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Prolonged exposure to air pollution and risk of acute kidney injury and related mortality: a prospective cohort study based on hospitalized AKI cases and general population controls from the UK Biobank

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Abstract

Background Previous investigations identified a connection between air pollution and kidney diseases. Nevertheless, there is a lack of comprehensive evidence on the long-term risks posed by air pollution with respect to acute kidney injury (AKI) and AKI-related death.

Methods This prospective cohort analysis included 414,885 UK Biobank (UKB) participants who did not exhibit AKI at the study's outset. AKI was defined based on ICD-10 codes recorded for hospitalized patients. Cox proportional hazards models were used to assess the association between prolonged exposure to air pollutants (particulate matter with diameters of 2.5 micrometers or less ($PM_{2.5}$), between 2.5 and 10 micrometers ($PM_{2.5-10}$), and 10 micrometers or less (PM_{10}), along with nitrogen dioxide (NO_2) and nitrogen oxides (NO_x)) and the risk of AKI and AKI-related death, adjusting for potential confounders including sex, age, ethnicity, education, income, lifestyle factors, and relevant clinical covariates. Restricted cubic splines were applied to evaluate non-linear dose-response relationships, and stratified analyses were performed to explore potential effect modification across subgroups.

Results Over an average follow-up duration of 11.7 years, 14,983 cases of AKI and 326 cases of AKI-related death were diagnosed. Quartile analysis showed individuals exposed to higher levels of these air pollutants had a significantly higher risk of developing AKI and AKI-related death compared to those in the lowest quartile (all $P < 0.05$). The RCS curves depicting the relationship between $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, NO_x, and the risk of AKI showed a significant departure from linearity ($P_{\text{for non-linearity}} < 0.05$), while the relationships between $PM_{2.5}$, NO_2, NO_x, and the risk of AKI-related death did not exhibit a significant departure from linearity ($P_{\text{for non-linearity}} > 0.05$). Sensitivity analyses confirmed the robustness of our findings.

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Conclusion Our study reveals a direct association between prolonged air pollution exposure and elevated risks of both AKI and AKI-related death. These findings offer scientific validation for the adoption of environmental and public health measures directed towards the reduction of air pollution. Such initiatives could potentially ease the impact associated with AKI and AKI-related death.

Keywords Air pollution, $PM_{2.5}$, NO_2, AKI, AKI-related death

Introduction

Acute kidney injury (AKI), previously termed acute renal failure, is marked by a swift decline in kidney function [1]. This condition frequently affects patients in intensive care units, with a prevalence rate ranging from 20 to 50% [2]. Moreover, AKI is intricately linked to the development and progression of chronic kidney disease (CKD) and end-stage renal disease (ESRD). The global mortality rate associated with AKI is higher than that of conditions like diabetes or heart failure, underlining its significant public health impact [3]. Despite advances in medical treatment, AKI remains associated with long-term health consequences, and identifying preventable risk factors is critical to reducing its incidence and mortality.

Epidemiological evidence indicates a strong link between air pollution exposure and the prevalence of kidney diseases [4, 5]. The kidneys, being a highly vascularized organ, facilitate the rapid translocation of inhaled air pollutants through systemic circulation, thereby promoting inflammatory responses and oxidative stress in the renal tissue [6]. Numerous studies have consistently shown that air pollution elevated the risk of developing CKD and its progression to ESRD [7–10]. Maladaptive repairs following repeated episodes of AKI stands out as a substantial pathological element fostering the development of CKD [11, 12]. However, research specifically addressing the long-term effects of air pollution on AKI is limited. Most existing studies are either retrospective or based on small sample sizes, which limits their generalizability. While one large prospective study has explored the association between air pollution and AKI, it was conducted exclusively within an American cohort and did not examine AKI-related death [13].

Given the growing evidence linking air pollution to chronic diseases, it is essential to investigate its role in the onset of AKI, a critical and potentially reversible condition. AKI is a key precursor to CKD, and maladaptive repairs following repeated episodes of AKI can contribute to CKD progression. The absence of large-scale, ethnically diverse prospective studies in this area represents a critical gap in the literature. Additionally, there is a pressing need to explore how air pollution exposure might contribute to AKI-related mortality, providing a comprehensive understanding of the full scope of health risks posed by air pollutants.

Particulate matter (PM) is categorized based on its aerodynamic diameter, which influences how deeply particles can penetrate the respiratory system and enter systemic circulation. $PM_{2.5}$ refers to particles with diameters of 2.5 micrometers or less, which can penetrate deep into the lungs and are often associated with adverse health outcomes. $PM_{2.5\text{-}10}$ includes particles with diameters between 2.5 and 10 micrometers, which are inhaled into the upper respiratory tract but may still reach the lungs. PM_{10} encompasses all particles with diameters of 10 micrometers or less. Prior studies have shown that smaller particles, such as $PM_{2.5}$, are more likely to penetrate the respiratory system and enter systemic circulation, potentially leading to greater adverse health effects, including AKI [13, 14]. In this prospective cohort study, we leveraged UK Biobank (UKB) data to investigate the connection between prolonged air pollution exposure – including $PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, NO_2 and NO_x – and the risk of AKI and AKI-related death. Our study fills critical gaps in the existing literature by analyzing both AKI incidence and mortality in a large, diverse UK population. We hypothesize that prolonged exposure to these air pollutants is associated with an increased risk of AKI and AKI-related death. The findings of this study have important implications for public health policy and efforts to mitigate the harmful effects of air pollution on kidney health.

Methods

Study design

UKB enrolled a participant pool exceeding 0.5 million individuals aged 40–69 years between 2006 and 2010 from various centers across England, Scotland, and Wales [15]. The recruitment strategy was designed to ensure geographical diversity, with participants drawn from urban and rural areas throughout the UK, representing a wide range of living environments. During the enrollment phase, participants engaged in touchscreen surveys, underwent anthropometric assessments, and contributed biological samples. Previous studies have comprehensively outlined the methodologies employed for data collection [15, 16]. All participants provided written consent, and the UKB study was approved by the local ethics committee [15]. Our study was executed under project number 93,044.

In the present study involving 502,387 participants, individuals diagnosed with AKI at or before recruitment (n=4,438) were excluded. Furthermore, we excluded those with incomplete air pollution data (n=40,972) and

other missing information ($n=42,092$), resulting in a final cohort of 414,885 individuals (Fig. 1).

Assessment of AKI and AKI-related death

We identified AKI cases using verified hospital admission records and ICD-10 codes: N17.0 (tubular necrosis), N17.1 (acute cortical necrosis), N17.2 (medullary necrosis), N17.8 (other types), and N17.9 (unspecified). AKI-related death was defined based on ICD-10 codes N17.0 (death caused by AKI with tubular necrosis) and N17.9 (death caused by unspecified AKI). A prior study conducted by the UKB assessed the accuracy of ICD-10 code N17 in identifying AKI, using the KDIGO guidelines as a benchmark. This evaluation showed a 95% positive predictive rate [17]. Calculations for the follow-up duration commenced from the initial evaluation date, reaching its conclusion at the earliest of the subsequent events: death, diagnosis of AKI, the date when follow-up was lost, or the termination of the follow-up period.

Assessment of air pollutants

As previously reported in the literature [18, 19], the LUR (land-use regression) model was used to evaluate the annual mean concentrations of air pollutants. This model integrates data from Geographic Information System to capture spatial variations in annual ambient air pollutant concentrations, considering factors like population density, traffic flow, topography, and land use. Associating air pollution data with individual records was accomplished by matching each participant's residential address, as provided during the baseline visit. The efficacy of the LUR model was examined through the leave-one-out cross-validation method, which provided R^2 values of 77%, 88%, 87%, and 88% for $PM_{2.5}$, PM_{10}, NO_2, and NO_x, respectively. Comprehensive data for $PM_{2.5}$, PM_{10}, and NO_x were available exclusively for the year 2010. However, data for NO_2 and PM_{10} were available for multiple years, including 2007 and 2010 for PM_{10}, and 2005, 2006, 2007, and 2010 for NO_2.

Assessment of covariates

Demographic and lifestyle factors such as age, sex, ethnicity, education level, average household income, smoking habits, and alcohol use were collected through a series of touchscreen questionnaires and in-person interviews conducted by trained research workers [15]. In contrast, clinical measurements, including BMI (kg/m^2), hypertension (ICD-10 code: I10), type 2 diabetes mellitus (T2DM, ICD-10 code: E11), type 1 diabetes mellitus (T1DM, ICD-10 code: E10), CKD (ICD-10 code: N18), atherosclerosis (ICD-10 code: I70), use of medication including nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin, ibuprofen, naproxen, celecoxib, indomethacin, meloxicam and diclofenac), angiotensin-converting enzyme inhibitors (ACEIs, including enalapril, lisinopril, benazepril, captopril and ramipril) and angiotensin II receptor blockers (ARBs, including losartan, valsartan, irbesartan, candesartan and telmisartan), and laboratory test results for creatinine, urate, BUN, total cholesterol, triglycerides, and C-reactive protein (CRP), were obtained from medical records and laboratory analyses.

Statistical analysis

The Kolmogorov–Smirnov test was applied to assess the distribution of the variables (Table S1). Baseline characteristics for continuous data were described as mean with standard deviation (SD) or median with interquartile range (IQR), while categorical data were summarized as percentages. No weighting was applied to the UKB data, as the cohort was not designed to be fully representative of the general population. We used a Cox proportional hazards regression model to assess the risk of AKI and AKI-related death in relation to prolonged exposure to air pollutants, controlling for covariates across three distinct models. Sex, age and ethnicity was adjusted in Model (1) Educational level, average household income, smoking habits, and alcohol use were further adjusted in Model (2) BMI, hypertension, T2DM, T1DM, CKD, atherosclerosis, use of medication including NSAIDs, ACEIs and ARBs, creatinine, urate, BUN, total cholesterol, triglyceride and CRP were further adjusted in Model (3) To assess potential multicollinearity among the explanatory variables, we performed a Variance Inflation Factor (VIF) analysis [20, 21]. The VIF quantifies how much the variance of a regression coefficient is inflated due to multicollinearity. According to standard guidelines, a VIF value greater than 10 indicates high multicollinearity, while values between 1 and 5 suggest moderate multicollinearity.

Moreover, adjusted Cox regression models with restricted cubic splines (RCS) were used to evaluate the dose-response relationship between air pollution exposure and AKI risk. Additionally, we used adjusted Cox regression models to develop RCS models, evaluating the dose−response relationship between air pollutants exposure and the risk of AKI. RCS allows for non-linear effects while maintaining smoothness in the function, which is particularly important in environmental epidemiology where the relationships between exposure and outcome may not be strictly linear. This approach enhances our ability to capture potential variations in risk across different levels of exposure. Automatic determination of node values during model fitting ensured an optimal capture of the nonlinear features in the data. Stratified analyses were conducted based on age, sex, BMI, educational attainment, and smoking habits to explore potential modification effects. Interaction effects were examined by introducing interaction terms between air pollution variables and stratification variables into the

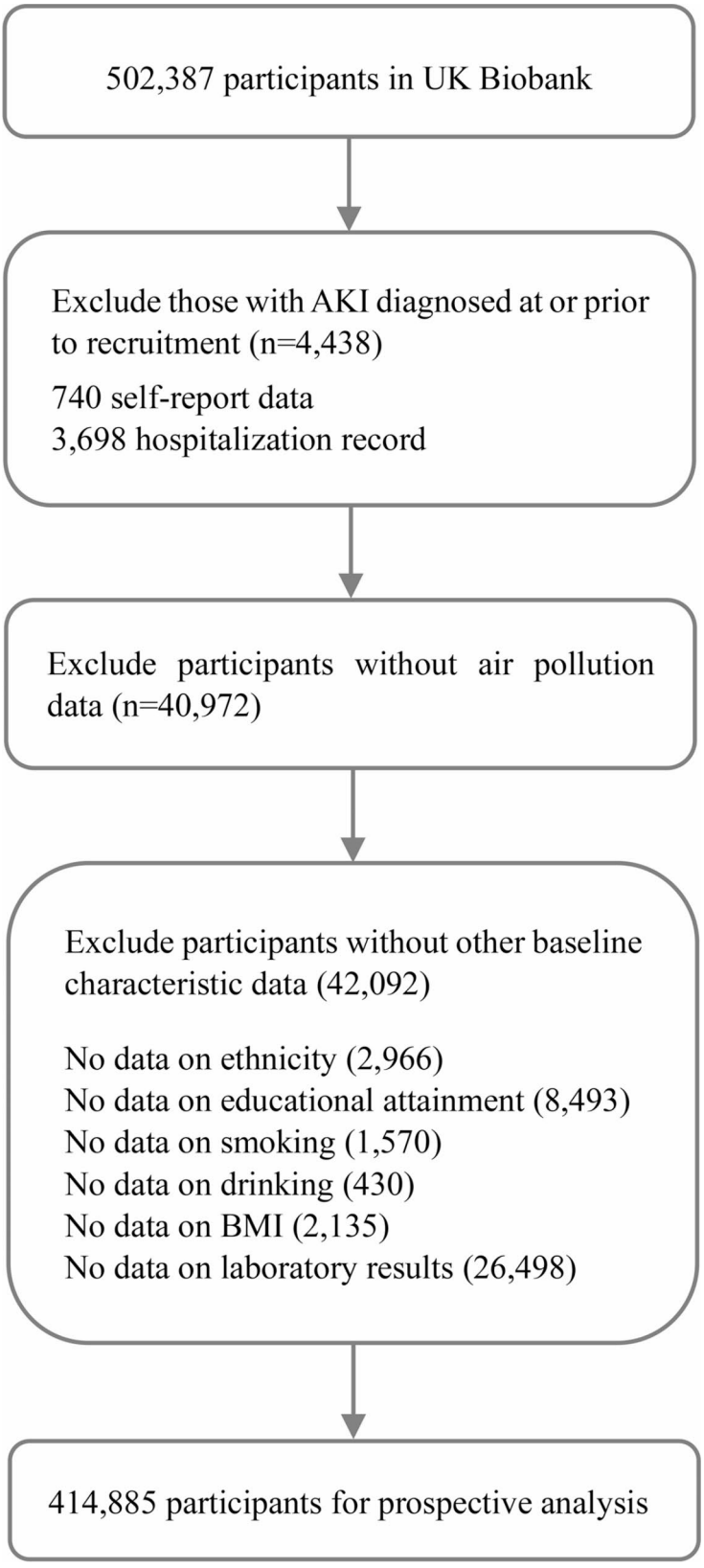

Fig. 1 Flowchart of UK Biobank participants included for final analysis

Table 1 Baseline characteristics of participants in the UK Biobank study

Characteristics	Total population	AKI			AKI-related mortality		
	(*n* = 414,885)	No (*n* = 399,902)	Yes (*n* = 14,983)	*P*	No (*n* = 414,559)	Yes (*n* = 326)	*P*
Age at enrollment, years, mean (SD)	56.5 (8.1)	56.3 (8.1)	61.5 (6.4)	< 0.001	56.5 (8.1)	63.4 (5.1)	< 0.001
Sex, n (%)				< 0.001			< 0.001
Male	189,429 (45.66)	180,207 (45.06)	9,222 (61.55)		189,209 (45.64)	220 (67.48)	
Female	225,456 (54.34)	219,695 (54.94)	5,761 (38.45)		225,350 (54.36)	106 (32.52)	
Ethnicity, n (%)				< 0.001			< 0.001
White	393,922 (94.95)	379,705 (94.95)	14,217 (94.89)		393,604 (94.95)	318 (97.55)	
Asian or Asian British	9,811 (2.36)	9,460 (2.37)	351 (2.34)		9,804 (2.36)	7 (2.15)	
Black or Black British	6,582 (1.59)	6,303 (1.58)	279 (1.86)		6,582 (1.59)	0 (0)	
Other	4,570 (1.10)	4,434 (1.11)	136 (0.91)		4,569 (1.10)	1 (0.31)	
Educational attainment, n (%)				< 0.001			< 0.001
College/university degree	134,078 (32.32)	130,805 (32.71)	3,273 (21.84)		134,026 (32.33)	52 (15.95)	
A/AS levels or equivalent or O levels/ GCSE or CSE or equivalent	161,621 (38.96)	156,750 (39.20)	4,871 (32.51)		161,512 (38.96)	109 (33.44)	
NVQ or HND or HNC or equivalent or other professional qualifications	49,237 (11.87)	47,002 (11.75)	2,235 (14.92)		49,189 (11.87)	48 (14.72)	
Other	69,949 (16.86)	65,345 (16.34)	4,604 (30.73)		69,832 (16.84)	117 (35.89)	
Average total household income				< 0.001			< 0.001
< 18,000	79,899 (19.26)	74,955 (18.74)	4,944 (33.00)		79,749 (19.24)	150 (46.01)	
18,000–30,999	91,426 (22.04)	88,018 (22.01)	3,408 (22.75)		91,348 (22.03)	78 (23.93)	
31,000–51,999	93,700 (22.58)	91,243 (22.82)	2,457 (16.40)		93,665 (22.59)	35 (10.74)	
52,000-100,000	73,122 (17.62)	71,838 (17.96)	1,284 (8.57)		73,112 (17.64)	10 (3.07)	
> 100,000	19,370 (4.67)	19,087 (4.77)	283 (1.89)		19,369 (4.67)	1 (0.31)	
Other	57,368 (13.83)	54,761 (13.69)	2,607 (17.40)		57,316 (13.83)	52 (15.95)	
Smoking, n (%)				< 0.001			< 0.001
Never	227,595 (54.86)	221,402 (55.36)	6,193 (41.33)		227,494 (54.88)	101 (30.98)	
Previous	144,842 (34.91)	138,405 (34.61)	6,437 (42.96)		144,678 (34.90)	164 (50.31)	
Current	42,448 (10.23)	40,095 (10.03)	2,353 (15.70)		42,387 (10.22)	61 (18.71)	
Drinking, n (%)				< 0.001			< 0.001
Never	17,634 (4.25)	16,773 (4.19)	861 (5.75)		17,618 (4.25)	16 (4.91)	
Previous	14,461 (3.49)	13,526 (3.38)	935 (6.24)		14,431 (3.48)	30 (9.20)	
Current	382,790 (92.26)	369,603 (92.42)	13,187 (88.01)		382,510 (92.27)	280 (85.89)	
BMI, kg/m^2, mean (SD)	27.4 (4.8)	27.3 (4.7)	29.5 (5.7)	< 0.001	27.4 (4.8)	30.0 (6.4)	< 0.001
Hypertension, n (%)				< 0.001			< 0.001
Yes	116,720 (28.13)	109,120 (27.29)	7,600 (50.72)		116,543 (28.11)	177 (54.29)	
No	298,165 (71.87)	290,782 (72.71)	7,383 (49.28)		298,016 (71.89)	149 (45.71)	
T2DM, n (%)				< 0.001			< 0.001
Yes	21,959 (5.29)	19,259 (4.82)	2,700 (18.02)		21,879 (5.28)	80 (24.54)	
No	392,926 (94.71)	380,643 (95.18)	12,283 (81.98)		392,680 (94.72)	246 (75.46)	
T1DM, n (%)				< 0.001			< 0.001
Yes	3,779 (0.91)	2,949 (0.74)	830 (5.54)		3,761 (0.91)	18 (5.52)	
No	411,106 (99.09)	396,953 (99.26)	14,153 (94.46)		410,798 (99.09)	308 (94.48)	
CKD, n (%)				< 0.001			< 0.001
Yes	16,410 (3.96)	11,459 (2.87)	4,951 (33.04)		16,290 (3.93)	120 (36.81)	
No	398,475 (96.04)	388,443 (97.13)	10,032 (66.96)		398,269 (96.07)	206 (63.19)	
Atherosclerosis				< 0.001			< 0.001
Yes	2,790 (0.67)	2,088 (0.52)	702 (4.69)		2,774 (0.67)	16 (4.91)	
No	412,095 (99.33)	397,814 (99.48)	1,4281 (95.31)		411,785 (99.33)	310 (95.09)	
Medication							
NSAIDs				< 0.001			< 0.001
Yes	111,177 (26.80)	105,140 (26.29)	6,037 (40.29)		111,007 (26.78)	170 (52.15)	
No	303,708 (73.20)	294,762 (73.71)	8,946 (59.71)		303,552 (73.22)	156 (47.85)	
ACEIs				< 0.001			< 0.001
Yes	14,375 (3.46)	12,926 (3.23)	1,449 (9.67)		14,337 (3.46)	38 (11.66)	

Table 1 (continued)

Characteristics	Total population	AKI			AKI-related mortality		
	(*n* = 414,885)	No (*n* = 399,902)	Yes (*n* = 14,983)	*P*	No (*n* = 414,559)	Yes (*n* = 326)	*P*
No	400,510 (96.54)	386,976 (96.77)	13,534 (90.33)		400,222 (96.54)	288 (88.34)	
ARBs				< 0.001			< 0.001
Yes	14,802 (3.57)	13,357 (3.34)	1,445 (9.64)		14,757 (3.56)	45 (13.80)	
No	400,083 (96.43)	386,545 (96.66)	13,538 (90.36)		399,802 (96.44)	281 (86.20)	
Laboratory results							
Creatinine, mmol/L, mean (SD)	72.3 (17.7)	71.9 (16.2)	82.0 (40.2)	< 0.001	72.3 (17.7)	84.4 (49.3)	< 0.001
Urate, μmol/L, mean (SD)	309.0 (80.0)	307.5 (79.2)	348.6 (91.3)	< 0.001	309.0 (80.0)	359.4 (90.7)	< 0.001
BUN, mmol/L, mean (SD)	5.4 (1.4)	5.4 (1.3)	6.1 (2.3)	< 0.001	5.4 (1.4)	6.3 (2.3)	< 0.001
Total cholesterol, mmol/L, mean (SD)	5.7 (1.1)	5.7 (1.1)	5.3 (1.3)	< 0.001	5.7 (1.1)	5.0 (1.3)	< 0.001
Triglyceride, mmol/L, mean (SD)	1.7 (1.0)	1.7 (1.0)	2.0 (1.2)	< 0.001	1.7 (1.0)	2.0 (1.2)	< 0.001
CRP, mg/L, mean (SD)	2.6 (4.3)	2.5 (4.2)	4.0 (6.0)	< 0.001	2.6 (4.3)	4.8 (6.8)	< 0.001
$PM_{2.5}$, μg/m^3, median (IQR)	9.92 (1.27)	9.92 (1.28)	10.02 (1.25)	< 0.001	9.92 (1.27)	10.17 (1.13)	< 0.001
$PM_{2.5-10}$, μg/m^3, median (IQR)	6.10 (0.79)	6.10 (0.79)	6.14 (0.81)	< 0.001	6.10 (0.79)	6.18 (0.75)	< 0.001
PM_{10}, μg/m^3, median (IQR)	16.02 (1.76)	16.01 (1.76)	16.10 (1.72)	< 0.001	16.02 (1.76)	16.18 (1.53)	< 0.001
NO_2, μg/m^3, median (IQR)	25.99 (9.80)	25.96 (9.82)	26.87 (9.63)	< 0.001	25.99 (9.80)	26.62 (8.75)	< 0.001
NO_x, μg/m^3, median (IQR)	42.04 (16.53)	41.99 (16.53)	43.41 (16.43)	< 0.001	42.04 (16.53)	44.11 (15.84)	< 0.001

AKI, acute kidney injury; SD, standard deviation; BMI, body mass index; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; CKD, chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BUN, blood urea nitrogen; IQR, interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 mm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 mm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 mm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides

Cox proportional hazards models. The *P* value for interaction was calculated to determine whether the effect of air pollution on AKI risk differed between subgroups. a significant *P* value for interaction terms (< 0.05) indicates heterogeneity between subgroups, meaning there are significant differences in their effects on the outcome in the study, which typically suggests the presence of an interaction effect.

Sensitivity analyses were undertaken to ensure the reliability of our results. Firstly, to mitigate the risk of reverse causation, we analyzed of the correlation between air pollutants and the occurrence of AKI as well as AKI-related death after removing cases occurring in the initial 3 years of follow-up. Secondly, to minimize potential misclassification of air pollution exposure resulting from changes in residence, our analysis was limited to participants who had resided in their homes for a minimum of 5 years. Thirdly, we performed the analysis by excluding extreme values, defined as percentiles outside the 1st to 99th percentiles, for these air pollutants. All statistical analyses were carried out using R software (version 4.3.1), with significance determined by a two-sided *p*-value of less than 0.05.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of individuals sorted by new-onset AKI and AKI-related death. After an average follow-up duration of 11.7 years, 14,983 cases of AKI and 326 cases of AKI-related death were diagnosed among 414,885 participants. Individuals with AKI and AKI-related death tend to be older, male, overweight, smokers, drinkers, with lower educational attainment and average total household income, have comorbidities such as hypertension, T2DM, T1DM, CKD and atherosclerosis, and use of medication such as NSAIDs, ACEIs and ARBs. In comparison to the normal population, participants with AKI or AKI-related death were often exposed to higher levels of air pollutants. Table S2 presents the Spearman correlation coefficients for the various air pollutants. The results of the Variance VIF analysis indicated that all VIF values for the explanatory variables in the model were between 1 and 2. This suggests that there are no significant multicollinearity issues among the covariates in our dataset. Therefore, all variables were retained in the final model, and the multicollinearity analysis further supports the robustness and reliability of our results.

Air pollutants and AKI

After adjusting for multiple variables, we found that exposure to elevated levels of air pollution were correlated with a heightened risk of AKI (Table 2). Specifically, there were 20% (95% CI:5–38%, *P* = 0.007), 6% (95% CI:3 – 10%, *P* < 0.001), 15% (95% CI:10 – 19%, *P* < 0.001), and 8% (95% CI:7 – 10%, *P* < 0.001) higher risks of AKI for each 5 micrograms per cubic meter increase in $PM_{2.5}$ and PM_{10}, each 10 micrograms per cubic meter increase in NO_2 and NO_x, respectively. While no statistically notable discrepancy in the risk of AKI was observed with an increase of 2.5 micrograms per cubic meter in $PM_{2.5\text{-}10}$. Quartile analysis showed individuals exposed to higher

Table 2 Multivariable-adjusted hazard ratios (95% CI) for air pollutants concentrations with the risk of AKI in the UK Biobank study

Characteristics	Cases/*n*	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
$PM_{2.5}$							
<=9.28	3,237/104,742	Reference	-	Reference	-	Reference	-
9.28–9.92	3,599/103,201	1.16 (1.11–1.22)	< 0.001	1.10 (1.05–1.15)	< 0.001	1.08 (1.03–1.13)	0.001
9.92–10.6	3,936/103,470	1.30 (1.24–1.37)	< 0.001	1.18 (1.12–1.23)	< 0.001	1.13 (1.08–1.19)	< 0.001
> 10.6	4,211/103,472	1.42 (1.36–1.49)	< 0.001	1.22 (1.17–1.28)	< 0.001	1.15 (1.10–1.21)	< 0.001
P for trend	-	-	< 0.001	-	< 0.001	-	< 0.001
Per 5 μg/m^3 increment	-	1.46 (1.26–1.68)	< 0.001	1.25 (1.08–1.44)	0.003	1.20 (1.05–1.38)	0.007
$PM_{2.5-10}$							
<=5.84	3,441/106,041	Reference	-	Reference	-	Reference	-
5.84–6.1	3,649/101,485	1.14 (1.09–1.19)	< 0.001	1.10 (1.05–1.15)	< 0.001	1.08 (1.03–1.13)	< 0.001
6.1–6.63	3,994/104,474	1.24 (1.19–1.30)	< 0.001	1.19 (1.14–1.25)	< 0.001	1.16 (1.11–1.21)	< 0.001
> 6.63	3,899/102,885	1.21 (1.15–1.27)	< 0.001	1.16 (1.10–1.21)	< 0.001	1.10 (1.05–1.16)	< 0.001
P for trend	-	-	< 0.001	-	< 0.001	-	< 0.001
Per 2.5 μg/m^3 increment	-	1.01 (0.96–1.07)	0.655	1.01 (0.95–1.07)	0.715	1.01 (0.94–1.07)	0.789
PM_{10}							
<=15.2	3,376/103,871	Reference	-	Reference	-	Reference	-
15.2–16.0	3,689/104,845	1.08 (1.04–1.14)	< 0.001	1.03 (0.99–1.08)	0.1826	1.01 (0.96–1.05)	0.710
16.0–17.0	3,953/102,564	1.26 (1.20–1.32)	< 0.001	1.18 (1.12–1.23)	< 0.001	1.14 (1.09–1.20)	< 0.001
> 17.0	3,965/103,605	1.23 (1.18–1.29)	< 0.001	1.15 (1.10–1.21)	< 0.001	1.10 (1.05–1.15)	< 0.001
P for trend	-	-	< 0.001	-	< 0.001	-	< 0.001
Per 5 μg/m^3 increment	-	1.12 (1.08–1.16)	< 0.001	1.09 (1.05–1.13)	< 0.001	1.06 (1.03–1.10)	< 0.001
NO_2							
<=21.3	3,140/103,854	Reference	-	Reference	-	Reference	-
21.3–26.0	3,610/103,664	1.18 (1.12–1.23)	< 0.001	1.10 (1.05–1.15)	< 0.001	1.09 (1.04–1.15)	< 0.001
26.0-31.1	4,015/103,799	1.37 (1.30–1.43)	< 0.001	1.23 (1.17–1.29)	< 0.001	1.20 (1.15–1.26)	< 0.001
> 31.1	4,218/103,568	1.54 (1.47–1.62)	< 0.001	1.35 (1.29–1.42)	< 0.001	1.28 (1.22–1.34)	< 0.001
P for trend	-	-	< 0.001	-	< 0.001	-	< 0.001
Per 10 μg/m^3 increment	-	1.23 (1.20–1.26)	< 0.001	1.18 (1.15–1.20)	< 0.001	1.15 (1.10–1.19)	< 0.001
NO_x							
<=34.0	3,167/103,722	Reference	-	Reference	-	Reference	-
34.0–42.0	3,589/103,751	1.17 (1.12–1.23)	< 0.001	1.10 (1.05–1.15)	< 0.001	1.07 (1.02–1.13)	0.003
42.0-50.5	3,985/103,716	1.36 (1.30–1.43)	< 0.001	1.22 (1.17–1.28)	< 0.001	1.18 (1.13–1.24)	< 0.001
> 50.5	4,242/103,696	1.50 (1.43–1.57)	< 0.001	1.29 (1.23–1.35)	< 0.001	1.21 (1.15–1.27)	< 0.001
P for trend	-	-	< 0.001	-	< 0.001	-	< 0.001
Per 10 μg/m^3 increment	-	1.14 (1.12–1.16)	< 0.001	1.10 (1.09–1.12)	< 0.001	1.08 (1.07–1.10)	< 0.001

$PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 mm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 mm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 mm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides. Model 1: adjusted for sex, age and ethnicity. Model 2: adjusted for sex, age, ethnicity, educational attainment, average total household income, smoking, and drinking. Model 3: adjusted for sex, age, ethnicity, educational attainment, average total household income, smoking, drinking, BMI, hypertension, T2DM, T1DM, CKD, atherosclerosis, use of medication including NSAIDs, ACEIs and ARBs, creatinine, urate, BUN, total cholesterol, triglyceride and CRP

levels of these air pollutants had a significantly higher risk of developing AKI and AKI-related death compared to those in the lowest quartile (Table 2). The RCS curves depicting the relationship between $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, NO_x, and the risk of AKI showed a significant departure from linearity ($P_{\text{for non-linearity}} < 0.05$, Fig. 2), indicating a complex, non-linear dose-response pattern.

In stratified analyses by age, sex, BMI, educational attainment, smoking habits, we observed positive associations between all these air pollutants and AKI in all subgroups. No significant heterogeneity or interaction effects were observed in any of the subgroups ($P_{\text{for interaction}} > 0.05$) (Table S3-S7).

Air pollutants and AKI-related death

Similarly, we found participants exposure to high levels of these air pollutants exhibited a higher risk of AKI-related death in comparison to those in the lowest quartile of air pollutants exposure (Table 3). The RCS curves illustrating the relationships between $PM_{2.5}$, NO_2, NO_x, and the risk of AKI-related death did not exhibit a significant departure from linearity ($P_{\text{for non-linearity}} > 0.05$, Fig. 3). Furthermore, we also found potential dose-response relationship

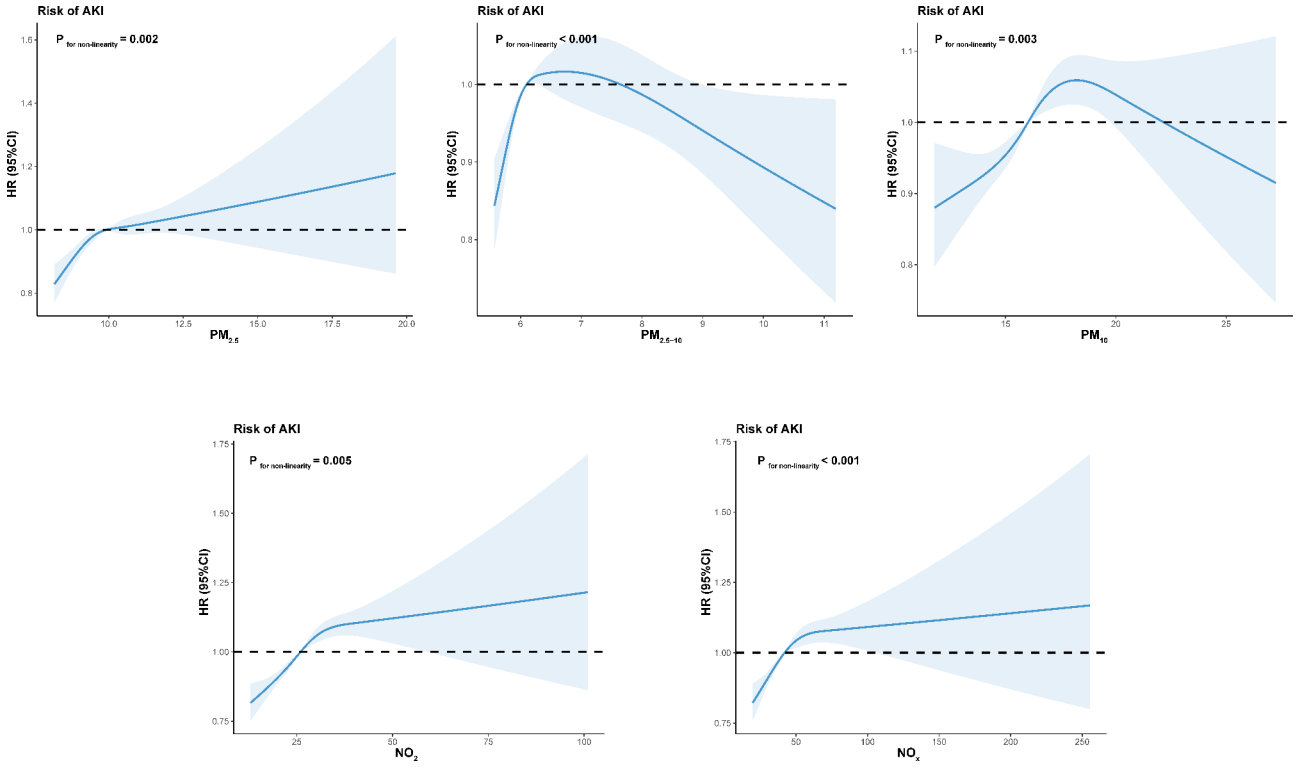

Fig. 2 Exposure – response relationship between air pollutants and the risk of AKI. HRs adjusted for sex, age, ethnicity, educational attainment, average total household income, smoking, drinking, BMI, hypertension, T2DM, T1DM, CKD, atherosclerosis, use of medication including NSAIDs, ACEIs and ARBs, creatinine, urate, BUN, total cholesterol, triglyceride and CRP

between all these air pollutants and the risk of AKI-related death (P for trend: 0.005 for $PM_{2.5}$, 0.048 for NO_2 and 0.014 for NO_x).

Sensitivity analyses

Sensitivity analyses provided robust support for the positive correlation between air pollutants, AKI, and AKI-related death the primary analysis. After removing cases from the first 3 years of follow-up, we observed positive correlations between exposure to all these air pollutants and the risk of AKI and AKI-related death (Table S8). Additionally, when the analysis excluded participants who resided in their current home for fewer than 5 years, the relationship between air pollutants, AKI, and AKI-related death remained unchanged (Table S9). Furthermore, when the analysis excluded participants who exposure to extreme values of air pollutants, the results remained consistent (Table S10).

Discussion

Recent studies have underscored the possible effects of air pollution on the AKI and AKI-related death. A time-series analysis of South Korea's National Health Insurance data indicated that short-term exposure to ozone (O_3), PM_{10}, CO, and sulfur dioxide was linked with an increase in emergency room visits for AKI, with O_3 having the highest impact, even at concentrations under WHO standards [7]. Similarly, a Chinese study revealed a heightened risk of hospital-acquired AKI associated with elevated levels of environmental NO_2 [22]. Both studies focus on the short-term effects of air pollution on the risk of AKI within Asian populations. Min et al. discovered that short-term exposure to $PM_{2.5}$, O_3, and NO_2 were correlated with an increased risk of death from AKI across 136 locations in six countries, with the risk peaking around 20 days after exposure [6]. However, these studies primarily focus on short-term exposure, underscoring the need for further research to investigate the long-term effects of air pollution on kidney health. A nationwide cohort study including more than 61 million Medicare beneficiaries revealed that prolonged exposure to $PM_{2.5}$, NO_2, and O_3 was correlated with an increased risk of first hospitalization for AKI, even at low levels of air pollutants [13]. However, this Medicare study focused only on individuals aged 65 and older and examined fewer pollutants ($PM_{2.5}$, NO_2, and O_3). Moreover, while the Medicare study adjusted for confounders such as age, sex, race, education, poverty level, income, smoking, and BMI, it did not account for key variables that we adjusted for, including participants' comorbidities, medication use, and laboratory markers.

Table 3 Multivariable-adjusted hazard ratios (95% CI) for air pollutants concentrations with the risk of AKI-related mortality in the UK Biobank study

Characteristics	Cases/*n*	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
$PM_{2.5}$							
<=9.28	58/104,684	Reference	-	Reference	-	Reference	-
9.28–9.92	73/103,128	1.34 (0.95–1.89)	0.097	1.24 (0.88–1.75)	0.220	1.34 (0.95–1.90)	0.096
9.92–10.6	98/103,372	1.88 (1.36–2.61)	< 0.001	1.65 (1.19–2.29)	0.003	1.60 (1.15–2.23)	0.005
> 10.6	97/103,375	1.98 (1.43–2.74)	< 0.001	1.62 (1.17–2.25)	0.004	1.50 (1.05–1.94)	0.025
P for trend	-	-	< 0.001	-	0.001	-	0.005
$PM_{2.5-10}$							
<=5.84	59/105,982	Reference	-	Reference	-	Reference	-
5.84–6.1	82/101,403	1.52 (1.09–2.13)	0.014	1.46 (1.04–2.03)	0.028	1.33 (0.96–1.87)	0.090
6.1–6.63	102/104,372	1.92 (1.39–2.65)	< 0.001	1.81 (1.32–2.50)	< 0.001	1.78 (1.14–2.18)	< 0.001
> 6.63	83/102,802	1.56 (1.12–2.18)	0.009	1.48 (1.06–2.06)	0.022	1.31 (1.02–1.86)	0.036
P for trend	-	-	0.004	-	0.010	-	0.028
PM_{10}							
<=15.2	61/103,810	Reference	-	Reference	-	Reference	-
15.2–16.0	81/104,764	1.32 (0.95–1.85)	0.098	1.25 (0.89–1.74)	0.192	1.18 (0.84–1.65)	0.278
16.0–17.0	97/102,467	1.77 (1.28–2.44)	0.005	1.62 (1.18–2.24)	0.003	1.57 (1.14–2.17)	0.006
> 17.0	87/103,518	1.57 (1.13–2.17)	0.007	1.44 (1.04-2.00)	0.029	1.35 (1.01–1.85)	0.048
P for trend	-	-	0.002	-	0.010	-	0.034
NO_2							
<=21.3	58/103,796	Reference	-	Reference	-	Reference	-
21.3–26.0	90/103,574	1.62 (1.16–2.25)	0.003	1.48 (1.06–2.06)	0.021	1.39 (1.00-1.94)	0.053
26.0-31.1	94/103,705	1.80 (1.30–2.50)	< 0.001	1.56 (1.12–2.17)	0.008	1.50 (1.07–2.08)	0.017
> 31.1	84/103,484	1.87 (1.33–2.61)	< 0.001	1.55 (1.10–2.17)	0.012	1.41 (1.01-2.00)	0.042
P for trend	-	-	< 0.001	-	0.015	-	0.048
NO_x							
<=34.0	62/103,660	Reference	-	Reference	-	Reference	-
34.0–42.0	83/103,668	1.42 (1.02–1.97)	0.037	1.30 (0.94–1.81)	0.117	1.27 (0.91–1.77)	0.159
42.0-50.5	81/103,635	1.49 (1.07–2.07)	0.019	1.29 (0.92–1.80)	0.136	1.33 (0.95–1.86)	0.093
> 50.5	100/103,596	1.99 (1.45–2.74)	< 0.001	1.63 (1.18–2.25)	0.003	1.52 (1.09–2.10)	0.012
P for trend	-	-	< 0.001	-	0.005	-	0.014

$PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 mm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 mm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 mm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides. Model 1: adjusted for sex, age and ethnicity. Model 2: adjusted for sex, age, ethnicity, educational attainment, average total household income, smoking, and drinking. Model 3: adjusted for sex, age, ethnicity, educational attainment, average total household income, smoking, drinking, BMI, hypertension, T2DM, T1DM, CKD, atherosclerosis, use of medication including NSAIDs, ACEIs and ARBs, creatinine, urate, BUN, total cholesterol, triglyceride and CRP

Similar to findings from previous studies, our analysis using UKB data revealed that prolonged exposure to air pollution is associated with increased risks of both AKI and AKI-related death. We also identified linear relationships between the levels of $PM_{2.5}$, NO_2, NO_x, and AKI-related death, while the relationship between $PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, NO_2, NO_x, and the risk of AKI showed a complex, non-linear dose-response pattern. Several potential factors may have contributed to this complexity. Measurement errors or misclassification of air pollution exposure could affect the accuracy of observed associations, particularly at higher pollutant levels. Additionally, individuals exposed to higher levels of air pollution may develop severe health conditions unrelated to AKI and may not survive long enough to develop AKI. There may also be a threshold effect beyond which further increases in air pollutants do not substantially elevate the risk of AKI. Finally, as fewer individuals are exposed to very high levels of pollution, this can lead to wider confidence intervals and less precise estimates at those levels.

The biological mechanisms through which prolonged exposure to air pollution could result in AKI remain incompletely elucidated, albeit several potential pathways are postulated. First, inhaled air pollutants swiftly access the kidneys through the bloodstream, leading to a decline in GFR through the promotion of inflammation, and oxidative stress in kidney tissue, which are believed to elevate the risk or severity of AKI, thereby increasing the susceptibility to AKI-related death [4, 23, 24]. The factors contributing to AKI are diverse and include hypotension, dehydration, drugs, infection, inflammation, vascular injury, ischemia, and urinary obstruction [3]. The

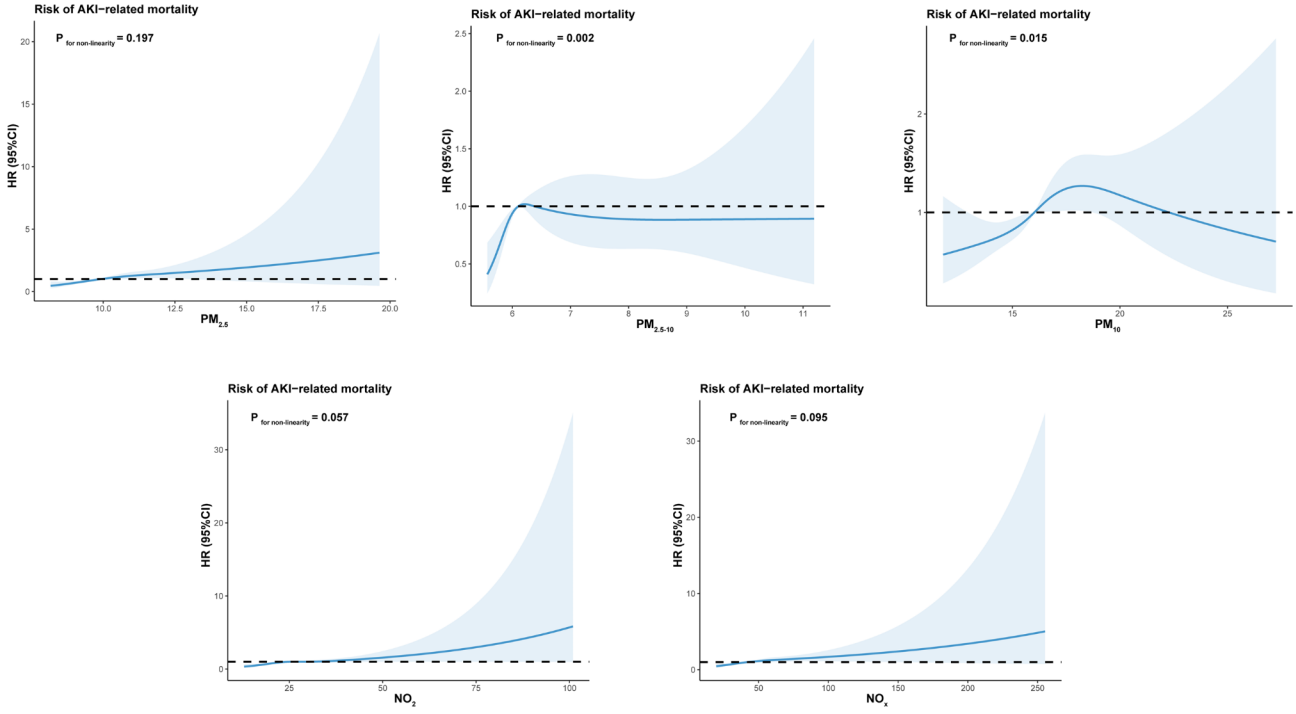

Fig. 3 Exposure – response relationship between air pollutants and the risk of AKI-related death. HRs adjusted for sex, age, ethnicity, educational attainment, average total household income, smoking, drinking, BMI, hypertension, T2DM, T1DM, CKD, atherosclerosis, use of medication including NSAIDs, ACEIs and ARBs, creatinine, urate, BUN, total cholesterol, triglyceride and CRP

harmful impact of air pollution may involve a complex 'multi-hit' process, overwhelming the kidneys' functional reserve and thereby increasing the risk of AKI and AKI-related death. In addition, comorbid conditions may act as intermediaries in mediating the effect of air pollution on the occurrence of AKI. These include hypertension, diabetes mellitus, cardiovascular disease, CKD, and sepsis, significantly increasing the likelihood of hospital-acquired AKI and AKI-related death [25–29]. Finally, the kidneys may experience direct cytotoxic effects due to the acute accumulation of air pollutants through systemic circulation [30, 31]. Experimental research involving both humans and mice supports these biological mechanisms, demonstrating that inhaled gold nanoparticles can travel from the respiratory system into the bloodstream, eventually being excreted in urine [23].

Our study boasts several key strengths. Firstly, a prospective study design was employed to evaluate the relationship between prolonged exposure to air pollution and the occurrence of AKI and AKI-related death. In addition, the considerable sample size enhanced our statistical prowess, allowing for a more robust characterization of the connection between air pollution and the development of AKI and AKI-related death. The associations persist with robustness even after adjusting for the confounding factors. This finding adds to the growing understanding of air pollution's impact on renal health, extending beyond the well-documented cardiovascular and respiratory risks. From a public health perspective, our results underscore the necessity for stricter air quality regulations and targeted interventions to reduce air pollution exposure, potentially easing the burden of AKI on healthcare systems. In terms of policy, these findings reinforce the need for pollution control measures, particularly in highly urbanized or industrial areas. Integrating kidney health into environmental policies could lead to broader health benefits, encouraging a multi-sectoral approach to mitigating the effects of air pollution.

However, the present study also had some limitations. First, we faced challenges in elucidating the intricate pathways and mediating conditions of AKI influenced by exposure to air pollution. The complexity of interactions between environmental pollutants and biological systems remains an area for future research. Second, given the restricted number of mortality cases, our capacity to conduct stratified analyses within subgroups was constrained, hindering an in-depth exploration of the correlation between air pollution and AKI-related death. Third, there are limitations in interpreting the onset of AKI based on the AKI ICD diagnostic codes of hospitalized patients. Studies have shown that relying solely on these codes may lead to an underestimation of AKI incidence, as not all cases are captured by hospitalization data [32, 33]. This may introduce classification bias in the detection of AKI cases, potentially leading to conservative estimates of the true association between

air pollution and AKI risk. Fourth, air pollutant concentrations were evaluated solely at baseline, neglecting temporal fluctuations in residential addresses and air pollutant levels over time, as well as individual-level influencing factors such as occupational exposure and secondhand smoke. This could introduce exposure misclassification, where the actual exposure of individuals may differ from the measured data, potentially diluting the observed associations. Fifth, air pollution constitutes a multifaceted and ever-changing blend of diverse substances, encompassing a multitude of anthropogenic and natural pollutants. The intricate interplay among these components presents challenges when endeavoring to scrutinize the individual associations of each. Sixth, the absence of data on cancer, a potential confounder, could have affected our ability to account for its influence in our models. Selection bias could arise if cancer patients, who may have higher AKI risks, are unevenly distributed across pollution exposure categories. Finally, a key limitation of this study is the restricted availability of air pollution data and may affect our ability to fully capture long-term exposure trends.

Conclusion

In summary, our study uncovered a direct association between prolonged exposure to air pollution and heightened risks of both AKI and AKI-related death. While we acknowledge the limitations related to exposure measurement, restricted availability of air pollution data, and the potential for unmeasured confounding factors, we believe our findings offer important insights into the environmental determinants of kidney health. These findings provide scientific validation for the adoption of environmental and public health measures directed towards the reduction of air pollution. Such initiatives could potentially ease the impact associated with AKI and AKI-related death, emphasizing the importance of integrating kidney health into public health policy and environmental regulations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20321-2.

Supplementary Material 1

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Author contributions

ML: formal analysis, investigation, methodology, visualization, writing – original draft; MG: data curation, methodology, software, writing – review & editing; JH: formal analysis, validation, writing – review & editing; DH: writing – review & editing; JW and ZC: investigation, visualization, writing – review & editing; JC: conceptualization, methodology, project administration, supervision, writing – review & editing.

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Data availability

The data used in this study are available to bona fide researchers upon successful application to the UK Biobank. Researchers can apply for access to these data by outlining their proposed use and obtaining approval from the UK Biobank Access Management Team.

Declarations

Ethics approval and consent to participate

This study was conducted using the UK Biobank resource under application number [93044], which obtained ethical approval from the North West Multi-centre Research Ethics Committee (MREC). All participants provided informed consent, and the study adhered to the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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