to 4.46)
Shuozhou	151.05	3.23 (−1.38 to 7.83)	2.14 (−0.91 to 5.19)	0.75 (−0.32 to 1.82)	0.50 (−0.21 to 1.21)
Taiyuan	724.98	23.75 (−8.98 to 56.48)	3.28 (−1.24 to 7.79)	11.74 (−4.44 to 27.91)	1.62 (−0.61 to 3.85)
Xinzhou	300.82	14.73 (−0.94 to 30.41)	4.90 (−0.31 to 10.11)	4.99 (−0.32 to 10.30)	1.66 (−0.11 to 3.42)
Yangquan	274.49	6.05 (−6.62 to 18.73)	2.21 (−2.41 to 6.82)	2.35 (−2.58 to 7.28)	0.86 (−0.94 to 2.65)
Yuncheng	237.83	14.16 (7.24 to 21.07)	5.95 (3.05 to 8.86)	5.44 (2.78 to 8.10)	2.29 (1.17 to 3.40)
Changzhi	462.84	7.19 (−8.31 to 22.69)	1.55 (−1.80 to 4.90)	2.36 (−2.73 to 7.46)	0.51 (−0.59 to 1.61)

Abbreviation: CNY=Chinese Yuan; CI=confidence interval.

Sensitivity Analysis

Several sensitivity analyses were performed to examine the robustness of our results. We conducted two-pollutant models to control the potential confounding effects of other air pollutants, including PM_{2.5}, O₃, and SO₂ in Supplementary Table S5. We also changed the df of temporal trend in the range of 5–8 and that of daily temperature and relative humidity in the range of 4–6 to examine the robustness of models (Supplementary Table S6).

The results of the sensitivity analysis indicated that our results were robust. Our two-pollutant models (Supplementary Table S5) suggest that the association was robust to the adjustment of co-pollutants (O₃, SO₂, and PM_{2.5}). In Supplementary Table S6 compared with our main models, the associations between NO₂ concentrations and outcomes were also generally similar by changing the dfs for the adjustment of meteorological factors and temporal trend.

SUPPLEMENTARY TABLE S3. The estimated avoidable length of hospital stays (LOS) for respiratory diseases in the 11 cities in Shanxi, China, 2017–2019.

City	Overall (thousand days)	25 µg/m ³		40 µg/m ³	
		Avoidable value (thousand days, 95% CI)	Population attributable fraction (%; 95% CI)	Avoidable value (thousand days, 95% CI)	Population attributable fraction (%; 95% CI)
Datong	866.97	39.18 (22.58 to 55.79)	4.52 (2.60 to 6.44)	7.74 (4.46 to 11.02)	0.89 (0.51 to 1.27)
Jincheng	430.01	25.93 (14.79 to 37.06)	6.03 (3.44 to 8.62)	9.58 (5.46 to 13.69)	2.23 (1.27 to 3.18)
Jinzhong	684.28	25.79 (4.22 to 47.37)	3.77 (0.62 to 6.92)	9.96 (1.63 to 18.30)	1.46 (0.24 to 2.67)
Linfen	578.60	37.52 (24.41 to 50.63)	6.49 (4.22 to 8.75)	14.10 (9.18 to 19.03)	2.44 (1.59 to 3.29)
Lyuliang	491.85	31.01 (13.05 to 48.97)	6.31 (2.65 to 9.96)	10.1 (4.25 to 15.94)	2.05 (0.86 to 3.24)
Shuozhou	234.09	7.82 (1.67 to 13.96)	3.34 (0.71 to 5.96)	1.82 (0.39 to 3.25)	0.78 (0.17 to 1.39)
Taiyuan	667.01	35.56 (9.65 to 61.47)	5.33 (1.45 to 9.22)	17.57 (4.77 to 30.38)	2.63 (0.72 to 4.55)
Xinzhou	309.92	13.38 (-0.06 to 26.81)	4.32 (-0.02 to 8.65)	4.53 (-0.02 to 9.08)	1.46 (-0.01 to 2.93)
Yangquan	304.5	9.87 (0.02 to 19.71)	3.24 (0.01 to 6.47)	3.84 (0.01 to 7.66)	1.26 (0.00 to 2.52)
Yuncheng	379.06	30.77 (20.22 to 41.32)	8.12 (5.33 to 10.90)	11.82 (7.77 to 15.88)	3.12 (2.05 to 4.19)
Changzhi	597.57	14.45 (-1.67 to 30.56)	2.42 (-0.28 to 5.11)	4.75 (-0.55 to 10.05)	0.79 (-0.09 to 1.68)

Abbreviation: CI=confidence interval.

SUPPLEMENTARY TABLE S4. Avoidable values and attributable fractions of COPD and asthma by controlling ambient NO₂ according to standards by 25 µg/m³, 40 µg/m³ in Shanxi Province, 2017–2019.

Disease	Variable	Avoidable value (95% CI)		Population attributable fraction (%; 95% CI)	
		25 µg/m ³	40 µg/m ³	25 µg/m ³	40 µg/m ³
COPD	Hospital cost (million CNY)	50.66 (25.06 to 76.26)	18.56 (9.18 to 27.94)	4.79 (2.37 to 7.22)	1.76 (0.87 to 2.64)
	Hospital stay (thousand day)	56.01 (30.49 to 81.54)	20.52 (11.17 to 29.87)	5.06 (2.76 to 7.37)	1.85 (1.01 to 2.70)
Asthma	Hospital cost (million CNY)	5.69 (0.72 to 10.65)	2.08 (0.27 to 3.90)	5.40 (0.69 to 10.11)	1.98 (0.25 to 3.70)
	Hospital stay (thousand day)	7.65 (3.45 to 11.85)	2.80 (1.26 to 4.34)	6.14 (2.77 to 9.52)	2.25 (1.02 to 3.49)

Abbreviation: CNY=Chinese Yuan; COPD=Chronic obstructive pulmonary disease; CI=confidence interval.

SUPPLEMENTARY TABLE S5. Sensitivity analyses on the PAF of NO₂ for hospital admission, hospital cost, and length of hospital stay at lag03 in two-pollutant models by meeting 25 µg/m³.

Two-pollutant model	Daily respiratory hospitalization	Hospitalization cost (thousand CNY)	Length of Hospital stay (days)
NO ₂ +SO ₂	2.13 (1.17, 3.09)	13.46 (7.15, 19.76)	18.79 (10.98, 26.60)
NO ₂ +O ₃	1.94 (1.26, 2.61)	12.07 (7.02, 17.11)	16.28 (10.55, 22.02)
NO ₂ +PM _{2.5}	1.84 (1.19, 2.50)	7.84 (4.39, 11.27)	12.76 (8.32, 17.21)

Abbreviation: CNY=Chinese Yuan; PAF=population attributable fraction.

SUPPLEMENTARY TABLE S6. Sensitivity analyses of the association between daily NO₂ and hospital admissions, hospital cost, and length of hospital stay by changing the degree of freedom in the smoothing functions.

Models	Daily respiratory hospitalizations	Hospitalization cost (thousand CNY)	Length of Hospital stay (days)
Varying df for temporal trend			
df=5	2.23 (1.44 to 3.02)	13.25 (8.09 to 18.42)	18.70 (12.21 to 25.18)
df=7	1.89 (1.25 to 2.53)	11.72 (7.07 to 16.36)	16.00 (10.72 to 21.28)
df=8	1.78 (1.20 to 2.37)	11.83 (7.57 to 16.08)	15.30 (10.55 to 20.05)
Varying df for temperature			
df=5	2.00 (1.32 to 2.69)	12.08 (7.20 to 16.97)	16.49 (10.87 to 22.10)
df=7	1.98 (1.30 to 2.66)	11.81 (6.98 to 16.65)	16.45 (10.75 to 22.15)
df=8	2.00 (1.31 to 2.68)	11.86 (7.02 to 16.71)	16.59 (10.87 to 22.32)
Varying df for relative humidity			
df=4	1.99 (1.30 to 2.68)	11.95 (7.13 to 16.76)	16.56 (10.88 to 22.23)
df=5	1.99 (1.29 to 2.68)	12.12 (7.18 to 17.07)	16.60 (10.93 to 22.27)
df=6	1.99 (1.30 to 2.68)	12.06 (7.11 to 17.01)	16.60 (10.92 to 22.29)

Abbreviation: CNY=Chinese Yuan.