Environment International 183 (2024) 108367

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Fluctuating risk of acute kidney injury-related mortality for four weeks after exposure to air pollution: A multi-country time-series study in 6 countries

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ARTICLE INFO

Keywords:
Acute kidney injury
Mortality

ABSTRACT

Background: Recent studies have reported that air pollution is related to kidney diseases. However, the global evidence on the risk of death from acute kidney injury (AKI) owing to air pollution is limited. Therefore, we investigated the association between short-term exposure to air pollution—particulate matter ≤ 2.5 μm ($PM_{2.5}$), ozone (O_3), and nitrogen dioxide (NO_2)—and AKI-related mortality using a multi-country dataset.

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https://doi.org/10.1016/j.envint.2023.108367
Received 29 October 2023; Accepted 1 December 2023
Available online 2 December 2023

Air pollution
Lag structure

Methods: This study included 41,379 AKI-related deaths in 136 locations in six countries during 1987–2018. A novel case time-series design was applied to each air pollutant during 0–28 lag days to estimate the association between air pollution and AKI-related deaths. Moreover, we calculated AKI deaths attributable to non-compliance with the World Health Organization (WHO) air quality guidelines.
Results: The relative risks (95% confidence interval) of AKI-related deaths are 1.052 (1.003, 1.103), 1.022 (0.994, 1.050), and 1.022 (0.982, 1.063) for 5, 10, and 10 $\mu g/m^3$ increase in lag 0–28 days of $PM_{2.5}$, warm-season O_3, and NO_2, respectively. The lag-distributed association showed that the risk appeared immediately on the day of exposure to air pollution, gradually decreased, and then increased again reaching the peak approximately 20 days after exposure to $PM_{2.5}$ and O_3. We also found that 1.9%, 6.3%, and 5.2% of AKI deaths were attributed to $PM_{2.5}$, warm-season O_3, and NO_2 concentrations above the WHO guidelines.
Conclusions: This study provides evidence that public health policies to reduce air pollution may alleviate the burden of death from AKI and suggests the need to investigate the several pathways between air pollution and AKI death.

1. Introduction

Acute kidney injury (AKI) is a sudden loss of kidney function within a few hours or a few days (Malhotra et al., 2019). AKI is a common complication observed in hospitalized patients in an intensive care unit, increasing the mortality rate from 15 to 60% (Singbartl and Kellum, 2012). Furthermore, the incidence of AKI is steadily increasing due to the increase in prevalence of chronic diseases with aging and changes in eating habits (Kellum et al., 2021; Patschan and Muller, 2016). The global burden of AKI-related mortality exceeds by far that of diabetes or heart failure, and AKI is growing as a worldwide public health concern (Kellum et al., 2021).

Exposure to air pollution has been suggested as a potential risk factor for kidney diseases (Bowe et al., 2017; He et al., 2022; Lee et al., 2022). Because the kidney is a highly vascularized organ that normally receives one fifth of the cardiac output, inhaled air pollutants can rapidly reach the kidneys via systematic circulation, promoting oxidative stress, inflammation, and DNA damage to the kidney tissue (Chade, 2013; Chen et al., 2021; Miller et al., 2017). Several epidemiological studies have reported that short- and long-term exposure to air pollution was associated with hospital visits for chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Bowe et al., 2017; Bowe et al., 2018; Lee et al., 2022); however, relevant studies on the risk of AKI death attributed to short-term exposure to air pollution are relatively sparse (Chu et al., 2023; He et al., 2022; Lee et al., 2022).

It is necessary to understand the possible mechanism to investigate AKI-related death attributed to exposure to air pollution, since pollution may be related to AKI-related death via complex pathways (Hsu et al., 2023). This can be mechanistically driven by increased risk of AKI itself, increased severity of AKI, and onset or deterioration of other diseases that lead to AKI (Lee et al., 2023; Singbartl and Kellum, 2012). Previous studies have reported that exposure to higher levels of air pollution is associated with increased risk of sepsis, diabetes mellitus, and cardiovascular disease, which are major drivers of AKI (Hystad et al., 2020; Patschan and Muller, 2016; Wang et al., 2021); thus, it is plausible that air pollution triggers AKI by developing a new disease or exacerbating the underlying disease. This indirect pathway through other diseases can take more time to progress from exposure to air pollution to AKI than the pathway through increased risk or severity of AKI (Malhotra et al., 2019). Nevertheless, few studies on short-term exposure to air pollution and AKI have examined the risk during a short lag period (e.g., 1 or 5 lag days) (Lee et al., 2022; Wei et al., 2019), which might not be sufficient to evaluate the overall impact of air pollution on AKI death through several pathways. Therefore, considering a relatively longer exposure period of air pollution than that in previous studies could provide more precise risk estimates of AKI-related deaths attributed to air pollution.

Because existing studies on short-term exposure to air pollution and AKI have been conducted in a single country (Cai et al., 2023; Lee et al., 2022; Wei et al., 2019), there is a limitation in generalizing the findings worldwide and investigating disproportionate risks by country or culture. Therefore, this study aimed to investigate the association between short-term exposure to ambient air pollution—particulate matter $\leq$ 2.5 μm ($PM_{2.5}$), ozone (O_3), and nitrogen dioxide (NO_2)—and AKI-related mortality in 136 locations of six countries, using a state-of-the-art study design with a long lag period (four weeks, i.e., 28-lag day period). In addition, because AKI is a highly burdensome disease that can lead to death coinciding with other diseases, this study calculated the attributable number and fraction of AKI-related death due to non-compliance with the World Health Organization (WHO) air quality guidelines to quantify the global burden of AKI-related deaths related to air pollution.

2. Methods

2.1. Study population and design

This study included 136 locations across six countries: Canada, Japan, Portugal, South Korea, Taiwan, and the UK. The study periods differed by country, ranging from January 1, 1987 to December 31, 2018. We obtained the data from the Multi-City Multi-Country (MCC) Collaborative Research Network (https://mccstudy.lshtm.ac.uk/). The data for each location included the daily time series of AKI-related death counts, mean concentration of three air pollutants ($PM_{2.5}$, O_3, and NO_2), and mean temperature. Detailed information on data collection is provided in Supplementary Material 1. We defined AKI-related deaths based on the International Classification of Diseases 10th Revision (ICD-10) codes: N17. For $PM_{2.5}$ and NO_2, a 24-hour average was calculated, while for O_3, the daily maximum 8-hour average was calculated. Because the levels of O_3 and subsequent health effects are more prominent during the warm season (Lee et al., 2023), we restricted the investigation on the association between O_3 and AKI deaths to the warm season. Because all study locations are in the Northern Hemisphere, the warm season was defined as the warmest six months (April to September).

We applied a novel case time-series design which is a methodology recently proposed for epidemiological analyses of short-term risks associated with time-varying exposures (Gasparrini, 2021). The design combines the flexible modeling structure of time-series analysis with the individual-level setting of the self-matched methods. This design considers multiple observational units (here, locations), defined as cases where data are collected longitudinally. The main design feature that defines the case time-series design is the splitting of the follow-up period into equally spaced time intervals, which results in a set of multiple case-level time series. Originally illustrated in individual-level analyses, this methodology can be adapted for studies using data aggregated over multiple areas (Gasparrini, 2022). Applying the case time-series design in small-area analysis can aid statistical power issues caused by small sample size by combining different time intervals of same area as the control. Moreover, we considered a relatively long lag period (28 lag days) to capture several pathways of the association between air

pollution and AKI-related death, as described in Supplementary Material 2. This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline (see the Supplementary Material 3).

2.2. Statistical analysis

We conducted a novel case time-series design with a quasi-Poisson distribution. The modeling framework is based on fixed-effects model and the model used in this study can be written as:

$$y_{it} \sim quasi-Poisson\ (\lambda_{it})$$

$$\log(\lambda_{it}) = \delta_{i(k)} + f(x_{it}, l) + \sum_{j=1}^{J} s_j(t) + h(z_{it})$$

where y_{it} represents the daily death count for AKI on day t in the i th location ($i = 1, \ldots, 136$). To allow within-location variation in baseline risks, the location/year/month strata indicator $\delta_{i(k)}$ was included in the model. The function $f(x, l)$ specifies the association with the concentration of air pollutants, modeled using a distributed lag model (DLM) with 28 lag days (Gasparrini et al., 2010). The lag dimension (l) was parametrized using a natural cubic spline including an intercept with three internal knots at 7, 14, and 21 lag days to capture the flexible lag effects of air pollution on AKI-related death. The term s_j represents functions expressed at different timescales to model temporal variations in the risk, and two functions of time t were included in the model: 1) natural cubic splines of the day of the year with 3 degrees of freedom and interaction with year indicators and 2) indicators for the day of the week. To consider the potential confounding effect, we adjusted for the daily mean temperature z using a distributed lag non-linear model (DLNM) with a basis term h: a quadratic B-spline with two internal knots (placed at the 50th and 90th percentiles of the location-specific temperature distribution) for the exposure–response relationship, and a natural cubic B-spline with an intercept and two internal knots placed at equally spaced log values of 10 lag days for the lag-response relationship. This model was fitted separately for three air pollutants ($PM_{2.5}$, O_3, and NO_2) and repeated the model for each country to estimate the disproportionate association by country. The results are presented as the relative risk (RR) of AKI-related death associated with 5 μg/m^3 (for $PM_{2.5}$) or 10 μg/m^3 (for O_3 and NO_2) increase in each air pollutant. All statistical analyses were conducted using the R software (version 4.1.0).

2.3. Attributable death of AKI due to air pollution

To evaluate the burden due to air pollution exposure, we estimated the attributable fraction and number of AKI-related deaths due to non-compliance with the 2021 WHO air quality guidelines (24-hour average $PM_{2.5}$: 15 μg/m^3, 24-hour average NO_2: 25 μg/m^3, and maximum 8-hour average O_3: 100 μg/m^3), following a method used in previous studies (Gasparrini et al., 2015; Gasparrini and Leone, 2014; Lee et al., 2022). For each pollutant, we calculated the daily attributable fraction (%) of AKI deaths due to air pollutant levels above the WHO guidelines. The daily attributable number of AKI deaths was calculated by multiplying the attributable fraction by the 28-day moving average of AKI death counts. For each pollutant, the total number of attributable deaths of AKI due to non-compliance with the WHO guidelines was provided as the sum of the contributions from all days of the series and the overall attributable fraction was calculated by dividing the total number of attributable deaths of AKI to the total number of AKI deaths. Detailed descriptions of attributable fractions and numbers are provided in Supplementary Material 4. The attributable fraction and number for each country were also computed following the same procedure by country.

2.4. Sensitivity analysis

We conducted several sensitivity analyses to examine the robustness of our findings. First, because the pollutants are correlated, and the mixture of pollutants could have a joint effect on the genitourinary system (Tavallali et al., 2020), we conducted a two-pollutant model. Second, the lag period was altered to 21 and 35 days for the air pollutant basis term. For the analysis with 21 lag days, we assigned the knots for lag days at 7 and 14 days, while the same lag parameterization for the analysis with 35 lag days was used as the main analysis. Third, the basis function for the lag was changed to a natural cubic spline including an intercept with three interval knots at equally spaced log values of 28 lag days. Finally, we conducted the model without the daily mean temperature.

3. Results

This study included 41,379 AKI-related deaths in 136 locations of six countries during the period 1987–2018 (Table 1). The median value of the daily concentration of each air pollutant differed by country, ranging from 6.58 (Canada) to 28.71 (Taiwan) μg/m^3 for $PM_{2.5}$, from 49.31 (Taiwan) to 127.94 (Japan) μg/m^3 for warm-season O_3, and from 24.61 (Portugal) to 47.25 (UK) μg/m^3 for NO_2. Fig. 1 shows the geographical distribution of the location-specific proportion of AKI-related deaths among total deaths at the 136 locations. The proportion of AKI deaths was higher in Eastern countries (Japan, South Korea, and Taiwan) than in Western countries.

Table 2 shows the pooled lag-cumulative associations between air pollution and AKI-related deaths by country. All types of air pollutants considered were associated with an increased risk of AKI-related death with RRs of 1.052 (95% confidence interval [CI]: 1.003, 1.103) for 5 μg/m^3 increase in $PM_{2.5}$, 1.022 (95% CI: 0.994, 1.050) for 10 μg/m^3 increase in warm-season O_3, and 1.022 (95% CI: 0.982, 1.063) for 10 μg/m^3 increase in NO_2. Risk estimates from the multi-pollutant models and sensitivity analyses were generally consistent with the main results (Supplementary Material 5. Table S1–S2). We also observed different risk estimates among countries showing that the risk of AKI death associated with air pollution was evident in the UK (RR = 1.248) for $PM_{2.5}$, Taiwan (RR = 1.114) and the UK (RR = 1.110) for warm-season O_3, and Portugal (RR = 1.108) for NO_2.

Fig. 2 shows the lag-distributed associations between air pollution and AKI-related deaths. The associated risks appeared immediately on the day (lag 0) of exposure to air pollution, gradually decreased, and started to increase reaching a peak at 22 and 21 days after the exposure to $PM_{2.5}$ and O_3, respectively. For NO_2, we further examined the lag-distributed association by extending the exposure period (35 lag days) because the risk seemed to re-increase near the 28-lag day in Fig. 2. We found that the risk of AKI death associated with NO_2 exposure eventually decreased to an RR close to 1 at 35 days after exposure to NO_2 (Supplementary Material 5. Fig. S1). Lag period-specific RRs of AKI deaths were prominent during 0–3 lag days (RR = 1.016 and 1.006) and 20–23 lag days (RR = 1.010 and 1.011) for $PM_{2.5}$ and O_3 based on the central estimates (Table 3). The country-specific lag-distributed associations are presented in Supplementary Material 5. Fig. S2.

Fig. 3 and Supplementary Material 4. Fig. S3 presents the attributable fraction and number of AKI-related deaths due to air pollutant levels above the 2021 WHO air quality guidelines. In six countries, a total of 784.6, 1185.7, and 2161.3 AKI-related death was attributed to $PM_{2.5}$, warm-season O_3, and NO_2 above the guidelines and the corresponding fraction was 1.9%, 6.3%, and 5.2% during the study period (Supplementary Material 5. Table S3). The attributable fraction was the highest in Taiwan for $PM_{2.5}$ (9.1%), Japan for warm-season O_3 (11.3%), and the UK for NO_2 (8.5%).

Table 1
Descriptive statistics of air pollution and AKI-related death for 6 countries.

Country	Locations (n)	Data period[a]	Daily mean concentration; median (Q1, Q3)			AKI-related death	
			$PM_{2.5}$ (μg/m^3)	O_3[b] (μg/m^3)	NO_2 (μg/m^3)	N	Proportion among total deaths (%)
Canada	26	1987–2015	6.58 (4.17, 10.36)	95.58 (70.92, 123.95)	46.33 (27.74, 69.68)	5,970	0.165
Japan	47	2011–2015	12.58 (8.25, 18.50)	127.94 (91.34, 163.04)	30.80 (20.39, 46.53)	19,088	0.302
Portugal	5	2005–2018	8.25 (5.17, 12.85)	124.15 (100.31, 149.76)	24.61 (11.88, 47.09)	1,478	0.228
South Korea	16	2002–2018	22.21 (14.81, 31.61)	59.34 (42.95, 75.82)	36.24 (26.08, 50.53)	9,174	0.207
Taiwan	3	2008–2016	28.71 (18.90, 43.28)	49.31 (36.77, 68.15)	35.53 (27.22, 45.56)	2,364	0.533
UK	39	2000–2016	9.50 (6.54, 14.83)	96.83 (75.06, 120.86)	47.25 (30.41, 67.83)	3,305	0.104
Overall	136	1987–2018	9.26 (5.68, 15.62)	92.26 (66.01, 123.70)	41.09 (25.86, 62.11)	41,379	0.222

[a] Data period is presented as overall period in which at least one of three air pollutants ($PM_{2.5}$, O_3, and NO_2) data exist.
[b] Maximum 8-hour averaged-ozone in warm season (April to September).
AKI = acute kidney injury; Q1 = first quantile; Q3 = third quantile.

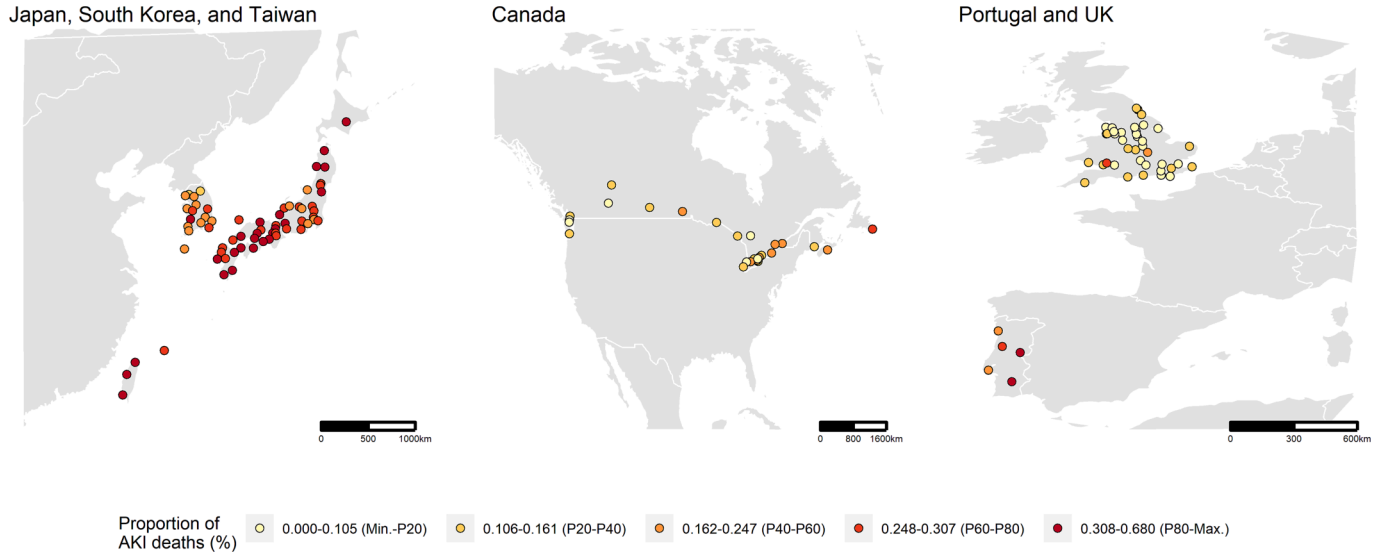

Fig. 1. Geographical distribution of location-specific proportion of AKI-related deaths among total deaths of 136 locations in six countries. AKI = acute kidney injury. P20, P40, P60, and P80 correspond to the 20th, 40th, 60th, and 80th percentile of proportion of AKI deaths, respectively.

Table 2
Association between air pollution and AKI-related death by country.

	RR (95% CI)[a]		
	$PM_{2.5}$	O_3[b]	NO_2
Canada	0.956 (0.824, 1.109)	0.959 (0.893, 1.029)	1.020 (0.946, 1.100)
Japan	1.050 (0.983, 1.123)	1.038 (1.009, 1.069)	1.031 (0.970, 1.095)
Portugal	1.104 (0.796, 1.531)	0.986 (0.857, 1.135)	1.108 (0.967, 1.270)
South Korea	1.011 (0.941, 1.086)	1.020 (0.930, 1.119)	0.994 (0.913, 1.083)
Taiwan	0.959 (0.879, 1.046)	1.114 (0.960, 1.294)	0.864 (0.692, 1.080)
UK	1.248 (1.072, 1.453)	1.110 (0.970, 1.270)	1.049 (0.957, 1.150)
Overall	1.052 (1.003, 1.103)	1.022 (0.994, 1.050)	1.022 (0.982, 1.063)

[a] RRs are presented as the value for 5, 10, and 10 μg/m^3 increase in $PM_{2.5}$, O_3, and NO_2, respectively.
[b] Maximum 8-hour averaged-ozone in warm season (April to September).
AKI = acute kidney injury; CI = confidence interval; RR = relative risk.

4. Discussion

This study investigated the association between short-term exposure to air pollution and AKI-related mortality in 136 locations across six countries. Exposure to $PM_{2.5}$, warm-season O_3, and NO_2 was associated with an increased risk of AKI-related mortality. Among six countries, the association was prominent in UK for $PM_{2.5}$, Taiwan and the UK for warm-season O_3, and Portugal for NO_2. For the lag-distributed association, we found that the estimated risk appeared immediately on the day (lag 0) of exposure to air pollution, then decreased, and increase again reaching the peak 22 and 21 days after the exposure to $PM_{2.5}$ and O_3, respectively. The attributable fraction of AKI-related deaths due to non-compliance with WHO air quality guidelines were 1.9%, 6.3%, and 5.2% for $PM_{2.5}$, warm-season O_3, and NO_2, respectively.

The findings of this study are consistent with those of previous studies examining short-term exposure to air pollution and kidney diseases. One time-stratified case-crossover study in China found that a 10 μg/m^3 increase in lag 0–1 days of $PM_{2.5}$ was associated with 0.49% (95% CI: 0.10%, 0.88%) increase and NO_2 was associated with a 1.26% (95% CI: 0.29%, 2.24%) increase in death from kidney diseases defined as ICD-10 codes "N00" to "N29" (Cai et al., 2023). Another time-stratified case-crossover study reported a positive association between short-term exposure (lag 0–1 days) to $PM_{2.5}$ and hospital admissions for AKI in the US Medicare population (Wei et al., 2019) and a time-series study in South Korea also showed that short-term exposure (lag 0–5 days) to PM_{10} and O_3 was associated with increased risk of emergency room visits for AKI and CKD (Lee et al., 2022). A recent case-crossover study in New York state in the US reported that the odds ratios (ORs) for a 5 μg/m^3 increase in daily mean $PM_{2.5}$ was 1.013 (95% CI: 1.001, 1.025) for AKI and 1.107 (95% CI: 1.018, 1.203) for glomerular diseases (Chu et al., 2023). Because these previous studies on short-term exposure to air pollution and kidney diseases were investigated based on the

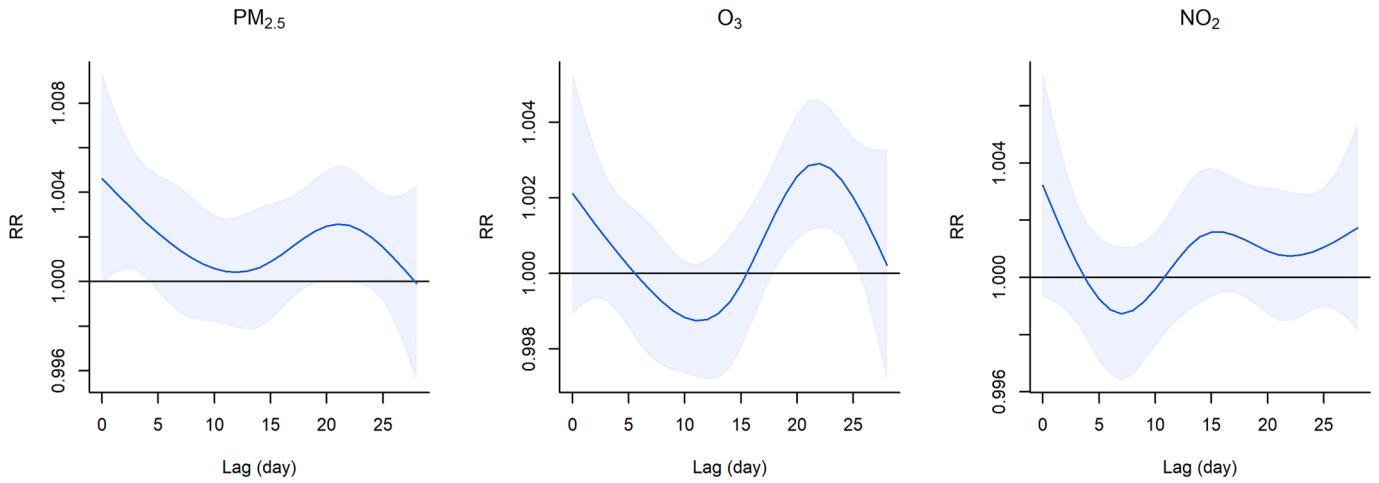

Fig. 2. Lag-distributed association between air pollution and AKI-related death. RRs (with 95% CI, shaded light blue) for $PM_{2.5}$, O_3, and NO_2 are presented as the value for 5, 10, and 10 μg/m^3 increase in each air pollutant, respectively. RR for ozone is based on the maximum 8-hour averaged-ozone in warm season (April to September). AKI = acute kidney injury; CI = confidence interval; RR = relative risk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Lag period-specific association between air pollution and AKI-related death.

	RR (95% CI)[a]		
	$PM_{2.5}$	O_3[b]	NO_2
0–3 lag days	1.016 (1.002, 1.029)	1.006 (0.997, 1.015)	1.007 (0.996, 1.019)
4–7 lag days	1.008 (0.998, 1.018)	1.000 (0.994, 1.007)	0.997 (0.988, 1.005)
8–11 lag days	1.003 (0.993, 1.013)	0.996 (0.990, 1.002)	0.998 (0.990, 1.006)
12–15 lag days	1.002 (0.992, 1.013)	0.997 (0.990, 1.003)	1.005 (0.996, 1.014)
16–19 lag days	1.007 (0.998, 1.016)	1.005 (0.999, 1.011)	1.006 (0.998, 1.013)
20–23 lag days	1.010 (1.000, 1.020)	1.011 (1.005, 1.018)	1.003 (0.994, 1.012)
24–28 lag days	1.005 (0.991, 1.019)	1.007 (0.997, 1.017)	1.006 (0.995, 1.019)

[a] RRs are presented as the value for 5, 10, and 10 μg/m^3 increase in $PM_{2.5}$, O_3, and NO_2, respectively.

[b] RRs for ozone are based on the maximum 8-hour averaged-ozone in warm season (April to September).

AKI = acute kidney injury; CI = confidence interval; RR = relative risk.

relatively short lag period (e.g., 1 day or 5 days) (Cai et al., 2023; Chu et al., 2023; Lee et al., 2022; Wei et al., 2019), the risk estimates of kidney disease may have been attenuated.

We examined the association between air pollution and AKI-related death during a longer lag period (lag 0–28 days) and observed that the estimated risk of pollution-related AKI death was prominent immediately (lag 0 day) and 22 and 21 days after exposure to $PM_{2.5}$ and warm-season O_3. This finding may be related to where AKI is acquired (community-acquired or hospital-acquired) (Hsu et al., 2023). Higher RR in the early lag period might be the result of direct and acute effect of air pollution on the kidney. Inhaled air pollutants rapidly reach the kidneys via systematic circulation and reduce glomerular filtration rate (GFR) by promoting oxidative stress, inflammation, and DNA damage to kidney tissue, which may increase susceptibility for AKI-related death through increased risk or severity of AKI (Chade, 2013; Chen et al., 2021; Miller et al., 2017). In addition, $PM_{2.5}$ accumulates in the kidneys through the bloodstream and can cause direct damage owing to the nephrotoxicity of its chemical constituents (e.g., heavy metals) (Chu et al., 2023; Li et al., 2019), although the related mechanisms are not well understood for O_3 and NO_2. These biological mechanisms are plausible based on experimental studies in humans and mice showing that inhaled gold nanoparticles translocated from the lungs into the systemic circulation and became detectable in the urine (Miller et al., 2017). On the other hand, higher RR in the late lag period could be explained by the mediation of comorbid conditions such as sepsis, CKD, cardiovascular disease, COPD, diabetes mellitus, and hypertension, which markedly increase the risk for hospital-acquired AKI leading to death (Hsu et al., 2023; Hystad et al., 2020; Patschan and Muller, 2016; Singbartl and Kellum, 2012; Wang et al., 2021). We conjectured that exposure to air pollution during earlier lag periods can cause or worsen these antecedent diseases, leading to AKI deaths in the hospital in the late period. However, the plausible pathways for generating AKI are vast and heterogeneous; thus, various mechanisms of air pollution and AKI need to be addressed in future studies to aid patients with AKI and improve their prognosis.

We also observed the disproportionate association between air pollution and AKI-related deaths by countries. The estimated risk was prominent in the UK of $PM_{2.5}$ and warm-season O_3, and in Portugal for NO_2. We thought that the prevalence of some chronic diseases or incidence of acute diseases which are major risk factors of AKI might be higher in European countries; thus, individuals with underlying disease are more vulnerable to AKI-related death. In addition, specific lifestyle factors and dietary habits in Europe, may have synergistic effect with air pollution. However, the related evidence is limited and further studies on the factors that can explain the different risks of air pollution in AKI are essential.

This study has several strengths. To the best of our knowledge, this is the first and largest study to examine the association between short-term exposure to air pollution and AKI-related death using a multi-country dataset. We applied a state-of-the-art statistical technique, case time-series design with DLMs, to address the statistical power loss caused by the small sample size related to AKI deaths and to assess the complex lag patterns of the association. The main contribution of this study is that it provides potential possibilities for the presence of various pathways between air pollution and AKI by examining their association during a long lag period. Finally, we estimated attributable death of AKI due to air pollution concentrations above the WHO guidelines. These findings provide implications for environmental and public health specialists to mitigate the excess burden of AKI-related death and present epidemiological evidence on the value of air pollution guidelines for potential AKI patients.

Nevertheless, this study has several limitations. First, the use of ICD-10 codes N17 to define AKI-related death may have major limitations.

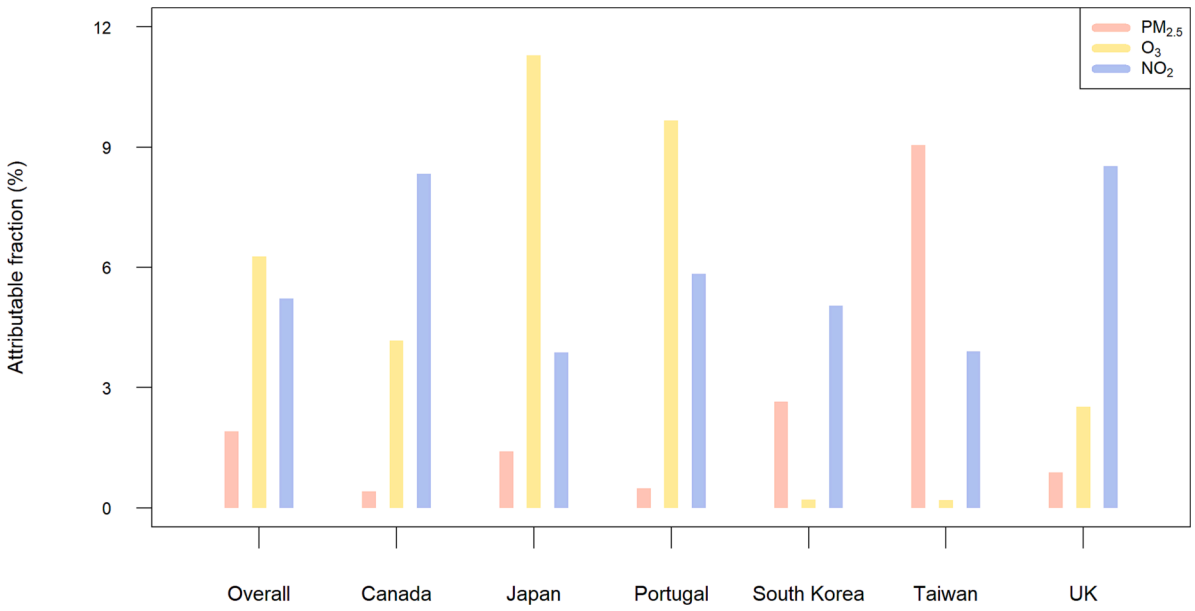

Fig. 3. Attributable fraction of AKI-related mortality due to air pollutant levels above the 2021 WHO air quality guidelines during the study period. 2021 WHO air quality guidelines—24-hour average $PM_{2.5}$: 15 μg/m^3 and NO_2: 25 μg/m^3; maximum 8-hour average O_3: 100 μg/m^3. Estimates for ozone are based on the maximum 8-hour averaged-ozone in warm season (April to September). AKI = acute kidney injury.

These codes have low sensitivity and underestimate AKI-related deaths (Hsu et al., 2023). Using a more accurate definition of AKI-related deaths may help infer better risk estimates in future studies. Second, some estimates were not statistically significant under the significance level 5 %, due to the small sample size, that is, the small number of AKI deaths per day. Third, although we suggested the potential presence of other diseases in the link between air pollution and AKI-related death, we could not identify related diseases owing to data limitations. In addition, we only considered AKI-related death as a outcome variable, although not all AKI lead to death and AKI can occur with few symptoms. Thus, future studies need to address the earlier detection of AKI events or incident AKI associated with air pollution to elucidate plausible mechanism from air pollution to AKI. Finally, we could not investigate the effect modification by CKD stages due to data limitations, although the onset of AKI in CKD patients is known to be more severe and difficult to recover (Kellum et al., 2021; Singbartl and Kellum, 2012).

In conclusion, this study found a positive association between short-term exposure to air pollution ($PM_{2.5}$, O_3, and NO_2) and AKI-related mortality in 136 locations in six countries, and the risk of AKI-related death fluctuated for four weeks after exposure to air pollution. Our findings provide scientific evidence that environmental and public health policies to reduce air pollution may alleviate the burden of death from AKI. Moreover, we suggest the potential presence of several pathways through which air pollution affects AKI death and the need to investigate the mediating diseases in future researches.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Youngrin Kwag reports administrative support was provided by Korea Ministry of Science and ICT. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

Data availability

Data will be made available on request.

Acknowledgments

This work was supported by Specialization Project of Pusan National University. This work was also supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (Ministry of Science and ICT) (No. 2022R1A2C2092353). This paper was also supported by Korea Institute for Advancement of Technology (KIAT) grant funded by the Korea Government (Ministry of Education-Ministry of Trade, Industry and Energy) (P0022108, Next Generation bio-health industry Innovation Talent Training Program). This work was also supported by BK21 Four, Korean Southeast Center for the 4th Industrial Revolution Leader Education and by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2023-00242528).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108367.

References

Bowe, B., Xie, Y., Li, T., Yan, Y., Xian, H., Al-Aly, Z., 2017. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: A cohort study. Lancet Planet Health 1, e267–e276.

Bowe, B., Xie, Y., Li, T., Yan, Y., Xian, H., Al-Aly, Z., 2018. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. J Am Soc Nephrol 29, 218–230.

Cai, M., Wei, J., Zhang, S., Liu, W., Wang, L., Qian, Z., Lin, H., Liu, E., McMillin, S.E., Cao, Y., Yin, P., 2023. Short-term air pollution exposure associated with death from kidney diseases: A nationwide time-stratified case-crossover study in China from 2015 to 2019. BMC Med 21, 32.

Chade, A.R., 2013. Renal vascular structure and rarefaction. Compr Physiol 3, 817–831.

Chen, Y., Cao, F., Xiao, J.P., Fang, X.Y., Wang, X.R., Ding, L.H., Wang, D.G., Pan, H.F., 2021. Emerging role of air pollution in chronic kidney disease. Environ Sci Pollut Res Int 28, 52610–52624.

Chu, L., Chen, K., Di, Q., Crowley, S., Dubrow, R., 2023. Associations between short-term exposure to PM(2.5), NO(2) and O(3) pollution and kidney-related conditions and

the role of temperature-adjustment specification: A case-crossover study in New York state. Environ Pollut 328, 121629.
Gasparrini, A., 2021. The Case time series design. Epidemiology 32, 829–837.
Gasparrini, A., 2022. A tutorial on the case time series design for small-area analysis. BMC Med Res Methodol 22, 129.
Gasparrini, A., Armstrong, B., Kenward, M.G., 2010. Distributed lag non-linear models. Stat Med 29, 2224–2234.
Gasparrini, A., Guo, Y., Hashizume, M., Lavigne, E., Zanobetti, A., Schwartz, J., Tobias, A., Tong, S., Rocklov, J., Forsberg, B., Leone, M., De Sario, M., Bell, M.L., Guo, Y.L., Wu, C.F., Kan, H., Yi, S.M., de Sousa Zanotti Stagliorio Coelho, M., Saldiva, P.H., Honda, Y., Kim, H., Armstrong, B., 2015. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. Lancet 386, 369–375.
Gasparrini, A., Leone, M., 2014. Attributable risk from distributed lag models. BMC Med. Res. Method. 14, 55.
He, P., Chen, R., Zhou, L., Li, Y., Su, L., Dong, J., Zha, Y., Lin, Y., Nie, S., Hou, F.F., Xu, X., 2022. Higher ambient nitrogen dioxide is associated with an elevated risk of hospital-acquired acute kidney injury. Clin Kidney J 15, 95–100.
Hsu, S., Bi, J., de Boer, I.H., 2023. Invited perspective: Still Hazy? Air pollution and acute kidney injury. Environ Health Perspect 131, 41302.
Hystad, P., Larkin, A., Rangarajan, S., AlHabib, K.F., Avezum, A., Calik, K.B.T., Chifamba, J., Dans, A., Diaz, R., du Plessis, J.L., Gupta, R., Iqbal, R., Khatib, R., Kelishadi, R., Lanas, F., Liu, Z., Lopez-Jaramillo, P., Nair, S., Poirier, P., Rahman, O., Rosengren, A., Swidan, H., Tse, L.A., Wei, L., Wielgosz, A., Yeates, K., Yusoff, K., Zatonski, T., Burnett, R., Yusuf, S., Brauer, M., 2020. Associations of outdoor fine particulate air pollution and cardiovascular disease in 157 436 individuals from 21 high-income, middle-income, and low-income countries (PURE): A prospective cohort study. Lancet Planet Health 4, e235–e245.
Kellum, J.A., Romagnani, P., Ashuntantang, G., Ronco, C., Zarbock, A., Anders, H.J., 2021. Acute kidney injury. Nat Rev Dis Primers 7, 52.
Lee, W., Prifti, K., Kim, H., Kim, E., Yang, J., Min, J., Park, J.Y., Kim, Y.C., Lee, J.P., Bell, M.L., 2022. Short-term exposure to air pollution and attributable risk of kidney diseases: A nationwide time-series study. Epidemiology 33, 17–24.
Lee, W., Wu, X., Heo, S., Kim, J.M., Fong, K.C., Son, J.Y., Sabath, M.B., Trisovic, A., Braun, D., Park, J.Y., Kim, Y.C., Lee, J.P., Schwartz, J., Kim, H., Dominici, F., Al-Aly, Z., Bell, M.L., 2023. Air pollution and acute kidney injury in the U.S. medicare population: A longitudinal cohort study. Environ Health Perspect 131, 47008.
Li, D., Li, Y., Li, G., Zhang, Y., Li, J., Chen, H., 2019. Fluorescent reconstitution on deposition of PM(2.5) in lung and extrapulmonary organs. Proc Natl Acad Sci U S A 116, 2488–2493.
Malhotra, R., Bouchard, J., Mehta, R.L., 2019. Community- and hospital-acquired acute kidney injury. Crit. Care Nephrology.
Miller, M.R., Raftis, J.B., Langrish, J.P., McLean, S.G., Samutrtai, P., Connell, S.P., Wilson, S., Vesey, A.T., Fokkens, P.H.B., Boere, A.J.F., Krystek, P., Campbell, C.J., Hadoke, P.W.F., Donaldson, K., Cassee, F.R., Newby, D.E., Duffin, R., Mills, N.L., 2017. Inhaled nanoparticles accumulate at sites of vascular disease. ACS Nano 11, 4542–4552.
Patschan, D., Muller, G.A., 2016. Acute Kidney Injury in Diabetes Mellitus. Int J Nephrol 2016, 6232909.
Singbartl, K., Kellum, J.A., 2012. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 81, 819–825.
Tavallali, P., Gharibi, H., Singhal, M., Schweizer, D., Cisneros, R., 2020. A multi-pollutant model: a method suitable for studying complex relationships in environmental epidemiology. Air Qual. Atmos. Health 13, 645–657.
Wang, Y., Liu, Z., Yang, L., Zhou, J., Li, J., Liao, H.L., Tian, X.J., 2021. Sepsis-related hospital admissions and ambient air pollution: A time series analysis in 6 Chinese cities. BMC Public Health 21, 1182.
Wei, Y., Wang, Y., Di, Q., Choirat, C., Wang, Y., Koutrakis, P., Zanobetti, A., Dominici, F., Schwartz, J.D., 2019. Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: Time stratified, case crossover study. BMJ 367, l6258.