

ORIGINAL ARTICLE

Long-term impact of PM_{2.5} exposure on diabetic kidney disease patients considering time-dependent medication adjustment

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ABSTRACT

Background. Ambient air pollutants adversely affect renal function and increase type 2 diabetes incidence. However, the impact of air pollution on diabetic kidney disease (DKD) patients remains underexplored, with limited consideration of medication-related effects. We assessed the influence of air pollutants on DKD patients while meticulously adjusting for medication use.

Methods. We retrospectively enrolled DKD patients. Primary and secondary outcomes included end-stage kidney disease (ESKD) and a composite (ESKD and mortality). Nationwide forecasted ultra-high-resolution air pollutant data [2.5- μ m particulate matter (PM_{2.5}), 10- μ m particulate matter (PM₁₀), nitrogen dioxide (NO₂), carbon monoxide (CO)] were obtained from the Ai-Machine learning Statistics Collaborative Research Ensemble for Air pollution, Temperature, and all types of Environmental exposures (AiMS-CREATE). Monthly updated ambient air pollutants and medication prescription information were considered time-varying variables in multivariable time-dependent Cox analyses.

Results. Patients ($n = 9482$) were followed for a median of 9 (ESKD) and 11 (composite outcome) years; 20.6% progressed to ESKD and 46.7% experienced composite outcomes. The DKD-stage patient distribution was 12.5% (stage 1–2), 35.8% (stage 3) and 51.6% (stage 4–5). Initial renin-angiotensin system blocker use increased from 37.4% to 58.5% during year 1 then gradually decreased. During follow-up, all four air pollutant concentrations significantly decreased, with CO exhibiting the most pronounced decline. The 1-month lagged PM_{2.5} exposure (Lag1_PM_{2.5}) was significantly associated with higher ESKD progression risk [adjusted hazard ratio [aHR] 1.28 [95% confidence interval (CI) 1.085–1.508]], whereas PM_{2.5} itself showed no significance [aHR 1.05 (95% CI 0.872–1.260)]. Both exposures increased the composite outcome risk

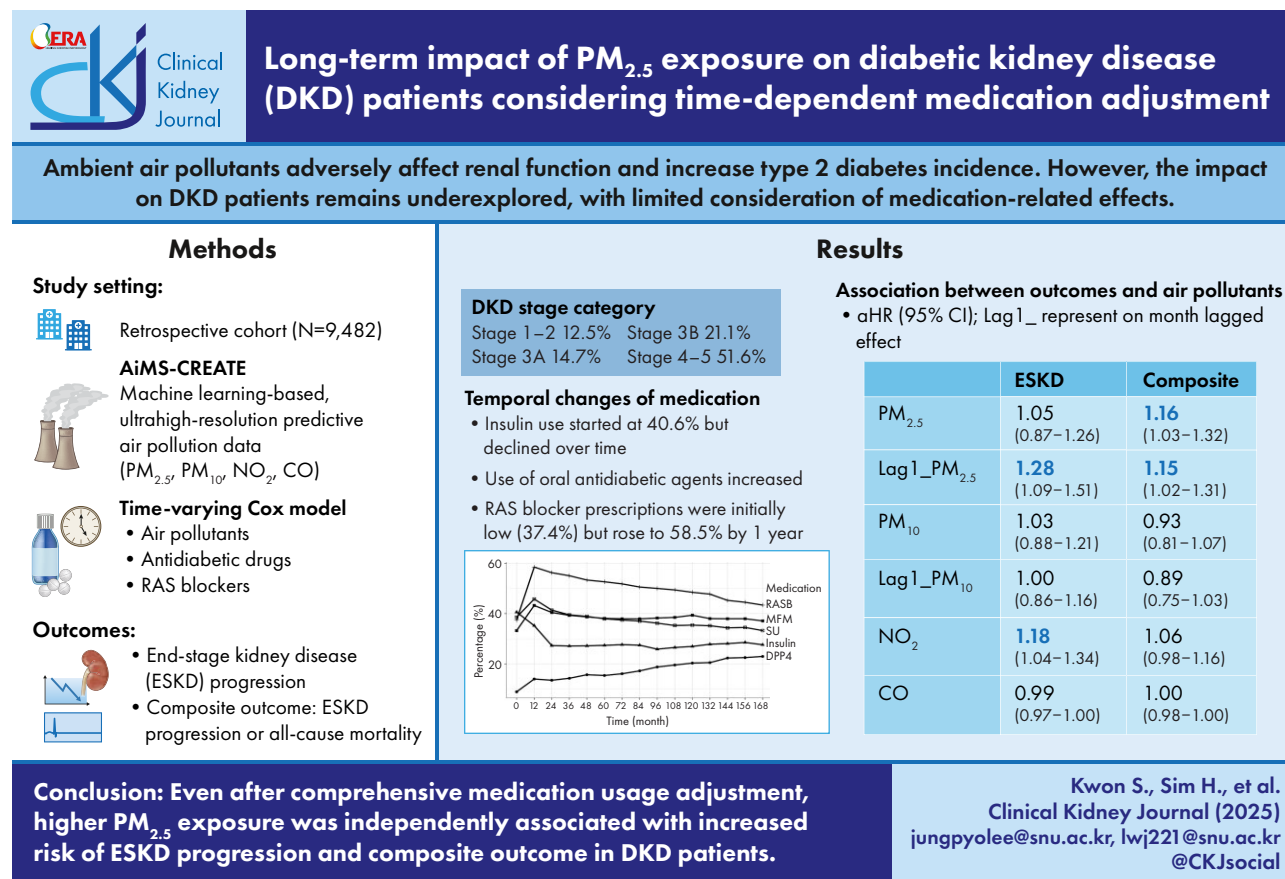
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(PM_{2.5} aHR 1.16 Lag1_PM_{2.5} aHR 1.15). PM₁₀ and Lag1_PM₁₀ showed no significant associations with either ESKD progression or composite outcomes. NO₂ exposure increased ESKD progression risk but was not associated with composite outcomes.

Conclusion. Even after comprehensive medication use adjustment, higher PM_{2.5} exposure was independently associated with an increased risk of ESKD progression and composite outcome in DKD patients.

GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, diabetic kidney disease, end-stage kidney disease, PM_{2.5}

INTRODUCTION

Growing evidence from both epidemiological and experimental research convincingly demonstrates the adverse impact of air pollution, which extends beyond the respiratory system to affect various extrapulmonary organs [1]. Among these organs, the kidneys, in particular, are known to be more susceptible, owing to their substantial blood supply, with ≈20% of the cardiac output directed toward renal circulation [2–4]. Moreover, circulating air pollutants can accumulate during blood filtration, posing a substantial risk to kidney function. Recent clinical studies have provided compelling evidence linking ambient fine particulate matter (PM) to the development of chronic kidney disease (CKD), progression to end-stage kidney disease (ESKD) and mortality in CKD/ESKD patients [2, 5–9]. Additionally, emerging evidence from recent investigations suggests a potential association between ambient air pollution exposure and an increased prevalence or incidence of type 2 diabetes (T2D) mellitus, with meta-analyses indicating significant associations of 2.5-μm par-

ticulate matter (PM_{2.5}) and 10-μm particulate matter (PM₁₀) with T2D incidence and prevalence [10, 11].

Patients with diabetic kidney disease (DKD) may exhibit a particular susceptibility to the effects of air pollutants due to their underlying conditions of diabetes and CKD. However, assessing the accurate effect of air pollutants on DKD requires comprehensive adjustments for well-known prognostic factors, including glycemic control and the use of diabetes medications and renin-angiotensin system (RAS) blockers [12–15]. Unfortunately, prior investigations focusing on the effects of air pollutant exposure on DKD patients have predominantly emphasized time-series changes in air pollution while patient factors that directly affect the course of DKD have been underestimated.

In this study we investigated the potential relationship between air pollution exposure and the deterioration of kidney function in patients with DKD. Through meticulous adjustments for confounding from medication use, we aim to provide valuable insights into the specific effects of air pollutant exposure in the context of DKD.

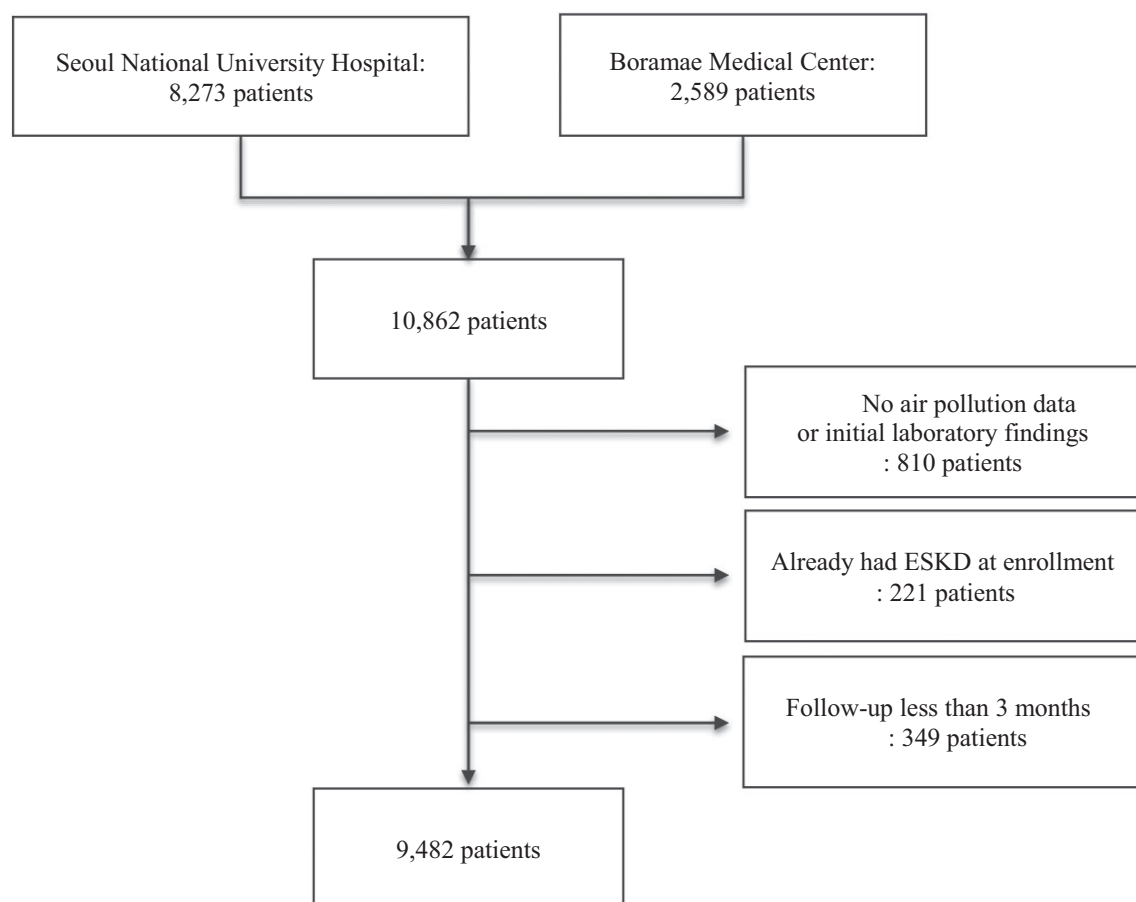


Figure 1: Flow diagram of the two tertiary referral centres in South Korea used for the present study.

MATERIALS AND METHODS

Study participants and design

A retrospective cohort study was conducted at two tertiary referral centres in South Korea. Patients who visited the nephrology outpatient clinic more than twice between 1 January 2000 and 31 December 31 2016 were screened. Among the initial pool of 51 457 CKD patients who were >18 years of age, those diagnosed with diabetes based on the International Classification of Diseases, Tenth Revision (ICD-10) code before enrolment were defined as DKD patients. Patients with defined DKD who had less than two serum creatinine measurements or lacked address information for air pollutant data were excluded from the study. Moreover, patients who were diagnosed with ESKD before enrolment, who progressed to ESKD or who died within 3 months of enrolment were excluded. Ultimately, a total of 9482 patients were enrolled (Fig. 1).

Baseline characteristics

The enrolment date was defined as the date of the first serum creatinine measurement. Baseline comorbidities were defined based on ICD-10 codes, including hypertension (I10.x-I12.x, I15.x and H350.x), dyslipidaemia (E78.x) and coronary artery disease (I20.x-25.x, I46.x and Z95.x). For laboratory findings, the value closest to the enrolment date was selected from blood tests conducted within 1 month before or after enrolment. The esti-

mated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. All prescription information on medication use [metformin, sulfonylurea (SU), dipeptidyl peptidase-4 inhibitor (DPP4i), insulin and RAS blockers] was obtained from electronic health records. Medication use was defined as having a prescription for >90 days within the previous 1-year period, and this variable was updated on a monthly basis as a time-varying covariate.

Due to the retrospective nature of the data, individual-level information on patients' socio-economic status and physical activity was not available. Instead, we matched average values based on the patient's residential area from publicly available data. Socio-economic status was assessed using the area deprivation index, which changes every 5 years [16]. For physical activity, annual values were available, and these were considered as time-varying confounders in the analysis [17].

Air pollutant measurement

We utilized monthly average machine learning-based, ultra-high-resolution predictive data with a 1 km × 1 km grid for four ambient air pollutants provided by the Ai-Machine learning Statistics Collaborative Research Ensemble for Air pollution, Temperature, and all types of Environmental exposures (AiMS-CREATE) group (<https://www.datascience4health.com/>) [15]: PM₁₀ (in µg/m³), PM_{2.5} (in µg/m³), nitrogen dioxide (NO₂; in ppb) and carbon monoxide (CO; in ppb). The overall R² values for

each ambient air pollutant were 0.867 for PM₁₀, 0.872 for PM_{2.5}, 0.756 for NO₂ and 0.506 for CO. We calculated the monthly mean concentrations of air pollutants (NO₂, CO, PM₁₀ and PM_{2.5}) by averaging their daily concentrations.

Outcomes

The primary outcome of the study was defined as the occurrence of incident ESKD. Secondary outcomes were a composite outcome of incident ESKD or all-cause mortality. Incident ESKD was determined based on the need for dialysis (either hemodialysis or peritoneal dialysis) lasting >3 months or undergoing renal transplantation. Mortality information was collected from electronic health records as well as the National Statistical Office of South Korea. The patients were followed until the event of interest or 31 December 2020, whichever came first.

Statistical analysis

A time-varying Cox model was used to investigate the effect of each air pollutant on the outcome. The Cox model included current air pollutant concentrations and 1-month lagged PM₁₀ and PM_{2.5} concentrations as time-varying covariates, with adjustment for the baseline characteristics. Additionally, the use of antidiabetic drugs (metformin, SU, DPP4i and insulin) and RAS blockers were considered time-varying confounders. We used the Akaike information criterion (AIC) to select the model. Furthermore, we performed two sensitivity analyses. First, we excluded CO from the model due to its lower R² value compared with the other ambient air pollutants. Second, we analysed a dataset that additionally included patients within the first 3 months to enhance the validity of the results. All the statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). In all analyses, $P < .05$ was considered to indicate statistical significance.

RESULTS

Baseline characteristics of the cohort

A total of 9482 patients were followed for a median of 9 years [interquartile range (IQR) 5–15] for ESKD and the composite outcome and 11 years (IQR 7–19) for all-cause mortality. Among them, 1950 (20.6%) patients progressed to ESKD and composite outcomes occurred in 4427 (46.7%) patients (Supplementary Fig. 1). In the overall cohort, the mean age was 59.3 ± 12.4 years, 14.8% were smokers and 3.2% were ex-smokers at enrolment. The prevalence of hypertension was 48.9% and that of dyslipidaemia was 14.2%, although the prevalence of coronary artery disease was relatively low at 2.7%. The mean eGFR at enrolment was 60.2 ± 24.3 ml/min/1.73 m². When categorized by DKD stage, there were 1186 patients (12.5%) with DKD stage 1–2, 1398 patients (14.7%) with stage 3A, 2002 patients (21.1%) with stage 3B and 4896 patients (51.6%) with stage 4–5.

Temporal changes in medication use

The level of glycated haemoglobin A1c (HbA1c) at enrolment was 7.5 ± 1.8% and the proportion of patients with an HbA1c of ≥9.0% was 1627 patients (17.2%; Table 1). Initially, insulin use was at a high rate of 40.6%, but it gradually decreased, with 35.2% of patients using insulin in the first year and 27.3% in the second year. As insulin use decreased, there was a trend toward increasing use of oral antidiabetic agents such as metformin, DPP4i

Table 1: Baseline characteristics of the overall study cohort (N = 9482).

Variables	Values
Age (years), mean ± SD	59.3 ± 12.4
Male, n (%)	5528 (58.3)
BMI, n (%)	
Non-obese	4512 (47.6)
Overweight	2348 (24.8)
Obese	529 (5.6)
Hospital, n (%)	
SNUH	7129 (75.2)
BMC	2353 (24.8)
Smoking, n (%)	
Current smoker	1402 (14.8)
Ex-smoker	300 (3.2)
Never smoker	6117 (64.5)
Comorbidities, n (%)	
Hypertension	4634 (48.9)
Dyslipidaemia	1342 (14.2)
CVD	260 (2.7)
Initial laboratory findings, mean ± SD	
eGFR (ml/min/1.73 m ²)	60.2 ± 24.3
HbA1c (%)	7.5 ± 1.8
Albumin (g/dl)	3.96 ± 0.6
Initial medication use, n (%)	
Metformin	2535 (33.3)
Sulfonylurea	2941 (38.6)
DPP4i	682 (8.9)
Insulin	3095 (40.6)
RAS blocker	2854 (37.4)

BMI: body mass index; SNUH: Seoul National University Hospital; BMC: Seoul Metropolitan Government Boramae Medical Center; CVD: cardiovascular disease.

and SU during the first year (initial: metformin 33.3%, SU 38.6%, DPP4i 8.9%; 1 year: metformin 40.5%, SU 45.8%, DPP4i 13.5%). Over time, SU and metformin use decreased while DPP4i use increased steadily (Fig. 2).

At the time of enrolment, the use of RAS blockers was relatively low, with only 37.4% of patients receiving prescriptions. However, as the follow-up period progressed, the percentage of patients receiving RAS blockers increased to 58.5% by month 12, followed by a gradual decrease thereafter (Fig. 2). When RAS blocker use was categorized based on hypertension status, 11.0% of the hypertensive patients and 6.9% of the non-hypertensive patients were prescribed RAS blockers at the time of enrolment in the study. After 12 months, 52.0% of the hypertensive patients and 36.2% of the non-hypertensive patients were using RAS blockers.

Monthly changes in air pollutants

The change in each air pollutant from January 2002 to December 2020 was assessed using the average daily concentration. Notably, air pollutant concentrations tended to increase during winter and decrease during summer (Supplementary Fig. 2). Over the follow-up period, all four air pollution concentrations exhibited a significant decreasing trend, with CO showing the most pronounced decline (estimated slope of −0.252, $P < .001$). For the air pollutants assessed in this study (NO₂, CO, PM₁₀ and PM_{2.5}), 11.2%, 7.8%, 23.6% and 17.4%, respectively, of the total variation in their concentrations were explained by the variable

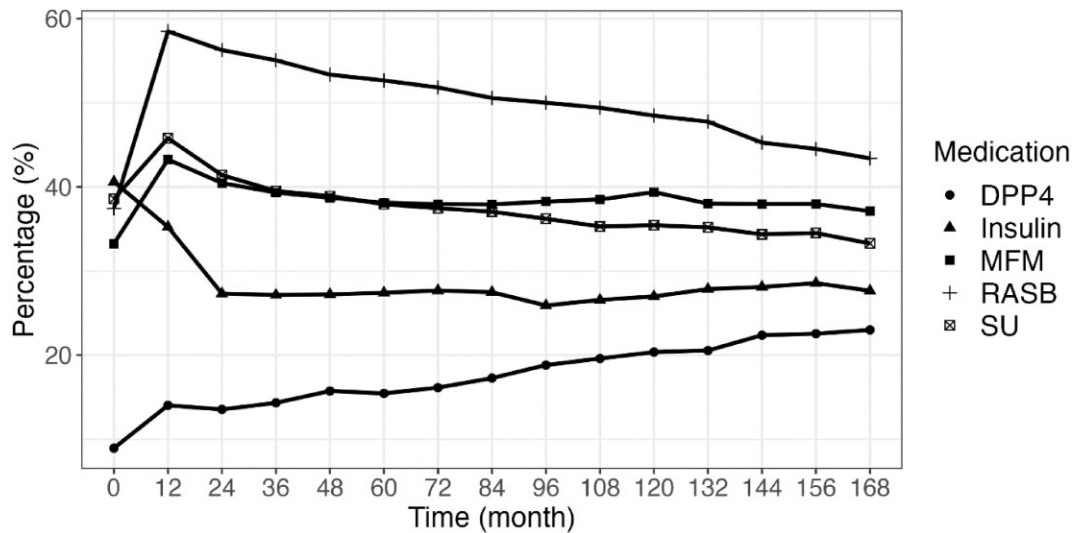


Figure 2: Temporal trends in the use of oral antidiabetic agents, insulin and RAS blockers in the present study. Medication use was updated monthly and is presented as the frequency among the tracked patients. MFM: metformin.

Table 2: Association between ESKD progression or composite outcome and air pollutant exposure.

Air pollutant (unit)	ESKD			Composite outcome		
	aHR	95% CI	P-value	aHR	95% CI	P-value
NO ₂ (10 ppb)	1.18	1.039–1.336	0.011	1.06	0.976–1.158	0.162
CO (10 ppb)	0.99	0.974–1.004	0.154	1.00	0.983–1.002	0.138
PM ₁₀ (10 µg/m ³)	1.03	0.880–1.212	0.695	0.93	0.806–1.070	0.307
Lag1_PM ₁₀ (10 µg/m ³)	1.00	0.861–1.161	0.997	0.89	0.752–1.028	0.190
PM _{2.5} (10 µg/m ³)	1.05	0.872–1.260	0.615	1.16	1.028–1.316	0.016
Lag1_PM _{2.5} (10 µg/m ³)	1.28	1.085–1.508	0.003	1.15	1.019–1.306	0.024

Air pollutants were considered time-dependent covariates. All analyses were adjusted for time-fixed confounders (age, sex, body mass index, smoking status, hospital status, comorbidities and initial laboratory findings) and time-dependent confounders (area deprivation index, physical activity, antidiabetic drug use and RAS blocker use).

Lag1_PM₁₀ and Lag1_PM_{2.5} represent 1-month lagged PM₁₀ and PM_{2.5} concentrations, respectively.

time when considering the number of variables used in a model (Supplementary Table 1).

The distribution of air pollutant concentrations across the region was determined by averaging data over 5-year intervals, except for the first interval from 2002 to 2005, thus confirming the continued decrease in air pollutant concentrations. PM₁₀ and PM_{2.5} concentrations were greater in the metropolitan area excluding Seoul than in Seoul (Supplementary Fig. 3 and Supplementary Fig. 4). Specifically, PM_{2.5} and PM₁₀ levels were notably elevated in the Seoul Metropolitan Area and Busan, with PM₁₀ showing a more rapid decrease than PM_{2.5}. The highest concentrations of NO₂ and CO were observed in Seoul, followed by the Seoul Metropolitan Area, Busan and Daegu (Supplementary Fig. 5 and Supplementary Fig. 6). PM_{2.5} and PM₁₀ concentrations can be interpreted as being greater in the east than in the west, while NO₂ and CO concentrations tend to be generally greater in urban areas.

PM_{2.5} exposure increases the risk of ESKD progression

The impact of each air pollutant was assessed while accounting for changes in the use of antidiabetic agents and RAS block-

ers. Increases in 1-month lagged PM_{2.5} exposure (Lag1_PM_{2.5}) were significantly associated with a higher risk of ESKD progression [adjusted hazard ratio [aHR] 1.28 [95% confidence interval (CI) 1.085–1.508]], while no statistically significant association was observed with PM_{2.5} exposure itself [aHR 1.05 (95% CI 0.872–1.260)]. Both PM_{2.5} and Lag1_PM_{2.5} exposures significantly increased the risk of the composite outcome [PM_{2.5} aHR 1.16 (95% CI 1.028–1.316), Lag1_PM_{2.5} aHR 1.15 (95% CI 1.019–1.306)]. In contrast, neither PM₁₀ exposure nor its lagged effect (Lag1_PM₁₀) showed any significant relationship with the risk of ESKD progression [PM₁₀ aHR 1.03 (95% CI 0.880–1.212), Lag1_PM₁₀ aHR 1.00 (95% CI 0.861–1.161)] or the composite outcome [PM₁₀ aHR 0.93 (95% CI 0.806–1.070), Lag1_PM₁₀ aHR 0.89 (95% CI 0.752–1.028)]. NO₂ exposure was associated with an increased risk of ESKD progression, but no such association was found for the composite outcome. CO exposure did not significantly correlate with either outcome (Table 2). These findings remained consistent even when patients who progressed to ESKD within the first 3 months were included (Supplementary Table 2). Furthermore, the results were unchanged after excluding CO, which had a lower R² value compared with other ambient air pollutants (Supplementary Table 3, Supplementary Table 4 for ESKD within the first 3 months included).

DISCUSSION

In the present retrospective cohort study, we investigated the associations between exposure to four air pollutants (NO_2 , CO, PM_{10} and $\text{PM}_{2.5}$) and kidney outcomes while accounting for changes in antidiabetic agent and RAS blocker use over time. Our high-resolution predicted air pollutant data confirmed a consistent reduction in air pollutant levels, consistent with prior research [18–20]. Notably, $\text{PM}_{2.5}$ levels, for which data were available only from 2015, exhibited a gradual decline over ≈ 20 years across South Korea. Furthermore, when accounting for changes in the use of antidiabetic agents and RAS blockers, higher $\text{PM}_{2.5}$ levels were associated with an increased risk of ESKD progression and composite outcomes in DKD patients. Our study highlights the detrimental impact of $\text{PM}_{2.5}$ concentrations on kidney outcomes in DKD patients, even after adjusting for the significant influence of medication use on prognosis.

Before adjusting for major drugs known to affect the prognosis of DKD patients [14, 21], we examined whether there were changes in the prescription patterns of these drugs during the follow-up period. Initially there was a high frequency of insulin use, but over 2 years the usage rate gradually decreased. Instead of discontinuing insulin, during the first year there was a predominant increase in the prescription of metformin, which is beneficial for cardiovascular and renal outcomes, and SU, which regulates postprandial blood glucose levels. However, later we observed a decrease in the use of not only insulin but also metformin and SU, along with an increase in the use of DPP4is, suggesting changes in drug utilization in response to worsening kidney function. The use of RAS blockers increased in $\approx 60\%$ of patients during the initial year but gradually decreased thereafter. This underscores that the prescribing of drugs with a significant impact on patient outcomes evolved during the follow-up period. Therefore, we recognized the importance of adjusting for post-enrolment drug use in retrospective studies, especially long-term observational studies.

The associations between exposure to several ambient air pollutants, including PM_{10} , NO_2 and CO, and the development and progression of CKD have been previously reported [2, 6, 8, 22–24]. Specifically, previous studies have suggested that increased $\text{PM}_{2.5}$ exposure in CKD patients is associated with worse renal outcomes [5, 7, 25]. However, due to the limited availability of nationwide $\text{PM}_{2.5}$ exposure data, which were accessible only for Seoul before 2015, it was difficult to observe the long-term effects of $\text{PM}_{2.5}$ exposure in the South Korean population. We addressed these constraints by employing nationwide predictive data with high spatial resolution whose accuracy and validity have already been validated in several previous studies [26, 27]. Previous research on ambient air pollutant exposure has mostly been population-based, making it possible to compare incidence rates. However, these studies had limitations in their incorporation of patient factors. Some studies have attempted to adjust for the initial eGFR to overcome this limitation, but there was a lack of adjustment for factors such as drug use, which left a gap in reflecting disease status [2, 5–7, 25]. Our study aimed to overcome these shortcomings by using hospital-wide data, allowing us to adjust for test results and drug use, among other factors. Notably, CKD can be caused by various diseases, and the prognostic factors may differ depending on the underlying condition. Therefore, it is essential to analyse CKD according to its cause, and we specifically targeted DKD patients, which is the most common cause of CKD. A recent retrospective cohort study also aimed to address this limitation by considering various initial laboratory findings and the duration of diabetes in DKD patients.

An association between higher ambient air pollutant exposure and an increased risk of ESKD was also found, particularly highlighting a strong association with $\text{PM}_{2.5}$ [11]. In our cohort, 72.8% of patients had an eGFR < 45 ml/min/1.73 m^2 and 51.6% had an eGFR < 30 ml/min/1.73 m^2 , indicating that there was a greater proportion of advanced DKD patients in this study than in previous studies. Given that the use of drugs with direct effects becomes more critical as the disease advances, these findings on the relationship between $\text{PM}_{2.5}$ and ESKD progression, considering changes in major drug use during the tracking period, provide significant clinical insights.

While the respiratory system is the primary target following inhalation of $\text{PM}_{2.5}$, this pollutant can disrupt multiple physiological barriers and translocate into the systemic circulation. $\text{PM}_{2.5}$ contains toxic components such as free radicals, organic chemicals and transition metals, which can generate or induce reactive oxygen species (ROS). These ROS disrupt cellular physiological and biochemical processes, leading to oxidative stress, inflammation and genotoxicity. These mechanisms alter the normal functions and fates of target cells, resulting in tissue and organ damage and contributing to the exacerbation of chronic diseases such as respiratory system damage, cardiovascular dysfunction, kidney disease and diabetes mellitus [28, 29]. Furthermore, a study showed that $\text{PM}_{2.5}$ exposure affects adipose tissue, inducing insulin resistance and mitochondrial alterations, which in turn influence the development and worsening of T2D in a C57BL/6 mouse model [30]. Another study in db/db mice suggests that $\text{PM}_{2.5}$ exposure aggravates kidney damage by promoting lipid metabolism disorders [31]. Although our study did not directly explore these underlying mechanisms, these prior studies provide additional support for the observed risks associated with $\text{PM}_{2.5}$ exposure in our research.

We made every effort to overcome the limitations we faced and used a time-varying Cox model to carefully adjust for diabetes and hypertension medication use. Despite these efforts, our study has several limitations. First, due to the retrospective nature of the cohort, we lacked individual-level data on confounders such as socio-economic status, physical activity and dietary patterns. To address this, we used patient address information and matched it with publicly available data. Additionally, while we matched air pollution exposure based on patients' residential addresses, this approach did not allow for a precise representation of individualized exposure levels. Overcoming this limitation would require a further comprehensive prospective cohort study. Second, our study utilized data from before 2020, which predates the widespread use of newer drugs such as sodium-glucose co-transporter 2 inhibitors, glucagon-like peptide-1 agonists and other medications like mineralocorticoid receptor antagonists, which were not available in Korea at the time. Future analyses should account for the effects of these medications. Third, there is a need for the development of advanced models that consider the time-varying feedback between changes in blood test results and medication adjustments. Finally, for global validation, it is essential to replicate our findings in other countries.

In this study we investigated the associations between exposure to air pollutants ($\text{PM}_{2.5}$, PM_{10} , NO_2 and CO) and kidney outcomes, adjusting for time-varying changes in the use of antidiabetic agents and RAS blockers after enrolment. Despite accounting for these medication adjustments, higher $\text{PM}_{2.5}$ exposure remained significantly associated with an increased risk of ESKD progression and composite outcomes in patients with DKD. Further research incorporating more detailed individual-level confounder data, the impact of recently

introduced medications of DKD and external validation across diverse populations is warranted.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

This study was approved by the institutional review boards (IRBs) of the Seoul National University Hospital (J-2310-035-1473) and the Seoul Metropolitan Government Boramae Medical Center (20-2023-46). This study was conducted in accordance with the principles of the Declaration of Helsinki. The IRBs waived the need for informed consent because of the retrospective nature of the study and because of the use of anonymous clinical data. Part of this study was presented as an oral presentation at the Korean Society of Nephrology Congress, Seoul, South Korea, in April 2023.

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AUTHORS' CONTRIBUTIONS

J.P.L. and W.J.L. were responsible for conception of the study design, overall supervision of the project and the decision to publish the findings. S.K. and W.H.L. were responsible for data collection. S.K., A.K., W.H.L. and S.H.H. were responsible for data quality control and coordination. H.M.S. was responsible for data analysis. M.P. was responsible for consultation on statistical analysis. H.K., H.H.S., D.K.K., L.S.L. and Y.S.K. were responsible for supporting data interpretation. S.K. and H.M.S. were responsible for writing and editing the manuscript. Each author contributed important intellectual content during manuscript drafting or revision, agreed to be personally accountable for their individual contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature, if appropriate.

DATA AVAILABILITY STATEMENT

The data presented in this study are available upon request from the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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