Supplementary Materials

Title

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

Authors

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Table of Contents

1. Data collection details

The dataset has been collected from the Multi-City Multi-Country (MCC) Collaborative Research Network (https://mccstudy.lshtm.ac.uk/) which is an international collaboration of research teams working on a program aiming to produce epidemiological evidence on associations between environmental stressors, climate, and health. Data obtained for this study includes daily time-series of AKI-related mortality, mean concentration of three air pollutants ($PM_{2.5}$, O_3, and NO_2) and mean temperature for 136 cities of 6 countries (Canada, Japan, Portugal, South Korea, Taiwan, and UK). Here we provide detailed data source from six countries.

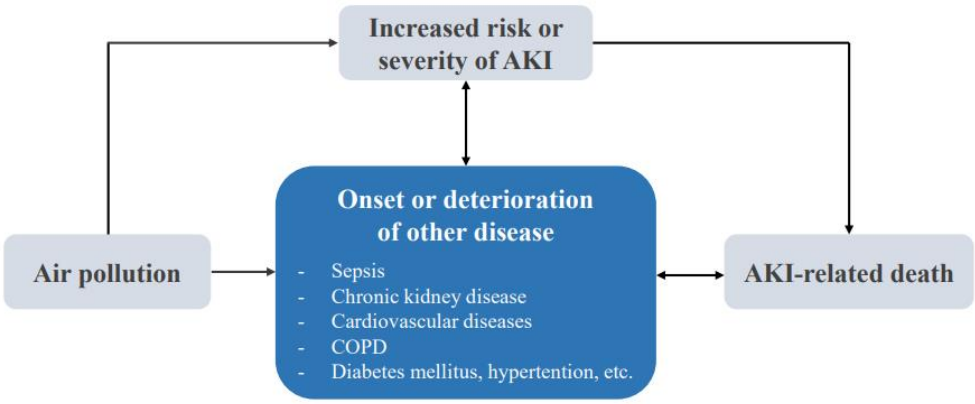
Country	Mortality	Air pollutant	Temperature
Canada	Statistics Canada	National Air Pollution Surveillance (NAPS) network of Environment Canada	Environment Canada
Japan	Ministry of Health, Labor and Welfare, Japan	Ministry of Environment of Japan	Japan Meteorological Agency
Portugal	Statistics Portugal	Online database of air quality through Portuguese Environment Agency	National Oceanic and Atmospheric Administration
South Korea	Korea National Statistics Office	Ministry of Environment of Korea	Korean Meteorological Office
Taiwan	Department of Health, Taiwan	Urban monitors of the local monitoring network, Taiwan	Central Weather Bureau of Taiwan
UK	Office for National Statistics, UK	UK Air Quality Archive	Meteorological Department of British Atmospheric Data Centre

The study periods differed by country and air pollutants, ranging from 1987 to 2018. Follow is detailed study period for each air pollutant by country.

	Study period			Overall study period
	$PM_{2.5}$	O3	NO_2	
Canada	1997–2015	1987–2015	1987–2015	1987–2015
Japan	2012–2015	2011–2015	2011–2015	2011–2015
Portugal	2005–2018	2005–2018	2005–2018	2005–2018
South Korea	2015–2018	2002–2018	2002–2018	2002–2018
Taiwan	2008–2016	2008–2016	2008–2016	2008–2016
UK	2000–2016	2000–2016	2000–2016	2000–2016
Overall	1997–2018	1987–2018	1987–2018	1987–2018

2. Plausible pathways between air pollution and AKI-related death

The following figure shows the plausible pathways of the association between air pollution and AKI-related death. Exposure to air pollution can lead to AKI-related death through 1) increased risk or severity of AKI and/or 2) onset or deterioration of other diseases (Lee et al., 2023; Singbartl and Kellum, 2012). Inhaled air pollutants rapidly reach the kidney via systematic circulation and reduce glomerular filtration rate (GFR) by promoting oxidative stress, inflammation, and DNA damage to kidney tissue, which may increase the risk of new AKI or the severity of underlying AKI, leading to AKI-related death (Chade, 2013; Chen et al., 2021; Miller et al., 2017). On the other hand, air pollution can occur or deteriorate other diseases such as sepsis, chronic kidney disease, cardiovascular diseases, COPD, diabetes mellitus, hypertension which are the major risk factor of AKI deaths (Hsu et al., 2023; Hystad et al., 2020; Patschan and Muller, 2016; Singbartl and Kellum, 2012; Wang et al., 2021). The pathway through the other diseases may take more time to get from air pollution to AKI-related death than the pathways through increased risk or severity of AKI. Therefore, to consider these several pathways between air pollution and AKI-related death, this study examined the association for four weeks which is relatively longer lag period than previous studies (Cai et al., 2023; Lee et al., 2022; Wei et al., 2019).



3. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	page 2 (Title)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	page 5 (Abstract)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 7 (Introduction)
Objectives	3	State specific objectives, including any prespecified hypotheses	page 8 (Introduction)
Methods			
Study design	4	Present key elements of study design early in the paper	page 9 (Methods – Study population and design)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 9 (Methods – Study population and design)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	NA.
		(*b*) *Cohort study*—For matched studies, give matching criteria and	NA.

		number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 9-10 (Methods – Study population and design)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supplementary Materials 1. Data collection details
Bias	9	Describe any efforts to address potential sources of bias	page 12 (Methods-Sensitivity analysis)
Study size	10	Explain how the study size was arrived at	page 9 (Methods – Study population and design)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 10 (Methods – Statistical analysis)
		(*b*) Describe any methods used to examine subgroups and interactions	page 11 (Methods – Statistical analysis)
		(*c*) Explain how missing data were addressed	NA.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable,	NA.

	describe analytical methods taking account of sampling strategy	
	(*e*) Describe any sensitivity analyses	page 12 (Methods – Sensitivity analysis)

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	page 12 (Results-Descriptive statistics)
		(b) Give reasons for non-participation at each stage	NA.
		(c) Consider use of a flow diagram	NA.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	page 12-13 (Results), & Table 1 and Figure 1
		(b) Indicate number of participants with missing data for each variable of interest	NA.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA.
		Cross-sectional study—Report numbers of outcome events or summary measures	NA.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	page 13-14 (Results), Table 2-3
		(*b*) Report category boundaries when continuous variables were categorized	NA.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	page 13-14 (Results), & Table S1-S3, Figure S1-S2

Discussion			
Key results	18	Summarise key results with reference to study objectives	page 15 (Discussion)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	page 17-18 (Discussion)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	page 18 (Discussion)
Generalisability	21	Discuss the generalisability (external validity) of the study results	page 18 (Discussion)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

4. Attributable fraction and number

Epidemiological studies usually present the effect estimates based on *ratio measures*, relative risk (RR) in this study. Although these measures are ideal for summarizing the association of interest, they offer limited information on the actual (socio-economic) impact of the exposure, which is critical for the planning and evaluation of public health intervention (Gasparrini and Leone, 2014). To evaluate the burden of the exposure, it is better to provide *excess measures* such as attributable fraction and attributable number. The theoretical nature of these measures is based on a counterfactual, where the observed condition is compared with a reference state which never occurred. This state postulates that the same population is followed in an identical situation where only the exposure level changes to the reference value (Gasparrini and Leone, 2014). In this study, we calculated fraction and number of attributable death of AKI due to noncompliance with 2021 WHO air quality guidelines, and attributable death can defined as mortality that are attributable to air pollution (von Cube et al., 2020). Here 'attributable' implies the deaths that would not have occurred had concentration of air pollution remain below the guidelines.

Calculation of attributable death

A general definition of the attributable fraction (AF) and number (AN) for a given exposure x can be provided by:

$$AF_x = 1 - \exp(-\beta_x) \text{ and } AN_x = n \cdot AF_x$$

with n as the total number of cases (Steenland and Armstrong, 2006). In this study, as we applied a distributed lag model (DLM), this framework needs to be considered to define attributable risk measures. The idea is to treat the associations with exposures at different lags as independent contributions to the risk (Gasparrini and Leone, 2014). The fraction and number of AKI death attributable to air pollution concentration x_t above the 2021 WHO air quality guidelines for a given day t in the series can be provided by:

$$AF_{x,t} = 1 - \exp(-\sum_{l=l_0}^{L} \beta_{x_t,l}) \text{ and } AN_{x,t} = AF_{x,t} \cdot \sum_{l=l_0}^{L} \frac{n_{t+l}}{L-l_o+1}$$

with L as the maximum lag period (here 28 days), $\sum \beta_{x_t,l}$ as the overall cumulative log-relative risk for air pollution concentration x_t above the guidelines in day t, and n_t as the number of AKI-related death in day t.

5. Supplementary table and figures

Table S1. Two-pollutant models for the association between air pollution and AKI-related death based on two-pollutant models; RR (95% CI)[a]

	$PM_{2.5}$	O_3[b]	NO_2
+ $PM_{2.5}$[c]	-	1.035 (0.995, 1.076)	1.021 (0.959, 1.087)
+ O_3	1.047 (0.992, 1.104)	-	1.035 (0.991, 1.080)
+ NO_2	1.040 (0.984, 1.098)	1.021 (0.993, 1.050)	-

[a]RRs 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, after adjusting (+) for other air pollutants.
[b]Ozone in warm season (April to September) for the daily 8-hour maximum.
AKI=acute kidney injury; CI=confidence interval; RR=relative risk

Table S2. Sensitivity analysis for the association between air pollution and AKI-related death based on lag periods, model parameter specification, and temperature adjustment; RR (95% CI)[a]

	$PM_{2.5}$	O_3[b]	NO_2
Main model[c]	1.052 (1.003, 1.103)	1.022 (0.994, 1.050)	1.022 (0.982, 1.063)
Up to 21 lag days	1.031 (0.993, 1.069)	1.008 (0.986, 1.031)	1.009 (0.978, 1.041)
Up to 35 lag days	1.059 (0.999, 1.122)	1.019 (0.985, 1.054)	1.021 (0.974, 1.072)
Three knots at equally spaced log values	1.054 (1.005, 1.106)	1.023 (0.995, 1.051)	1.022 (0.983, 1.064)
Without temperature adjustment	1.049 (1.001, 1.099)	1.023 (0.995, 1.051)	1.021 (0.982, 1.061)

[a]RRs 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.

[b]Ozone in warm season (April to September) for the 8-hour maximum.

[c]Unless otherwise specified, the model considered the lag structure up to 28 days with three knots at 7, 14, and, 21 days and daily mean temperature was adjusted for in the model.

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

Table S3. Attributable number and fraction of AKI-related mortality due to air pollutant levels above the 2021 WHO air quality guidelines during the study period

	Attributable number (#)			Attributable fraction (%)		
	$PM_{2.5}$	O_3[a]	NO_2	$PM_{2.5}$	O_3[a]	NO_2
Canada	24.5	115.1	497.1	0.4	8.3	4.2
Japan	266.6	961.4	740.5	1.4	3.9	11.3
Portugal	7.2	60.0	86.2	0.5	5.8	9.7
South Korea	242.8	8.9	462.1	2.6	5.0	0.2
Taiwan	214.0	2.1	92.1	9.1	3.9	0.2
UK	29.2	38.2	281.8	0.9	8.5	2.5
Overall	784.6	1185.7	2161.3	1.9	6.3	5.2

Note: 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

[a]Ozone in warm season (April to September) for the 8-hour maximum.

AKI=acute kidney injury.

Figure S1. Lag-distributed association between NO_2 and AKI-related death for 35 days. RR (with 95% CI, shaded light blue) is presented as the value for 10 μg/m^3 increase in NO_2. AKI=acute kidney injury; CI=confidence interval; RR=relative risk.

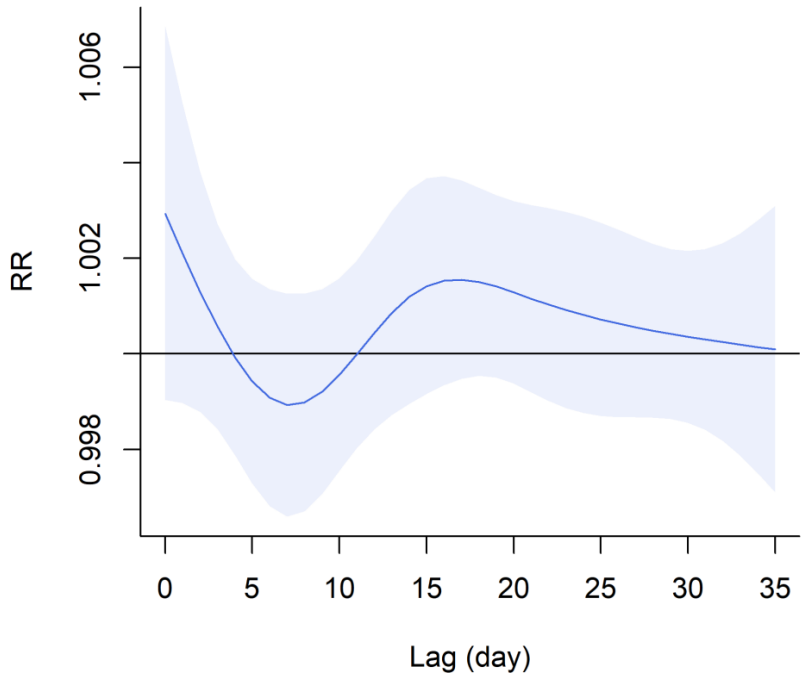


Figure S2. Lag-distributed association between air pollution and AKI-related death by country. RRs (with 95% CI, shaded light blue) for $PM_{2.5}$, O_3, and NO_2 are presented as the value for 5, 10, and 10 μg/m^3 increase in each air pollutant, respectively. RR for ozone is based on the maximum 8-hour averaged-ozone in warm season (April to September). AKI=acute kidney injury; CI=confidence interval; RR=relative risk.

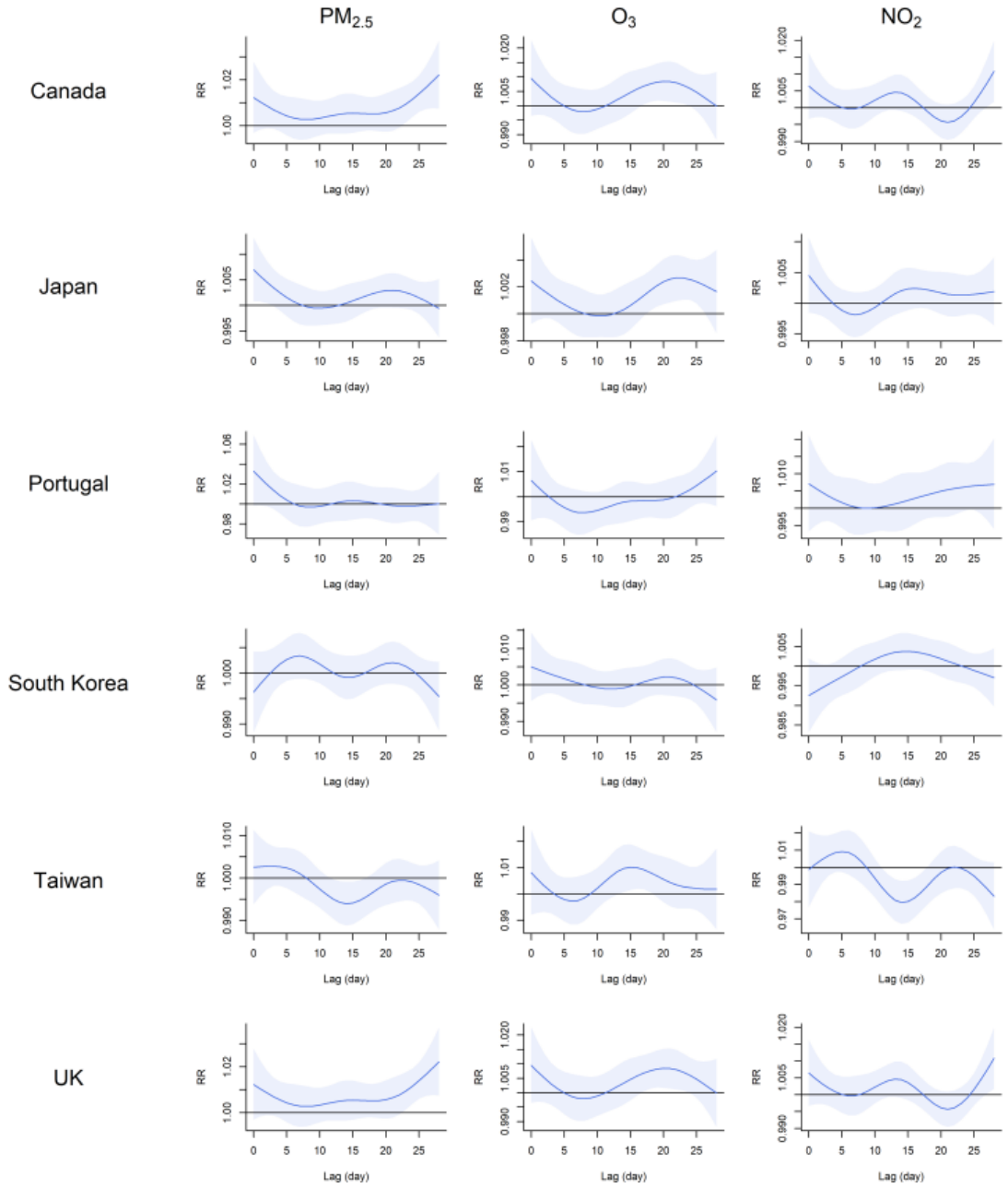
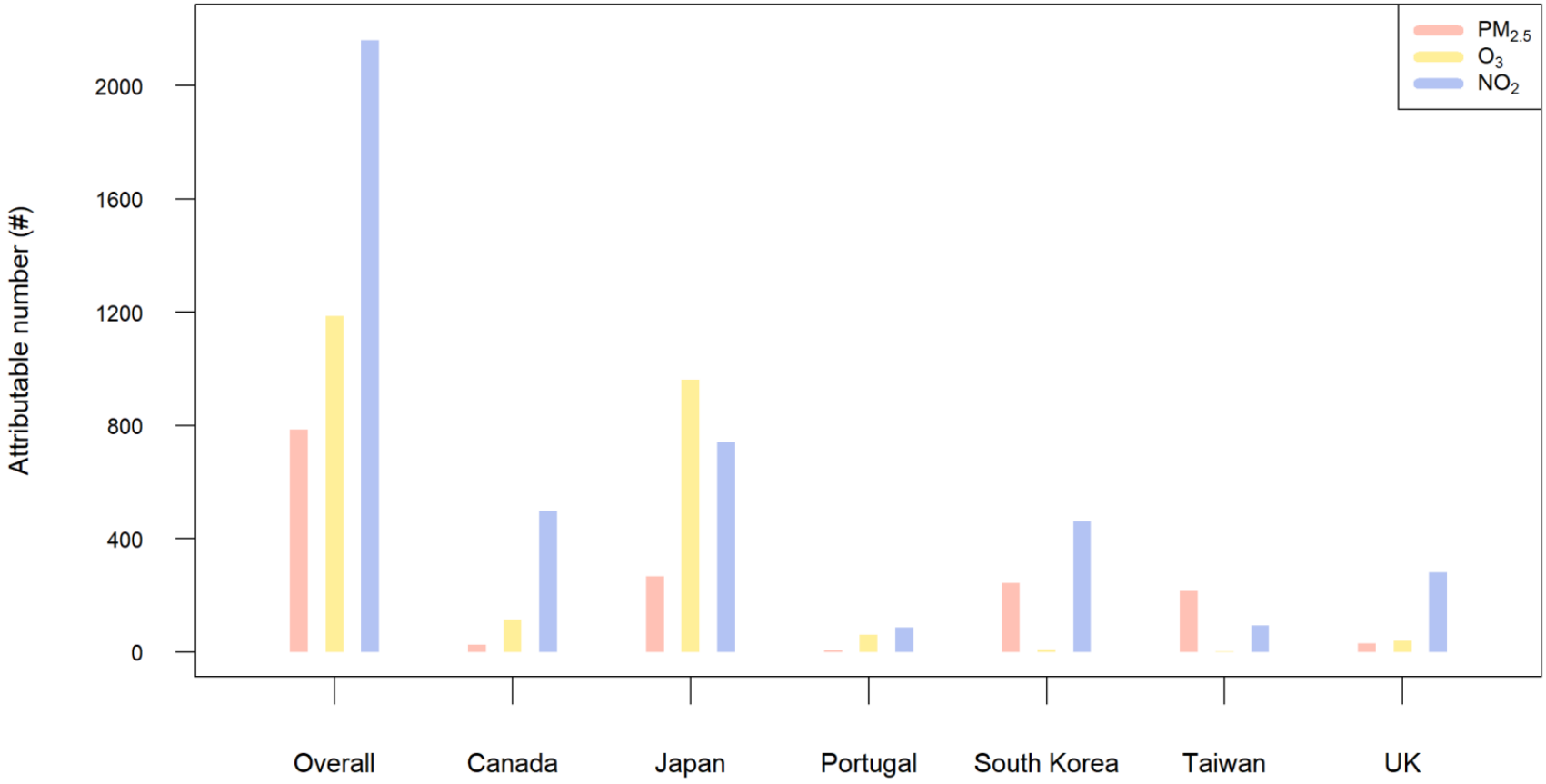


Figure S3. Attributable number of AKI-related mortality due to air pollutant levels above the 2021 WHO air quality guidelines during the study period. 2021 WHO air quality guidelines—24-hour average $PM_{2.5}$: 15 μg/m^3 and NO_2: 25 μg/m^3; maximum 8-hour average O_3: 100 μg/m^3. Estimates for ozone are based on the maximum 8-hour averaged-ozone in warm season (April to September). AKI=acute kidney injury.



6. References for the supplementary materials

Cai, M.; Wei, J.; Zhang, S.; Liu, W.; Wang, L.; Qian, Z.; Lin, H.; Liu, E.; McMillin, S.E.; Cao, Y.; Yin, P. 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 2023;21:32

Chade, A.R. Renal vascular structure and rarefaction. Compr Physiol 2013;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. Emerging role of air pollution in chronic kidney disease. Environ Sci Pollut Res Int 2021;28:52610-52624

Gasparrini, A.; Leone, M. Attributable risk from distributed lag models. BMC Medical Research Methodology 2014;14:55

Hsu, S.; Bi, J.; de Boer, I.H. Invited Perspective: Still Hazy? Air Pollution and Acute Kidney Injury. Environ Health Perspect 2023;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. 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 2020;4:e235-e245

Lee, W.; Prifti, K.; Kim, H.; Kim, E.; Yang, J.; Min, J.; Park, J.Y.; Kim, Y.C.; Lee, J.P.; Bell, M.L. Short-term Exposure to Air Pollution and Attributable Risk of Kidney Diseases: A Nationwide Time-series Study. Epidemiology 2022;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. Air Pollution and Acute Kidney Injury in the U.S. Medicare Population: A Longitudinal Cohort Study. Environ Health Perspect 2023;131:47008

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. Inhaled Nanoparticles Accumulate at Sites of Vascular Disease. ACS Nano 2017;11:4542-4552

Patschan, D.; Muller, G.A. Acute Kidney Injury in Diabetes Mellitus. Int J Nephrol 2016;2016:6232909

Singbartl, K.; Kellum, J.A. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 2012;81:819-825

Steenland, K.; Armstrong, B. An overview of methods for calculating the burden of disease due to specific risk factors. Epidemiology 2006;17:512-519

von Cube, M.; Timsit, J.F.; Schumacher, M.; Motschall, E.; Schumacher, M. Quantification and interpretation of attributable mortality in core clinical infectious disease journals. Lancet Infect Dis 2020;20:e299-e306

Wang, Y.; Liu, Z.; Yang, L.; Zhou, J.; Li, J.; Liao, H.L.; Tian, X.J. Sepsis-related hospital admissions and ambient air pollution: a time series analysis in 6 Chinese cities. BMC Public Health 2021;21:1182

Wei, Y.; Wang, Y.; Di, Q.; Choirat, C.; Wang, Y.; Koutrakis, P.; Zanobetti, A.; Dominici, F.; Schwartz, J.D. Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case crossover study. BMJ

2019;367:l6258