

ORIGINAL ARTICLE

Higher ambient nitrogen dioxide is associated with an elevated risk of hospital-acquired acute kidney injury

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ABSTRACT

Background. Previous studies have suggested that long-term exposure to air pollution increases the risk of chronic kidney disease and its progression. However, the effect of air pollution on the risk of acute kidney injury (AKI) has not been studied. We aim to evaluate the transient effect of air pollution on the risk of hospital-acquired AKI (HA-AKI).

Methods. We selected from the Epidemiology of AKI in Chinese Hospitalized patients cohort AKI cases in which the onset date could be unambiguously determined. We obtained city-specific daily averages of the ambient level of particulate matter (2.5 μm and 10 μm), carbon monoxide, nitrogen dioxide (NO₂), sulfur dioxide (SO₂) and ozone (O₃) from the Ministry of Environmental Protection of China. We used the time-stratified case-crossover approach to examine the association between the ambient level of air pollutants and the risk of HA-AKI in the selected cases.

Results. A total of 11 293 AKI cases that met the inclusion and exclusion criteria were selected. In univariable analysis, the ambient levels of NO₂ and SO₂ were significantly associated with the risk of HA-AKI. In the multivariable analysis that incorporated all six pollutants in the same model, NO₂ was the sole pollutant whose level remained associated with the risk of AKI ($P < 0.001$). The relationship between the level of NO₂ and the risk of HA-AKI appeared to be linear, with an estimated odds ratio of 1.063 (95% confidence interval 1.026–1.101) for each increment of 1 median absolute deviation in the exposure. The association was consistent across the subgroups stratified by age, gender, baseline estimated glomerular filtration rate, AKI severity, need for intensive care and season.

Conclusions. Higher ambient levels of NO₂ are associated with an increased risk of HA-AKI in hospitalized adults in China.

Keywords: air pollution, case-crossover, hospital-acquired acute kidney injury, nitrogen dioxide

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INTRODUCTION

The burden of disease and death attributable to air pollution is becoming a public health challenge worldwide, especially in developing countries [1, 2]. Numerous experimental and epidemiological studies have demonstrated that air pollution adversely affects respiratory and cardiocerebral vascular health [3–5]. Recently, long-term exposure to air pollution has also been linked to an increased risk of chronic kidney disease (CKD) in different populations [6–8]. However, the transient effect of air pollution on acute kidney diseases has not been fully studied in humans.

Acute kidney injury (AKI), characterized by an abrupt loss of kidney function, is a common and serious complication observed in hospitalized patients and is associated with increased mortality and adverse outcomes, including development and progression of CKD [9–12]. Maladaptive repairs after repeated AKIs have been recognized as a major pathological cause for CKD [13, 14]. Thus we hypothesized that exposure to air pollution may also increase the risk of hospital-acquired AKI (HA-AKI). Case-crossover is a design for investigating the transient effects of an exposure on the onset of acute outcomes [15] and is frequently used in studying the acute adverse effects of air pollution on health [16, 17]. A key feature of this design is that it requires only cases and each case serves as its own control, thus eliminating confounding by subject characteristics such as overall health status and presence of risk factors.

In this study we used a time-stratified case-crossover design to study the association between the ambient level of air pollutants, including particulate matter [2.5 μm ($\text{PM}_{2.5}$) and 10 μm (PM_{10})], nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3) and AKI in 11 293 AKI cases identified from the Epidemiology of AKI in Chinese Hospitalized patients (EACH) study [18, 19].

MATERIALS AND METHODS

Study population

The study population was drawn from the EACH study, a retrospective cohort of 3044 224 inpatients admitted from 2013 to 2015 at 25 tertiary academic medical centers across China [18, 19]. We obtained patient-level data from the electronic hospitalization databases and laboratory databases from the participating centers. The hospitalization records consisted of the patients' age, sex, date of admission, diagnosis at admission, date of discharge, operational procedures, total cost incurred during the hospitalization and survival status at discharge. The laboratory data included the values and time of serum creatinine tests. The current study included 11 293 hospitalized adults with AKI whose onset dates of AKI could be unambiguously determined. The flowchart of the study population and the patients selected for subsequent analyses is presented in [Supplementary data, Figure S1](#). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Nanfang Hospital (NFEC-2014-098) and individual consent for this retrospective analysis was waived.

Identification of AKI cases and determination of the onset dates

Assessment of the transient effect of air pollution on HA-AKI requires accurate determination of the onset date of AKI, which is only possible when serum creatinine is measured daily. In

many AKI cases, the onset date cannot be accurately determined due to long intervals between serum creatinine tests. We screened patients' creatinine data for HA-AKI events of which the onset date could be determined within ± 1 day. Specifically, the creatinine data of every qualified event met the following criteria: having three consecutive creatinine tests, with values of c_1 , c_2 and c_3 and testing times of t_1 , t_2 and t_3 , respectively; the time interval was ≤ 30 days between the first two tests ($t_2 - t_1 \leq 30$ days) and ≤ 48 h between the second and third test ($t_3 - t_2 \leq 48$ h); there was no evidence of AKI between t_1 and t_2 , indicated by $|c_2 - c_1| < 26.5 \mu\text{mol/L}$ and $c_2/c_1 < 1.5$ and $c_1/c_2 < 1.5$; and there was evidence of AKI between t_2 and t_3 , indicated by $c_3 - c_2 \geq 26.5 \mu\text{mol/L}$ or $c_3/c_2 \geq 1.5$. The onset date of AKI was defined as the midpoint between the second and third test (t_2 and t_3). Since the true onset time of these AKI cases was bounded by t_2 and t_3 and the time interval between t_2 and t_3 was ≤ 48 h, the estimated onset time (midpoint between t_2 and t_3) should be within 1 day of the true onset time. For patients with multiple qualified events, only the earliest one was selected.

Exposure to air pollution

We obtained air pollution data for each city from 1 January 2014 to 31 December 2015, including daily average concentrations of $\text{PM}_{2.5}$, PM_{10} , NO_2 , CO, SO_2 and O_3 , from the Ministry of Environmental Protection of China (<http://zhb.gov.cn/hjzl/>). Since daily air pollution data before 1 January 2014 were not available for most cities, we only included HA-AKI cases with onset dates within 2014–2015 in the analysis. We used the daily average of each air pollutant in the city where the hospital resided as the exposure of the inpatients. We also obtained the daily average temperature data of each city over the same period from the Chinese weather website (<http://www.tianqi.com>).

We staged AKI using the peak creatinine level within 14 days after the onset date, according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, and classified Stages 2 and 3 AKI as severe AKI.

Statistical analysis

We used the time-stratified case-crossover approach [15] to examine the association between the daily average of each air pollutant ($\text{PM}_{2.5}$, PM_{10} , NO_2 , SO_2 , CO and O_3) and HA-AKI in the selected AKI cases. In the analysis, we excluded the AKI cases that fell into one of the following categories: age < 18 or ≥ 100 years, baseline estimated glomerular filtration rate (eGFR) < 30 mL/min and extremely low baseline creatinine values ($< 40 \mu\text{mol/L}$). We used the onset dates of AKI to index the case days and selected the days that matched the onset dates by the year, the month and the day of the week as controls. We performed conditional Poisson regression analyses to estimate the effects of each air pollutant on AKI with different lag times (Lag 0, 1, 2 or 3 days) and with adjustment for the daily temperature (single-pollutant models). We used these values of lag time to accommodate the possible lags between the time of exposure and AKI onset. We standardized the estimated effect size using the median absolute deviation (MAD) of each air pollutant, because the distributions of air pollutants were far from normal and MAD is a more robust statistic for the spread of distribution than standard deviation. We plotted the smoothed curves of the ambient level of each air pollutant and the risk of HA-AKI. We also performed analyses that included the six air pollutants in a single regression model (six-pollutant model).

Table 1. Characteristics of the selected HA-AKI cases by AKI severity^a

Variable	Mild AKI (n = 8118)	Severe AKI (n = 3175)	Total (n = 11 293)
Age (years), median (q25–q75)	61.4 (50.0–72.0)	61.9 (50.0–72.8)	61.6 (50.0–72.1)
Male, n (%)	5480 (67.5)	2144 (67.5)	7624 (67.5)
Baseline creatinine ($\mu\text{mol/L}$), median (q25–q75)	85 (66–111)	76 (58–100)	82 (63–108)
eGFR (mL/min), median (q25–q75)	78 (55–97)	86 (62–102)	80 (57–99)
Need intensive care, n (%)	2691 (33.1)	962 (30.3)	3653 (32.3)
Season of onset, n (%)			
Q1	1982 (24.4)	802 (25.3)	2784 (24.7)
Q2	2086 (25.7)	796 (25.1)	2882 (25.5)
Q3	1995 (24.6)	763 (24.0)	2758 (24.4)
Q4	2055 (25.3)	814 (25.6)	2869 (25.4)
Temperature at onset ^b , °C	21 (13, 26)	20 (12, 26)	21 (13, 26)

q25, 25th quantile; q75, 75th quantile.

^{a,b}Severe AKI is defined as Stage 2 or 3 AKI.

Table 2. Distribution of daily average concentration of air pollutants

Air pollutant	Minimum	q25	Median	q75	Maximum	MAD
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	6	32	49	72	545	27.9
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	4	52	93	118	977	46.7
NO ₂ ($\mu\text{g}/\text{m}^3$)	5	34	45	57	146	16.9
SO ₂ ($\mu\text{g}/\text{m}^3$)	3	11	16	24	145	8.5
CO (mg/m ³)	0.37	0.79	0.97	1.22	6.01	0.30
O ₃ ($\mu\text{g}/\text{m}^3$)	5	63	100	152	496	62.3

q25, 25th quantile; q75, 75th quantile.

We further performed analyses to examine possible modifications of the effects of the air pollutant by age (>60 years and ≤60 years), gender (male and female), baseline eGFR (>60 and ≤60 mL/min/1.73 m²), AKI severity (mild and severe), need for intensive care and season (quarter of the year).

We performed all statistical analyses using R software, version 3.6.1 with package gnm version 1.1-1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided and P-values <0.05 were considered statistically significant.

RESULTS

We screened the serum creatinine data in inpatients of the EACH cohort and identified a total of 16 886 HA-AKI cases with unambiguous onset time (± 1 day) according to the KDIGO criteria. We excluded the AKI cases with any of the following conditions: age <18 or ≥100 years, baseline eGFR <30 mL/min/1.73 m² or baseline creatinine ≤40 $\mu\text{mol/L}$ (Supplementary data, Figure S1). A total of 11 293 cases that met the inclusion and exclusion criteria were selected and their characteristics were summarized in Table 1. Among these, 3175 (28.1%) were severe AKI (Stage 2 or 3). The median age was 61.6 years, 67.5% were males, the median eGFR at baseline was 82 mL/min/1.73 m² and 32.3% required intensive care during hospitalization. The number of HA-AKI cases distributed evenly among the four quarters of the year.

The distributions of the exposure level in the study population, measured as the daily average concentration of the air pollutants, are summarized in Table 2. The correlations were high between PM_{2.5} and PM₁₀ ($r = 0.91$); intermediate among PM, NO₂,

SO₂ and CO ($r = 0.5$ – 0.7); and low between O₃ and other pollutants ($r < 0.2$) (Supplementary data, Table S1).

In the analyses of single-pollutant models, daily average levels of NO₂ and SO₂ were significantly associated with the risk of HA-AKI (Table 3). The association was the strongest when the lag time was 1–2 days and substantially attenuated with increased lag time. PM_{2.5}, PM₁₀, CO and O₃ were not significantly associated with the risk of HA-AKI regardless of the lag time. In the analysis that included all six pollutants in a single model, NO₂ was the sole pollutant whose concentration remained to be associated with the risk of HA-AKI, with an estimated relative risk (RR) of 1.063 [95% confidence interval (CI) 1.026–1.101] for each increment of one MAD in the exposure ($P < 0.001$). The relationship between the level of NO₂ and the risk of HA-AKI appeared to be linear (Figure 1).

In the subgroup analyses, the effect of exposure to NO₂ on the risk of HA-AKI did not significantly differ among the subgroups stratified by age (≤60 years), gender, baseline eGFR (≤60 mL/min), AKI severity, need for intensive care and season (Table 4).

DISCUSSION

To the best of our knowledge, this is the first population study to evaluate the transient effect of air pollution on the risk of HA-AKI. We observed a linear relationship between the ambient level of NO₂ and the risk of AKI. Every MAD increase in ambient NO₂ was associated with a 6.3% increase in the risk of AKI. The association was consistent across the subgroups stratified by age, gender, baseline eGFR, AKI severity, need for intensive care and season. The ambient level of SO₂ was also associated with the risk of AKI in the single-pollutant analysis. However, the association disappeared after adjusting for the level of NO₂.

More than 90% of the AKI events are attributed to ischemic injuries [20]. Previous studies have shown that exposure to air pollution increases the risk of ischemic cardiocerebral vascular disease, such as acute myocardial infarction (AMI) and stroke [21, 22]. Similar to what we observed in the cases of HA-AKI, a recent retrospective analysis found that moderate to high levels of NO₂ were significantly associated with a higher risk of AKI hospitalization, while O₃ was not shown to be a risk factor for AKI [23]. A large study in Alberta, Canada [24] found that a higher ambient level of NO₂, but not CO, NO, O₃ or PM_{2.5}, was associated with an elevated risk of AMI, and the association was the strongest with a 1-day lag. Meanwhile, the ambient level of

Table 3. RRs of HA-AKI by a 1 MAD increase in the ambient level of air pollutants

Pollutant	RR (95% CI) from single-pollutant models ^a				RR (95% CI) from six-pollutant model with 1-day lag
	No lag	1-day lag	2-day lag	3-day lag	
PM _{2.5}	1.000 (0.981, 1.020)	1.008 (0.987, 1.028)	1.006 (0.986, 1.026)	1.006 (0.986, 1.026)	0.963 (0.922, 1.007)
PM ₁₀	1.009 (0.986, 1.032)	1.022 (0.999, 1.047)	1.018 (0.994, 1.042)	1.023 (0.999, 1.047)	1.029 (0.980, 1.082)
NO ₂	1.042 (1.016, 1.067)	1.051 (1.025, 1.077)	1.046 (1.020, 1.072)	1.036 (1.011, 1.062)	1.063 (1.026, 1.101)
SO ₂	1.021 (1.001, 1.041)	1.022 (1.002, 1.043)	1.030 (1.010, 1.051)	1.017 (0.997, 1.038)	1.000 (0.975, 1.026)
CO	1.009 (0.987, 1.031)	1.014 (0.992, 1.036)	1.009 (0.987, 1.032)	1.008 (0.986, 1.030)	0.996 (0.964, 1.029)
O ₃	1.003 (0.971, 1.036)	0.997 (0.965, 1.030)	1.031 (0.998, 1.065)	1.012 (0.979, 1.046)	0.988 (0.955, 1.022)

^aRRs (95% CIs) were estimated from the conditional Poisson regression models with adjustment for ambient temperature and scaled by 1 MAD of the daily concentration of the air pollutant. Since a 1-day lag produced the strongest association in the single-pollutant models, the six-pollutant model was analyzed with a 1-day lag only.

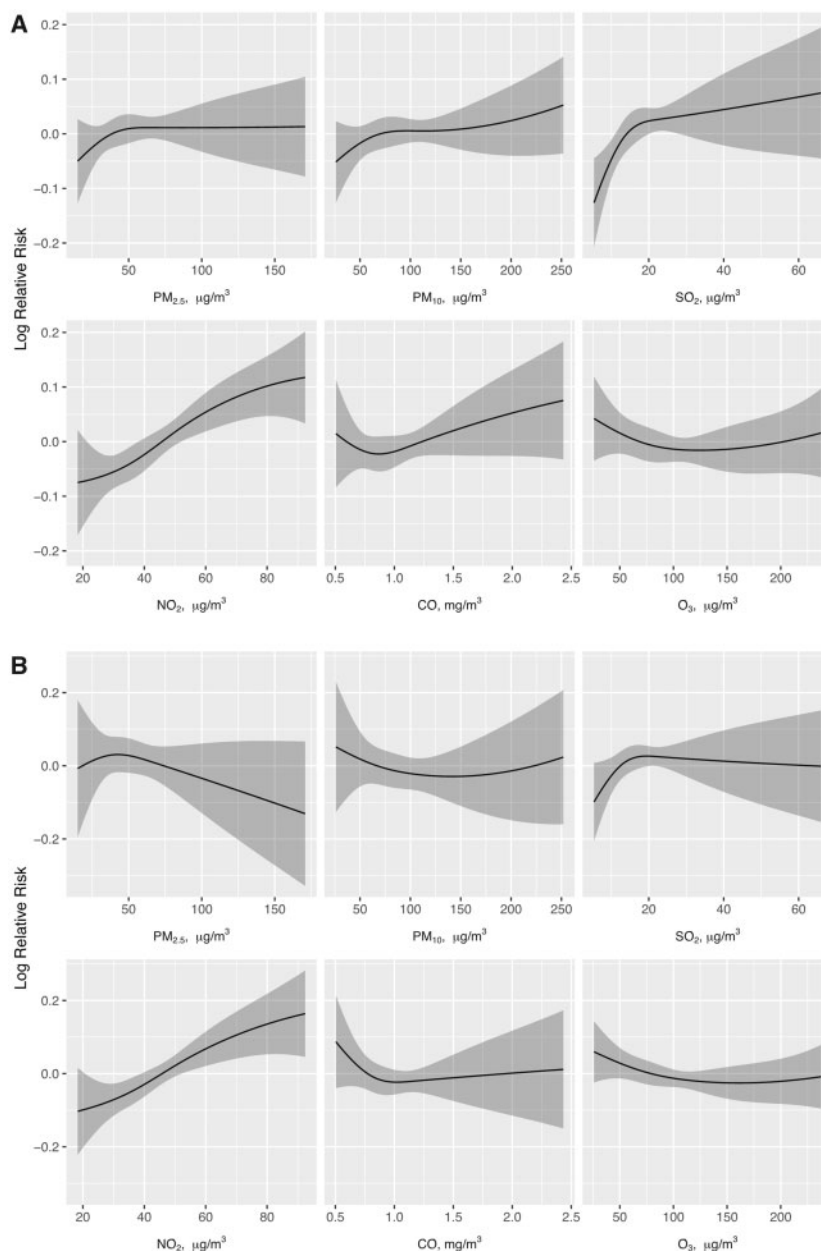


FIGURE 1: The smooth curves of the ambient levels of air pollutants and the RR of HA-AKI. (A) The effect of the daily average of each air pollutant on the risk of HA-AKI was estimated from single-pollutant models. (B) The effect of the daily average of each air pollutant on the risk of HA-AKI was estimated from the six-pollutant model that included all six air pollutants in a single regression model. The 95% CIs of the estimates are given by the shaded areas.

Table 4. Subgroup analyses of the effect of ambient NO₂ on the RR of HA-AKI

Variable	Subgroup	n	RR (95% CI) ^a	P for interaction
Age (years)	≤60	5118	1.082 (1.036–1.130)	–
	>60	6175	1.054 (1.010–1.099)	0.29
Gender	Male	7624	1.052 (1.012–1.095)	–
	Female	3669	1.098 (1.044–1.154)	0.11
Baseline eGFR (mL/min/1.73 m ²)	≤60	8137	1.068 (1.027–1.110)	–
	>60	3156	1.066 (1.011–1.123)	0.95
AKI severity	Mild	8118	1.061 (1.021–1.103)	–
	Severe	3175	1.082 (1.026–1.141)	0.50
Intensive care	Yes	3653	1.081 (1.030–1.135)	–
	No	7640	1.058 (1.016–1.102)	0.42
Season	Q1	2784	1.085 (1.032–1.141)	–
	Q2	2882	1.096 (1.027–1.169)	0.80
	Q3	2758	1.037 (0.959–1.121)	0.31
	Q4	2869	1.045 (0.992–1.100)	0.22

^aRRs (95% CIs) were scaled by 1 MAD of the daily concentration of NO₂.

NO₂ has also been linked to the risk of ischemic stroke [25] and vascular dementia [26]. In animal models, there is a dose-response effect of exposure to NO₂ on endothelial dysfunction and inflammatory response [27]. We speculate that ischemic AKI, together with AMI and ischemic stroke, share similar etiological pathways in acute response to changes in ambient NO₂. It is worth noting that an elevated ambient level of NO₂ may not directly cause AKI, but rather increases an individual's susceptibility to AKI when a causing factor is present.

Previous studies have implicated long-term exposure to air pollution in the development and progression of CKD [6, 7]. Repeated AKIs have been recognized as an important cause in the etiology of CKD. Thus it is plausible that the observed effect of air pollution on the risk of CKD may be partially mediated by the increased risk of AKI as a result of elevated exposure. Among the six pollutants examined in our study, only the ambient NO₂ level appeared to be independently associated with the risk of AKI. In comparison, the associated patterns between air pollution and the risk of CKD are more complex, as multiple pollutants, including PM_{2.5}, PM₁₀, NO₂ and CO, are implicated. Further studies are needed to fully understand these differences and the underlying mechanisms.

Our study has several strengths. First, accurate determination of the onset time of AKI is crucial for estimating the transient effect of air pollution on AKI. The large size of the EACH cohort with time-stamped serum creatinine data allowed us to identify a sufficient number of AKI cases with well-defined onset dates. Second, we used a time-stratified case-crossover design in the association analysis, which is robust to possible confounding by the characteristics of the patients, such as overall health status and the presence of risk factors. Our study also has limitations. First, since all AKI cases occurred during hospitalization, use of the exposure level at the exact locations of the participating hospitals would be desirable. Instead, we used the average levels of the air pollutants in the cities where the participating hospitals were located as surrogates for the exposure. This may result in an underestimation of the effect of air pollution. Second, our study cohort was from China, where the level of air pollution is much higher than in many developed countries. Whether our findings can be generalized to other populations needs further investigation.

In summary, higher ambient levels of NO₂ were significantly associated with an increased risk of AKI in hospitalized patients in China. Ambient NO₂ is mainly derived from traffic and

industrial fuel combustion and has been recognized as an important driver of increasing greenhouse gas emissions globally [28, 29]. Our findings call for more awareness among policy-makers, industries, medical researchers and the public of the adverse effects of air pollution on kidney health.

SUPPLEMENTARY MATERIAL

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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