ORIGINAL RESEARCH

Environmental PM$_{2.5}$ Exposure: An Ignored Factor Associated with Blood Cadmium Level in Hemodialysis Patients

Ching-Wei Hsu[1,2], Ming-Jen Chan[1,2], Cheng-Hao Weng [1,2], Tsung-Yu Tsai[1,2], Tzung-Hai Yen [1,2], Wen-Hung Huang [1,2]

[1]Department of Nephrology and Clinical Poison Center, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan, Republic of China; [2]Chang Gung University, College of Medicine, Taoyuan, Taiwan, Republic of China

Correspondence: Wen-Hung Huang, Department of Nephrology and Clinical Poison Center, Chang Gung Memorial Hospital, 199, Tung-Hwa North Road, Taipei, Taiwan, Republic of China, Tel +886-3-3281200-8181, Fax +886-3-3288662, Email williammedia@gmail.com

Background: The negative impacts of particulate matter with an aerodynamic diameter of 2.5 μm or less (PM$_{2.5}$) are well known. Patients undergoing maintenance hemodialysis (HD) have significantly higher blood cadmium levels (BCLs) than healthy individuals. As elemental cadmium can be found in the PM$_{2.5}$ particle fraction, we conducted this study to assess the effect of environmental PM$_{2.5}$ exposure and other clinical variables on BCLs in maintenance HD patients.

Patient and Methods: This cross-sectional study included 754 hD patients who had previously participated in a BCL study. Demographic, hematological, biochemical and dialysis-related data were collected for analysis. For each patient, the mean PM$_{2.5}$ concentrations in the living environment during the previous 12 and 24 months were recorded and analyzed.

Results: Of all patients, the median BCL of was 0.36 μg/L (range: 0.21, 0.79 μg/L). The mean PM$_{2.5}$ concentration was 28.45 ± 3.57 μg/m^3 during the 12 months and 29.81 ± 3.47 μg/m^3 during the 24 months, respectively. From a multivariate linear regression analysis, log BCL was positively associated with the mean PM$_{2.5}$ concentration during the previous 12 and 24 months. In addition, log BCL was positively associated with the number of days with PM$_{2.5}$ concentrations above the standard level during the previous 12 and 24 months. Moreover, according to the tertiles of days with a daily mean PM$_{2.5}$ concentration above the normal limit in the previous 24 months, patients with the highest exposure days exhibited a significantly higher BCL than those in the other two patient groups.

Conclusion: Chronic environmental exposure to PM$_{2.5}$ is significantly associated with BCLs in maintenance HD patients, and exposure to PM$_{2.5}$-bound cadmium may contribute to the harmful effects on health in this population. Further studies are needed to confirm these observations and to explore the underlying mechanisms.

Keywords: air pollution, cadmium, hemodialysis, particulate matter, PM$_{2.5}$

Introduction

The toxic metals are utilized widely in agricultural and industrial applications, such as pesticides, batteries, alloys and numerous other products.[1] Prolonged and excessive exposure of toxic metals may result in damage to multiple organs.[1] The kidney is a target organ for metal toxicity due to its properties of filtration, reabsorption and concentration of divalent ions.[1] A number of environmental toxins such as cadmium, lead, mercury and arsenic have been linked to renal damage and the progression of chronic kidney disease.[2,3] Although there is evidence to suggest a strong association between exposure to toxic metals and chronic kidney disease, the pathophysiological mechanisms are complex and not clearly understood.[3]

Cadmium is a toxic metal with considerable environmental and occupational concern.[4] The toxicity of cadmium is associated with several clinical complications such as renal damage, bone disease and cancers.[4,5] Notably, cadmium may cause clinical diseases even at very low exposure levels that are far below the limits set by the World Health Organization.[4] A recent report of 13,958 US adults indicated a significant association between environmental exposure

1

of cadmium and all-cause, cancer, cardiovascular disease, and coronary heart disease mortalities.[6] A study of the Swedish population revealed that the exposure of occupational or relatively low environmental levels of cadmium may be a determinant for the development of end-stage renal disease (ESRD).[7] In maintenance hemodialysis (HD) patients, the blood cadmium levels (BCLs) are higher than those of general population and are associated with increased mortality.[8,9] There are studies demonstrated that BCLs are significantly associated with malnutrition, inflammation and even protein-energy wasting in patients with maintenance HD or peritoneal dialysis.[10,11]

In recent decades, air pollution has become a serious problem because of its toxicological effects on human health and the environment.[12] A study of more than 8000 adults suggested that the fine-particulate air pollution contributes to the excess mortality in certain U.S cities.[13] Of these fine particulates, the pollution by particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) is a crucial issue in the developing countries. The epidemiologic evidences indicated that $PM_{2.5}$ is associated with the increased risks of stroke, cardiovascular events and all causes of mortality in general population.[13–15] An environmental study reported that almost all lead, manganese and cadmium components are found in $PM_{2.5}$ particle fraction.[16] The industrial activities may substantially contribute to the content of cadmium in $PM_{2.5}$ particles.[17] A study showed that the cadmium levels in $PM_{2.5}$ particles above the background level indicated moderate to high contamination of the environment.[18]

In 2015, we reported that BCL is an important determinant of mortality in maintenance HD patients.[8] Reviewing the relevant literatures, studies on the relationship between environmental $PM_{2.5}$ and BCL in patients with ESRD are limited, and this relationship remains uncertain. Based on our 2015 survey of HD patients,[8] we conducted a cross-sectional study to explore the potential associations between environmental $PM_{2.5}$ exposure, BCL and other clinical variables in patients undergoing maintenance HD.

Materials and Methods
Ethics Statement
This study was conducted in accordance with the Declaration of Helsinki guidelines and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, an academic medical center in Taiwan (IRB number: 98–1937B). Because this was a retrospective cross-sectional study, the informed consent was waived. All the data were analysed anonymously. All medical records during the study period, including medical history, laboratory data, and inclusion and exclusion criteria, were reviewed by nephrologists. In addition, all individual information was securely protected and was only available to the investigators. The study protocols were complied with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Patients
As stated above, this study was built on our report published in 2015, and all 937 patients in that study were initially included.[8] In the previous work, all participants were recruited from the three HD centers of our hospital (Taipei, Linkou, and Taoyuan). We only enrolled patients who were older than 18 years old with dialysis vintage for more than 6 months, and had previous blood cadmium studies.[8] Patients were excluded if they had histories of occupational exposure to cadmium, metal intoxication, or living in metal-contaminated areas. Patients also were excluded if they had the following criteria: cancers, active infection, hospitalization or surgery during the last three months before enrollment. Of the 937 patients in the previous report, 170 patients were smokers and 13 patients had no $PM_{2.5}$ data available. Finally, this study included 754 maintenance HD patients (Figure 1).

Most patients had been undergoing 4 h of HD three times per week. The patients utilized single-use dialyzers fitted with modified cellulose-based, polyamide or polysulfone membranes. The standard reverse osmosis system was equipped for water purification. In all patients, the dialysate had a standard ionic composition in a bicarbonate-based buffer.

We collected the following data from dialysis charts and/or electronic medical records, including demographics, co-morbidities, dialysis-related and biochemical data. Smoking behavior (defined as persons who had smoked in the past 30 days before study) was also recorded.
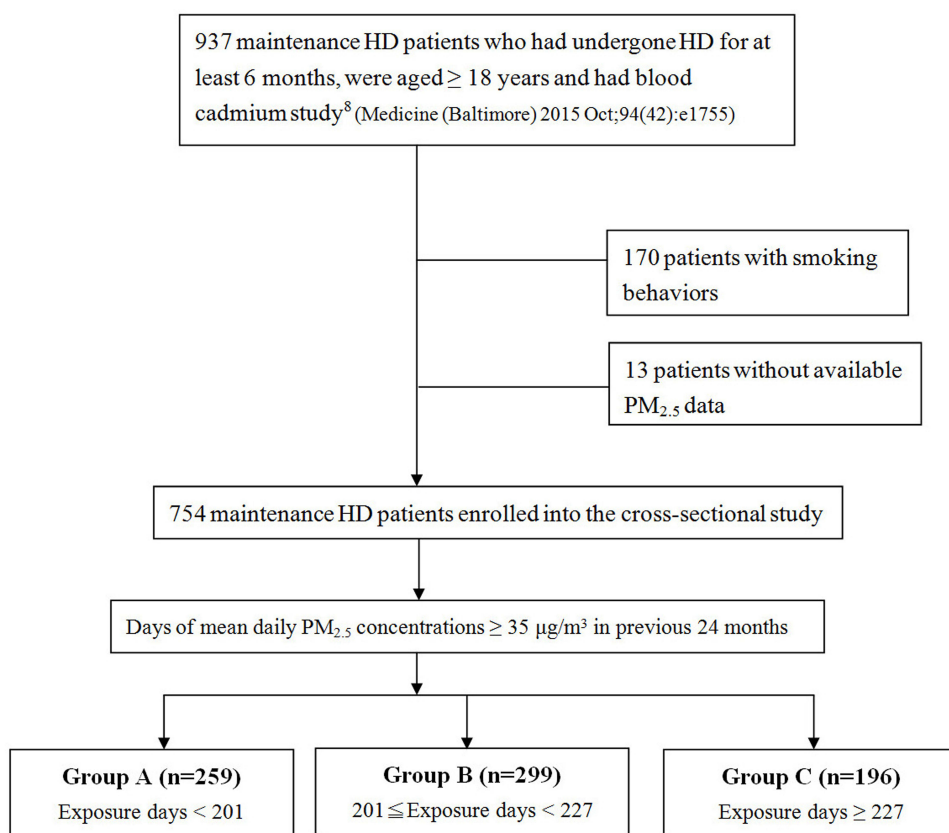
Figure 1 Flow chart of patient selection and grouping.
Abbreviations: HD, hemodialysis; PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

Measurements of Biochemical Parameters

We collected the blood samples during stable outpatient HD sessions to minimize the influence of acute events. The samples were drawn in syringes and needles which were batch-tested and shown not to be contaminated with heavy metals. All samples were taken from the arterial end of the vascular access immediately before the beginning of mid-week HD session, and then centrifuged and stored at −70 °C until used in assays.

We measured the high-sensitivity C-reactive protein (hsCRP) levels by immunonephelometry (Nanopia CRP; Daiichi Inc, Tokyo, Japan), with a detection limit of 0.15 mg/L. We determined the intact parathyroid hormone (iPTH) levels via a chemiluminometric immunoassay (ADVIA Centaur iPTH; Siemens Medical Solutions Diagnostics, New York, NY), with a reference range of 7 to 53 pg/mL. All other parameters were measured using an automated analyzer with a standard laboratory approach. We calculated the protein catabolism rate using validated equations and the data were normalized to the actual body weight.[19] We evaluated the clearance of urea in study patients using the method described by Daugirdas[20] and the data were expressed as Kt/Vurea. Serum calcium levels were corrected using serum albumin levels according to the formula: corrected calcium (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 - serum albumin [g/dL]).

Measurements of Cadmium Levels

Based on the previous study, all 754 patients enrolled had BCL data.[8] The main methods used to measure cadmium levels in the previous study were as follows. To ensure that patients were not exposed to contamination of cadmium during HD, we collected at least 2 samples of water and dialysate from the outlets of reverse osmosis systems and from the inlets of dialysate portion of the dialyzers at each HD center by using cadmium-free plastic bottles. Cadmium levels were measured as previously described.[21,22] Briefly, 900 μL of modifier solution in deionized water and 100 μL of whole blood, or 100 μL of modifier solution and 900 μL dialysate were added to a 1.5-mL Eppendorf tube and immediately

shaken. After overnight storage at 4°C, the tubes were warmed to room temperature, and then whirl-mixed for 5–10 s. The mixed sample was transferred to graphite furnace sampler cups and measured by electro-thermal atomic absorption spectrometry (SpectrAA-220Z; Varian, Palo Alto, CA) with Zeeman's background correction and an L'vov platform. The coefficient of variation for cadmium measurements was 5.0% or less. External quality control was maintained via participation in the National Quality Control Program conducted by the Taiwan government.

Air Quality Status and Analysis

The Taiwan government monitored and recorded the concentrations of air pollution by a network of 27 monitoring stations. We analyzed the data from the Taiwan Air Quality Monitoring Network near or in the study patients' living areas, including the database on the air quality status. The level of $PM_{2.5}$ was checked every hour for 1 year. We calculated the average of approximately 8760 ($24 \times 365 = 8760$) pieces of data from every monitoring station to determine the previous 1-year average level of $PM_{2.5}$ in this study. $PM_{2.5}$ data were generally obtained from monitoring stations in the same district. If a patient lived between 2 monitoring stations, we selected the data of the nearest station for analysis. If a patient lived in a district without a monitoring station, we referenced data from the nearest station (<15 km). Terrain was also considered; the data of the nearest monitoring station on the same side of a mountain that a patient lived on were analyzed. Because no previous study has focused on this issue, we evaluated the mean concentrations of $PM_{2.5}$ in the previous 12 and 24 months for each patient. The normal limit of mean 24 hour $PM_{2.5}$ is defined as level < 35 μg/m^3.[23]

According to the tertiles of days with a daily mean $PM_{2.5}$ concentration $\geq$ 35 μg/m^3 in previous 24 months, we stratified patients into three subgroups for statistical analysis.

Statistical Analysis

We used Kolmogorov–Smirnov test to determine the distribution of continuous variables, and a *P*-value of > 0.05 indicated the normal distribution of data. Continuous variables with normal distribution were presented as mean ± standard deviation, and non-normal variables were expressed as median with interquartile range. Categorical variables are presented as number with percentage. We conducted logarithmic conversion for the non-normally distributed variables, including BCL, hsCRP, iPTH and ferritin. We used one-way analysis of variance (ANOVA) to compare the BCLs among the three groups. To identify factors associated with BCL, we used the linear regression models to determine the correlation between BCL and clinical variables, including baseline data, environmental $PM_{2.5}$ concentrations and the days of $PM_{2.5}$ exceeding the standard level over the past 12 and 24 months before study. All potential variables ($P < 0.1$) in univariate linear regression analysis were selected into multivariate linear regression model with forward stepwise methods. The standardized regression coefficient (β) and 95% confidence interval (CI) were obtained by these models.

We performed data analyses by using Statistical Package for Social Sciences (SPSS), Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at a value of $P < 0.05$.

Results

Characteristics of the Study Population

A total of 754 patients (304 men and 450 women) met the study criteria and were enrolled into this study. The mean age was 56.7 ± 13.3 years, and the mean HD vintage was 6.86 ± 5.37 years. The median BCL was 0.36 μg/L (range: 0.21, 0.79 μg/L). Table 1 lists the demographic and clinical characteristics, including age, gender, body mass index (weight/height^2), co-morbidities, dialysis-related and biochemical data, and environmental $PM_{2.5}$ information. Of all patients, 40.3% were men, 22.1% had diabetes mellitus, 38.3% had hypertension and 4.1% had previous cardiovascular diseases. The mean serum albumin level was 4.05 ± 0.34 g/dL and the median hsCRP level was 2.78 mg/L (range: 1.34, 6.13 mg/L). We analyzed the $PM_{2.5}$ data in the previous 12 and 24 months, which were recorded from the 36 monitoring stations of Taiwan Air Quality Monitoring Network. The mean environmental $PM_{2.5}$ concentration was 28.45 ± 3.57 μg/m^3 during the 12 months, and 29.81 ± 3.47 μg/m^3 during the 24 months before analysis.

Table 1 Demographics, Clinical Characteristics, Blood Cadmium Level and PM$_{2.5}$ Data of Study Patients (n = 754)

Characteristics	Total (n = 754)
Demographics	
Age (years)	56.7 ± 13.3
Gender (male)	304 (40.3%)
Body mass index (kg/m^2)	22.03 ± 3.18
Co-morbidity	
Diabetes mellitus	167 (22.1%)
Hypertension	289 (38.3%)
Previous CVD	31 (4.1%)
Hepatitis B virus infection	81 (10.7%)
Hepatitis C virus infection	147 (19.6%)
Dialysis-related data	
Hemodialysis vintage (years)	6.86 ± 5.37
Erythropoietin (U/kg/week)	78.88 ± 46.84
Fistula as blood access	604 (80.1%)
Hemodiafiltration	150 (19.9%)
Kt/V urea (Daugirdas)	1.83 ± 0.32
Normalized protein catabolic rate (g/kg/day)	1.2 ± 0.269
Residual daily urine of >100 mL	156 (20.7%)
Biochemical data	
Hemoglobin (g/dL)	10.4 ± 1.32
Albumin (g/dL)	4.05 ± 0.34
Creatinine (mg/dL)	10.6 ± 2.34
Corrected-calcium (mg/dL)	9.95 ± 0.91
Phosphate (mg/dL)	4.76 ± 1.32
Ferritin (μg/L)*	329.2 (148, 519.8)
Intact parathyroid hormone (pg/mL)*	129.65 (50.8, 295.25)
hsCRP (mg/L)*	2.78 (1.34, 6.13)
Cardiovascular risks	
Cholesterol (mg/dL)	173.01 ± 37.44
Triglyceride (mg/dL)	159.17 ± 115.47
Low-density lipoprotein (mg/dL)	96.41 ± 30.22
Environmental factors	
Mean environmental PM$_{2.5}$ (μg/m^3), previous 12 months	28.45 ± 3.57

(Continued)

Table 1 (Continued).

Characteristics	Total (n = 754)
Days of $PM_{2.5} > 35$ µg/m³, previous 12 months	111.49 ± 24.5
Mean environmental $PM_{2.5}$ (µg/m³), previous 24 months	29.81 ± 3.47
Days of $PM_{2.5} > 35$ µg/m³, previous 24 months	219.58 ± 51.47
Blood cadmium level (µg/L)*	0.36 (0.21, 0.79)

Notes: Data are presented as mean ± standard deviation or number (percentage). *Non-normal distribution data are presented as median (interquartile range).
Abbreviations: CVD, cardiovascular disease; hsCRP, high sensitivity C-reactive protein; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 µm or less.

Based on the tertiles of days with a daily mean $PM_{2.5}$ concentration ≥ 35 µg/m³ in previous 24 months, we stratified patients into three groups and obtained the following results: the group A (exposure days < 201, n = 259) with mean BCL = 0.789 ± 0.090 µg/L, the group B (201 ≤ exposure days < 227, n = 299) with mean BCL = 0.750 ± 0.089 µg/L, and the group C (exposure days ≥ 227, n = 196) with mean BCL = 1.095 ± 0.136 µg/L. As shown in Figure 2, the patients in group C had a significantly higher BCL than those in groups A and B ($P < 0.05$).

Water and Dialysate Cadmium Levels

The cadmium of all the water and dialysate samples (n = 12) were less than 0.1 µg/L. This is far below the American Association for Advancement of Medical Instrumentation standards (cadmium, < 10 µg/L).

Associations Among BCLs and $PM_{2.5}$ and Other Clinical Variables

In univariate linear regression analysis, log BCL was positively associated with age, log hsCRP, the mean $PM_{2.5}$ concentrations of the previous 12 months and 24 months, and the days with a daily mean $PM_{2.5}$ concentration exceeding the standard level in the previous 12 and 24 months. In contrast, log BCL was negatively associated with serum albumin and creatinine levels (Table 2).
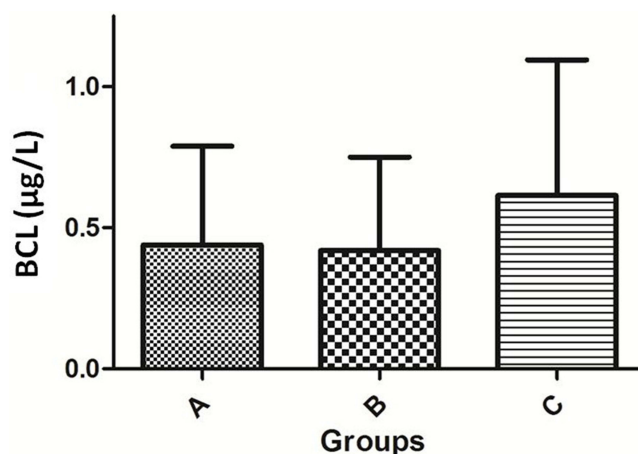

Figure 2 Comparison of the BCLs of three patient groups based on the number of days with a daily mean $PM_{2.5}$ concentration ≥ 35 µg/m³ in the previous 24 months. Patients in group C had a significantly higher BCL than those in groups A and B ($P < 0.05$).
Notes: Mean BCL in the previous 24 months: group A, 0.789 ± 0.090 µg/L; group B, 0.750 ± 0.089 µg/L; group C, 1.095 ± 0.136 µg/L. Days of exposure: group A, < 201 days; group B, 201 to 227 days; group C, ≥ 227 days.
Abbreviation: BCL, blood cadmium level.

Table 2 Associations Between Log BCL, Clinical Variables and PM$_{2.5}$ Data in Study Patients (n = 754), Analyzed by Univariate Linear Regression Analysis

Characteristics	Univariate Linear Regression	
Variables	Standardized Coefficients (*β*) (95% Confidence Interval)	*P*-value
Age (years)	0.138 (0.002, 0.007)	<0.001
Male sex	−0.069 (−0.126, 0.003)	0.060
Body mass index (kg/m^2)	0.022 (−0.007, 0.013)	0.548
Diabetes mellitus (Yes)	0.036 (−0.038, 0.114)	0.326
Hypertension (Yes)	0.002 (−0.063, 0.067)	0.949
Previous CVD (Yes)	0.030 (−0.093, 0.225)	0.415
Hepatitis B virus infection (Yes)	−0.061 (−0.188, 0.015)	0.094
Hepatitis C virus infection (Yes)	0.029 (−0.047, 0.112)	0.429
Hemodialysis duration (years)	−0.030 (−0.008, 0.003)	0.410
Use of erythropoietin (Yes)	−0.026 (−0.178, 0.083)	0.475
Fistula as blood access (Yes)	−0.034 (−0.116, 0.042)	0.356
Hemodiafiltration (Yes)	−0.057 (−0.141, 0.016)	0.120
Kt/V urea (Daugirdas)	0.023 (−0.066, 0.130)	0.522
Normalized protein catabolic rate (g/kg/day)	0.033 (−0.064, 0.171)	0.372
Non-anuria	−0.009 (−0.087, 0.068)	0.814
Hemoglobin (g/dL)	−0.003 (−0.025, 0.023)	0.937
Albumin (g/dL)	−0.127 (−0.253, −0.071)	<0.001
Creatinine (mg/dL)	−0.141 (−0.040, −0.013)	<0.001
Corrected calcium (mg/dL)	−0.058 (−0.062, 0.006)	0.109
Phosphate (mg/dL)	0.038 (−0.011, 0.036)	0.292
Log Ferritin	0.038 (−0.032, 0.103)	0.304
Log intact parathyroid hormone	−0.060 (−0.096, 0.008)	0.098
Log hsCRP	0.080 (0.007, 0.134)	0.029
Cholesterol (mg/dL)	0.041 (0.0001, 0.0010)	0.260
Triglyceride (mg/dL)	0.021 (0.00001, 0.00010)	0.571
Environmental PM$_{2.5}$ (μg/m^3), previous 12 months	0.086 (0.002, 0.019)	0.018
Environmental PM$_{2.5}$ (μg/m^3), previous 24 months	0.092 (0.003, 0.021)	0.011
Days of PM$_{2.5}$ exceeding the daily standard level in previous 12 months	0.082 (0.0001, 0.0030)	0.025
Days of PM$_{2.5}$ exceeding the daily standard level in previous 24 months	0.094 (0.0001, 0.0010)	0.010

Abbreviations: BCL, blood cadmium level; CVD, cardiovascular disease; hsCRP, high sensitivity C-reactive protein; PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

All potential variables with $P < 0.1$ in univariate linear regression analysis were selected into multivariate linear regression model with a stepwise method for further analysis. After adjusting for these potential variables, log BCL was positively associated with the mean PM$_{2.5}$ concentration in previous 12 months (β: 0.076, 95% CI [0.001, 0.018], $P = 0.037$) (Table 3). After adjusting for these potential variables, log BCL was positively associated with the days of PM$_{2.5}$ exceeding the standard level in previous 12 months (β: 0.072, 95% CI [0.0001, 0.0030], $P = 0.047$) (Table 4). Similarly, log BCL was positively associated the mean PM$_{2.5}$ concentration in previous 24 months (β: 0.087, 95% CI [0.002, 0.020], $P = 0.017$) (Table 5), and positively associated with the days of PM$_{2.5}$ exceeding the standard level in previous 24 months (β: 0.086, 95% CI [0.0001, 0.0010], $P = 0.019$) (Table 6).

Table 3 Associations Between Log BCL, Clinical Variables and PM$_{2.5}$ Concentration in the Previous 12 Months, Analyzed by Multivariate Linear Regression Analysis with a Stepwise Method

Characteristics	Multivariate Linear Regression	
Variables	**Standardized Coefficient (*β*) (95% Confidence Interval)**	*P*-value
Age (years)	0.086 (0.0001, 0.0050)	0.032
Albumin (g/dL)		
Creatinine (mg/dL)	−0.104 (−0.034, −0.005)	0.009
Log intact parathyroid hormone		
Log hsCRP		
Mean environmental PM$_{2.5}$ concentration in previous 12 months	0.076 (0.001, 0.018)	0.037

Abbreviations: BCL, blood cadmium level; hsCRP, high sensitivity C-reactive protein, PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

Table 4 Associations Between Log BCL, Clinical Variables and Days with High PM$_{2.5}$ in the Previous 12 Months, Analyzed by Multivariate Linear Regression Analysis with a Stepwise Method

Characteristics	Multivariate Linear Regression	
Variables	**Standardized Coefficient (*β*) (95% Confidence Interval)**	*P*-value
Age (years)	0.085 (0.0001, 0.0050)	0.033
Albumin (g/dL)		
Creatinine (mg/dL)	−0.104 (−0.034, −0.005)	0.009
Log intact parathyroid hormone		
Log hsCRP		
Days of PM$_{2.5}$ exceeding the standard level in previous 12 months	0.072 (0.0001, 0.0030)	0.047

Abbreviations: BCL, blood cadmium level; hsCRP, high sensitivity C-reactive protein, PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

Table 5 Associations Between Log BCL, Clinical Variables and PM$_{2.5}$ Concentration in the Previous 24 Months, Analyzed by Multivariate Linear Regression Analysis with a Stepwise Method

Characteristics	Multivariate Linear Regression	
Variables	**Standardized Coefficient (β)** **(95% Confidence Interval)**	*P*-value
Age (years)	0.086 (0.000, 0.005)	0.030
Albumin (g/dL)		
Creatinine (mg/dL)	−0.105 (−0.034, −0.005)	0.008
Log intact parathyroid hormone		
Log hsCRP		
Mean environmental PM$_{2.5}$ concentration in previous 24 months	0.087 (0.002, 0.020)	0.017

Abbreviations: BCL, blood cadmium level; hsCRP, high sensitivity C-reactive protein, PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

Table 6 Associations Between Log BCL, Clinical Variables and Days with High PM$_{2.5}$ in the Previous 24 Months, Analyzed by Multivariate Linear Regression Analysis with a Stepwise Method

Characteristics	Multivariate Linear Regression	
Variables	**Standardized Coefficient (β)** **(95% Confidence Interval)**	*P*-value
Age (years)	0.085 (0.0001, 0.0050)	0.034
Albumin (g/dL)		
Creatinine (mg/dL)	−0.105 (−0.034, −0.005)	0.009
Log intact parathyroid hormone		
Log hsCRP		
Days of PM$_{2.5}$ exceeding the standard level in previous 24 months	0.086 (0.0001, 0.0010)	0.019

Abbreviations: BCL, blood cadmium level; hsCRP, high sensitivity C-reactive protein, PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

Discussion

The analytical results of this study demonstrated a significant association between environmental PM$_{2.5}$ exposure and BCLs in maintenance HD patients. Following the adjustment for potential variables, a positive correlation was observed between BCLs and the mean PM$_{2.5}$ concentration, as well as the number of days during the previous 12 and 24 months in which PM$_{2.5}$ levels exceeded the standard level in these patients. Based on a review of the published literature, this study may be the first to examine the association between PM$_{2.5}$ exposure and BCLs in ESRD population.

Air pollution has become a major issue in recent decades and has a profound impact on human health.[13,14] It is the single largest environmental contaminant causing a variety of diseases worldwide.[24] There are several sources of the air pollutants, which are mainly emitted from the use of vehicles, fuel combustion and industrial activities in developing countries.[12] As stated by the World Health Organization, the six primary air pollutants that have been identified as having a detrimental impact on human health and the environment are particulate air pollutants, ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides, and lead.[12] Of these pollutants, PM$_{2.5}$ can enter the bloodstream and affect whole body of humans by deeply penetrating into the lung and damaging alveoli.[15,25,26] The ambient PM$_{2.5}$ may cause 4 million deaths annually from cardiopulmonary impairment such as heart diseases, respiratory infections, chronic

pulmonary complications, cancers and others.[24] In addition to cardiopulmonary diseases, $PM_{2.5}$ may have contributed to other clinical complications, such as triggering diabetes mellitus and increasing the risk of adverse birth outcomes.[27] Of note, $PM_{2.5}$ can contribute to a range of harmful effects in humans at very low levels of environmental exposure, well below national standards.[27] In basic studies, $PM_{2.5}$ has detrimental effects on kidneys with normal glomerular filtration rate.[28] The proposed mechanism of renal damage by $PM_{2.5}$ is complicated, including $PM_{2.5}$ accumulation in kidneys, endothelial dysfunction, renin-angiotensin system abnormalities, inflammation, oxidative stress, DNA damage, apoptosis, autophagy and others.[28] In epidemiologic studies, $PM_{2.5}$ is significantly correlated with lower glomerular filtration rate, higher prevalence of chronic kidney disease, and the increased risk of ESRD in general population.[28–31] Although studies have demonstrated a correlation between $PM_{2.5}$ and renal damage, the precise mechanisms remain unclear and warrant further investigation due to the complex composition of $PM_{2.5}$ particles.[12,13,16,17]

Cadmium is a ubiquitous environmental pollutant in the natural and occupational environments.[5,32] The higher levels of cadmium in the human body were associated with an increased risk of all-cause, cardiovascular and cancer mortality.[5,6] Exposure to cadmium has been reported in several ways over the past decades, including working in a cadmium-using factory, eating contaminated food, living in cadmium-contaminated areas, smoking cigarettes, and others.[5,8] It is noteworthy that cadmium could be carried by atmospheric $PM_{2.5}$ particle because of its large specific surface area and the strong capacity to carry heavy metals.[26] The cadmium incorporated with $PM_{2.5}$ can enter the human body by inhalation and potentially damage several organs.[13–15] In an experimental study in rats, low concentrations of cadmium in $PM_{2.5}$ particles had been found to induce genetic toxicity by damaging DNA or chromosomes.[33] A recent in vitro experiment demonstrated the pivotal role of cadmium accumulation by $PM_{2.5}$ in renal injury.[34] The findings revealed that $PM_{2.5}$ extract significantly reduced the survival of renal tubular epithelial cells. In epidemiological studies, the presence of cadmium in $PM_{2.5}$ particles above the background concentration has been linked to higher levels of environmental contamination and adverse effects on human health. A study conducted in China indicated that cadmium in $PM_{2.5}$ particles is carcinogenic to humans, as the lifetime cancer risk posed by cadmium exceeds the threshold range for cancer risk.[35] A recent study demonstrated that cadmium levels in children's blood are associated with $PM_{2.5}$ exposure, and that $PM_{2.5}$-bound cadmium exposure contributes to the development of serious health risks in children.[36] Nevertheless, further detailed and comprehensive studies are required to clarify the mechanisms underlying these processes.

In the healthy population, studies have shown an association between BCLs and exposure to $PM_{2.5}$. A study of 300 children provided evidence that the levels of cadmium in both $PM_{2.5}$ and blood are markedly elevated in an area engaged in the recycling of electronic waste compared to a reference area, with an increased prevalence of respiratory symptoms such as coughing.[37] A study of 13,626 children found a significant correlation between ambient $PM_{2.5}$ exposure and BCL, suggesting that environmental countermeasures are essential to reduce its impact on health.[36] As blood cadmium has a very long half-life of about 7 to 16 years, it can serve as a useful marker for assessing body burden in the general population and is also likely to be a good index of body cadmium burden in ESRD patients.[11] In the present study of patients undergoing maintenance HD, linear regression analysis showed that both mean $PM_{2.5}$ concentrations and the number of days with $PM_{2.5}$ above the standard level were positively associated with BCLs in the previous 12 and 24 months. Furthermore, according to the tertiles of days with a daily mean $PM_{2.5}$ concentration above the normal limit in the previous 24 months, patients with the highest exposure days exhibited a significantly higher BCL than those in the other two patient groups. All these findings strongly suggest that inhaled $PM_{2.5}$ particles may lead to chronic accumulation of cadmium in the bodies of ESRD patients. To our knowledge, this may be the first study to indicate an association between $PM_{2.5}$ exposure and body burden of cadmium in chronic dialysis patients. Although the diversity and complexity of $PM_{2.5}$ components make it difficult to determine the exact effects of cadmium accumulation, the loss of normal ability to excrete cadmium in urine and the difficulty of eliminating cadmium by dialysis may be the main reasons for the accumulation of cadmium in the blood of these patients.[10] However, further research is needed to clarify this observation.

There were some limitations of this study. First, the daily intake of cadmium from food was not available. However, our dialysis centers routinely educate patients about dietary control, especially the importance of avoiding heavy metals. Second, the causal relationship between $PM_{2.5}$ and BCLs could not be determined because of the cross-sectional design of this study. Hence, we used the mean $PM_{2.5}$ levels in the previous 12 and 24 months for the analysis of BCLs, which is

similar to a semi-cohort study. The findings suggest a potential correlation between exposure to PM$_{2.5}$ and the body burden of cadmium in chronic dialysis patients. Third, as the study was conducted at a single center with a smaller sample size than other national surveys, the possibility of selection bias and a type 2 statistical error could not be discounted. A longitudinal prospective study with a larger sample size measuring PM$_{2.5}$ exposure and BCLs at multiple time points is needed to assess the external validity of this study.

Conclusion

This study demonstrated that chronic exposure to PM$_{2.5}$ is closely associated with BCLs in maintenance HD patients and that exposure to PM$_{2.5}$-bound cadmium may contribute to adverse health effects in this population. The World Health Organization has classified cadmium as a human carcinogen and cancer is a common cause of death in ESRD patients.[5,8,9] Our results strongly support for the strict enforcement of relevant legislations to protect the environment from the detrimental impacts on chronic dialysis patients. Further longitudinal studies are needed to confirm the analytical results presented here.

Abbreviations

BCL, blood cadmium level; β, standardized regression coefficient; CI, confidence interval; ESRD, end-stage renal disease; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; PM$_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

Data Sharing Statement

The datasets for the current study were available from the corresponding author on reasonable request.

Acknowledgments

We would like to thank all the parents who participated in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors declare that there are no conflicts of interest in this work.

References

1. Lentini P, Zanoli L, Granata A, et al. Kidney and heavy metals - The role of environmental exposure (Review). *Mol Med Rep*. 2017;15 (5):3413–3419. doi:10.3892/mmr.2017.6389
2. Díaz García JD, Arceo E. Renal damage associated with heavy metals: review work. *Rev Colomb Nefrol*. 2018;5(1):43–53. doi:10.22265/acnef.5.2.254
3. Sabath E, Robles-Osorio ML. Renal health and the environment: heavy metal nephrotoxicity. *Nefrología*. 2012;32:279–286.
4. Jarup L. Cadmium overload and toxicity. *Nephrol Dial Transplant*. 2002;17(Suppl 2):35–39. doi:10.1093/ndt/17.suppl_2.35
5. Jarup L, Berglund M, Elinder CG, et al. Health effects of cadmium exposure--a review of the literature and a risk estimate. *Scand J Work Environ Health*. 1998;24(Suppl 1):1–51.
6. Menke A, Muntner P, Silbergeld EK, et al. Cadmium levels in urine and mortality among U.S. adults. *Environ Health Perspect*. 2009;117 (2):190–196. doi:10.1289/ehp.11236
7. Hellstrom L, Elinder CG, Dahlberg B, et al. Cadmium exposure and end-stage renal disease. *Am J Kidney Dis*. 2001;38(5):1001–1008. doi:10.1053/ajkd.2001.28589

8. Hsu CW, Yen TH, Chen KH, et al. Effect of blood cadmium level on mortality in patients undergoing maintenance hemodialysis. *Medicine*. 2015;94(42):e1755. doi:10.1097/MD.0000000000001755

9. Vanholder R, Cornelis R, Dhondt A, et al. The role of trace elements in uraemic toxicity. *Nephrol Dial Transplant*. 2002;17(Suppl 2):2–8. doi:10.1093/ndt/17.suppl_2.2

10. Hsu CW, Lin JL, Lin-Tan DT, et al. Association between blood cadmium levels and malnutrition in peritoneal dialysis. *BMC Nephrol*. 2014;15(1):17. doi:10.1186/1471-2369-15-17

11. Hsu CW, Lin JL, Lin-Tan DT, et al. Association of environmental cadmium exposure with inflammation and malnutrition in maintenance haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(4):1282–1288. doi:10.1093/ndt/gfn602

12. Ghorani-Azam A, Riahi-Zanjani B, Balali-Mood M. Effects of air pollution on human health and practical measures for prevention in Iran. *J Res Med Sci*. 2016;21(1):65. doi:10.4103/1735-1995.189646

13. Dockery DW, Pope CA, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med*. 1993;329(24):1753–1759. doi:10.1056/NEJM199312093292401

14. Pope CA, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109(1):71–77. doi:10.1161/01.CIR.0000108927.80044.7F

15. Yitshak Sade M, Novack V, Ifergane G, et al. Air pollution and ischemic stroke among young adults. *Stroke*. 2015;46(12):3348–3353. doi:10.1161/STROKEAHA.115.010992

16. Hrsak J, Sega K, Balagovic I. Lead, manganese, and cadmium content in PM10 and PM2.5 particle fractions--a pilot study. *Arh Hig Rada Toksikol*. 2000;51(2):243–247.

17. Thomaidis NS, Bakeas EB, Siskos PA. Characterization of lead, cadmium, arsenic and nickel in PM(2.5) particles in the Athens atmosphere, Greece. *Chemosphere*. 2003;52(6):959–966. doi:10.1016/S0045-6535(03)00295-9

18. Maina EG, Gachanja AN, Gatari MJ, et al. Demonstrating $PM_{2.5}$ and road-side dust pollution by heavy metals along Thika superhighway in Kenya, sub-Saharan Africa. *Environ Monit Assess*. 2018;190(4):251. doi:10.1007/s10661-018-6629-z

19. Sargent JA. Control of dialysis by a single-pool urea model: the national cooperative dialysis study. *Kidney Int Suppl*. 1983;(13):S19–25.

20. Daugirdas JT. The post: pre-dialysis plasma urea nitrogen ratio to estimate K.t/V and NPCR: mathematical modeling. *Int J Artif Organs*. 1989;12(7):411–419.

21. Lin JL, Lin-Tan DT, Chu PH, et al. Cadmium excretion predicting hospital mortality and illness severity of critically ill medical patients. *Crit Care Med*. 2009;37(3):957–962. doi:10.1097/CCM.0b013e318198675c

22. Lind Y, Engman J, Jorhem L, et al. Cadmium accumulation in liver and kidney of mice exposed to the same weekly cadmium dose continuously or once a week. *Food Chem Toxicol*. 1997;35(9):891–895. doi:10.1016/S0278-6915(97)00068-9

23. Gao Y, Nelson ED, Field MP, et al. Characterization of atmospheric trace elements on PM2.5 particulate matter over the New York–new jersey harbor estuary. *Atmos Environ*. 2002;36(6):1077–1086. doi:10.1016/S1352-2310(01)00381-8

24. Thangavel P, Park D, Lee YC. Recent insights into particulate matter (PM(2.5))-mediated toxicity in humans: an overview. *Int J Environ Res Public Health*. 2022;19(12):7511. doi:10.3390/ijerph19127511

25. Dockery DW, Stone PH. Cardiovascular risks from fine particulate air pollution. *N Engl J Med*. 2007;356(5):511–513. doi:10.1056/NEJMe068274

26. Xing YF, Xu YH, Shi MH, et al. The impact of PM2.5 on the human respiratory system. *J Thorac Dis*. 2016;8(1):E69–E74. doi:10.3978/j.issn.2072-1439.2016.01.19

27. Feng S, Gao D, Liao F, et al. The health effects of ambient PM2.5 and potential mechanisms. *Ecotoxicol Environ Saf*. 2016;128:67–74. doi:10.1016/j.ecoenv.2016.01.030

28. Xu W, Wang S, Jiang L, et al. The influence of PM(2.5) exposure on kidney diseases. *Hum Exp Toxicol*. 2022;41:9603271211069982. doi:10.1177/09603271211069982

29. Chen SY, Chu DC, Lee JH, et al. Traffic-related air pollution associated with chronic kidney disease among elderly residents in Taipei City. *Environ Pollut*. 2018;234:838–845. doi:10.1016/j.envpol.2017.11.084

30. Lin SY, Ju SW, Lin CL, et al. Air pollutants and subsequent risk of chronic kidney disease and end-stage renal disease: a population-based cohort study. *Environ Pollut*. 2020;261:114154. doi:10.1016/j.envpol.2020.114154

31. Wang J, Li D, Sun Y, et al. Air pollutants, genetic factors, and risk of chronic kidney disease: findings from the UK Biobank. *Ecotoxicol Environ Saf*. 2022;247:114219. doi:10.1016/j.ecoenv.2022.114219

32. Mezynska M, Brzoska MM. Environmental exposure to cadmium-a risk for health of the general population in industrialized countries and preventive strategies. *Environ Sci Pollut Res Int*. 2018;25(4):3211–3232. doi:10.1007/s11356-017-0827-z

33. Li Q, Liu H, Alattar M, et al. The preferential accumulation of heavy metals in different tissues following frequent respiratory exposure to PM2.5 in rats. *Sci Rep*. 2015;5(1):16936. doi:10.1038/srep16936

34. Kuang X A study on the key role of cadmium accumulation induced by PM2.5 exposure in renal injury. *ISEE conference abstracts*. 2018.

35. Zhao XL, Jiang GG, Song ZL, et al. Concentrations of heavy metals in PM2.5 and health risk assessment around Chinese New Year in Dalian, China. *Open Geosci*. 2021;13(1):1366–1374. doi:10.1515/geo-2020-0308

36. Wu Y, Yang X, Wang H, et al. Relationship between ambient PM2.5 exposure and blood cadmium level in children under 14 years in Beijing, China. *J Hazard Mater*. 2021;403:123871. doi:10.1016/j.jhazmat.2020.123871

37. Zeng X, Xu X, Zheng X, et al. Heavy metals in PM2.5 and in blood, and children's respiratory symptoms and asthma from an e-waste recycling area. *Environ Pollut*. 2016;210:346–353. doi:10.1016/j.envpol.2016.01.025