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Long-Term Exposure to Fine Particulate Matter ($PM_{2.5}$) and Cardiovascular Disease Mortality among Renal Transplant Recipients

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Abstract

***Background*:** Substantial evidence has established links between air pollution and increased risks of overall morbidity and mortality, especially for respiratory and cardiovascular diseases. However, little research has explored these relationships among highly sensitive populations, such as renal transplant recipients. Despite the improvement in quality of life after renal transplantation, cardiovascular diseases (CVD) are major causes of graft loss and mortality. The present study was designed to assess the association between long-term ambient fine particulate matter ($PM_{2.5}$) and risk of CVD-related mortality, including CHD, stroke, sudden cardiac arrest, and CHF, among renal transplant recipients.

***Methods*:** This retrospective cohort study consists of transplant data from 2001 to 2015, and includes 93,857 non-smoking, adult renal transplant recipients who have lived in the

contiguous United States at the same location throughout the study period. Annual-average concentrations for the three ambient air pollutants ($PM_{2.5}$, O_3, and NO_2) were assigned to subjects' residential ZIP codes. Cox proportional hazard models were used to assess the association between $PM_{2.5}$ and CVD mortality risk.

***Results*:** In the multivariable-adjusted models, a 10 ug/m^3 increase in ambient $PM_{2.5}$ levels was associated with increased risk of total CVD (HR=1.85, 95 % CI: 1.57 – 2.17), CHD (HR=2.20, 95 % CI: 1.53 – 3.17), stroke (HR=1.82, 95%CI: 1.15 – 2.89), and cardiac arrest (HR=1.77, 95% CI: 1.42 – 2.19). There was no clear association between $PM_{2.5}$ and risk of CHF mortality.

***Conclusions*:** The findings of this study provide strong evidence supporting an adverse effect of ambient $PM_{2.5}$ in this vulnerable group. Positive associations were found between $PM_{2.5}$ and all CVD mortality outcomes, except CHF mortality. Our findings raise the question of whether increased emphasis should be placed on implementing preventive strategies to lessen the impact of air pollution on CVD risk.

Keywords

Air pollution; fine particulate matter; cardiovascular disease; mortality; renal transplantation

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States, responsible for more deaths than cancer and chronic lower respiratory disease combined, according to 2015 statistics from the American Heart Association [1]. While heart disease is a concern for the population as a whole, some groups are at greater risk for developing and dying from CVDs. One such vulnerable group is renal transplant recipients [2, 3]. The incidence for CVDs is much higher among people with end-stage renal disease (ESRD) and continues even after renal transplantation, which can be partially explained by commonly shared risk factors between ESRD patients and renal transplant recipients, such as hypertension, diabetes mellitus, obesity, and dyslipidemia [4-6]. For most patients with ESRD, renal transplantation is the treatment of choice [7]. Transplantation has been associated with better health outcomes and lower health care costs compared with dialysis. In 2015 alone, a total of 18,805 kidney transplant procedures were performed in the U.S., with 83,978 patients on the waiting list for kidney transplantation [7]. Despite the gains in overall health, renal transplant recipients are still at much higher risk of morbidity and mortality from CVD compared to the general public, identifying a critical need for reducing CVD among this vulnerable population [2, 3, 8, 9].

In addressing CVD risk among renal transplant recipients, it is important to consider risk factors and identify potential opportunities for intervention. In addition to the traditional risk factors, numerous epidemiological studies have linked ambient air pollutants, especially fine particulate matter, with CVD morbidity and mortality [10-20]. In 2015, ambient $PM_{2.5}$ pollution alone was classified as the fifth-ranking mortality risk factor worldwide [13]. Approximately 4.2 million deaths and 130.1 million disability-adjusted life-years have been attributed to ambient $PM_{2.5}$ levels, causing a 20% increase in death compared with 1990 estimates [13]. Moreover, higher risk rates

associated with ambient air pollutant levels have been observed among subpopulations, such as renal transplant recipients [18], smokers [21], females [22, 23], and people with diabetes [24-26]. In contrast, a reduction in $PM_{2.5}$ levels and change in the composition of $PM_{2.5}$ has been linked to a decline in CVD morbidity and mortality [27-30].

To date, very few studies have assessed the potential adverse effects of ambient air pollutants on renal transplant recipients, and even fewer studies have focused on particulate matter. In 2011, Spencer-Hwang, et al., reported a positive association between ambient O_3 levels and risk of CHD mortality (RR=1.34; 95% CI, 1.03 – 1.76) among renal transplant recipients during the 7 year study period [18]. However, the researchers did not find a significant association between CHD mortality and ambient PM_{10} levels (RR=0.95; 95% CI, 0.79 – 1.15). Unfortunately, this study lacked data on ambient $PM_{2.5}$ levels, which are more strongly associated with CVD mortality than PM_{10} [11, 23, 31].

While PM_{10} has been significantly associated with adverse health outcomes [32, 33], it is thought that $PM_{2.5}$ can have a stronger effect, since its smaller particle size can penetrate deeper into the lungs, and is more easily transported into the blood stream, where it can cause greater damage [34].

In a 2016 study of mice, Nemmar, et al. found a significant association between prolonged exposure to diesel exhaust particles, consisting primarily of particulate matter, and the aggravation of chronic renal failure due to oxidative stress, inflammation and DNA damage [35].

There are few studies on the relationship between ambient air pollution and health outcomes among renal transplant recipients in general, and especially that of fine particulate matter. The purpose of this study was to assess the association between annual levels of ambient fine particulate matter ($PM_{2.5}$), and risk of CVD-related mortality, including CHD, stroke, sudden cardiac arrest, and CHF after controlling for potential confounders among renal transplant recipients in the United States.

2. Materials and Methods

2.1 Study Population

Study participants were identified from the U.S. Renal Data System (USRDS), a national data repository containing extensive demographic (including updated residential ZIP codes), diagnostic, hospital site, and mortality data for persons living with ESRD [7].

The study population (N=106,354) includes renal transplant recipients, 18 years and older, who had their first transplant procedure between 2001 and 2015, with a minimum of one year of graft survival, and who have lived in the contiguous U.S. at the same ZIP code throughout follow-up. Subjects were followed until date of CVD mortality or censoring, which occurred at the time of death due to other causes or at the end of the follow-up period (12/31/2015). Subjects with prevalent CVD (n=9,269) at the time of transplant and, in addition, current smokers without CVD (n=3,228) were excluded (Table S1). Thus, the final analytic study population consists of 93,857 non-smoking renal transplant recipients.

The study was approved by the Loma Linda University Institutional Review Board (IRB) as required.

2.2 Outcome Assessment

Fatal cases of CHD were identified from the USRDS using the Centres for Medicare & Medicated Services (CMS) ESRD Death Notification codes (Table S2 in the Supplement) [36]. Primary cause of death among renal transplant recipients was used to classify study participants into cases and non-cases based on the mortality categories in the ESRD Death Notification Form [37]. The following are the fatal CVD outcomes assessed and their definitions:

Total CVD mortality: A subject classified with a total CVD mortality event if the underlying cause of death was CHD, CHF, stroke or sudden cardiac arrest as they are defined below.

CHD mortality: Underlying cause of death was myocardial infarction or atherosclerotic heart disease.

CHF mortality: Underlying cause of death was congestive heart disease.

Stroke mortality: Underlying cause of death was cerebrovascular accident, including intracranial haemorrhage or ischemic brain damage/anoxic encephalopathy.

Sudden cardiac arrest mortality: Underlying cause of death was cardiac arrhythmia or cardiac arrest, cause unknown.

2.3 Pollutant Exposure Assignment

To obtain robust estimates of air pollutants, integrated empirical geographic (IEG) regression models developed by Kim et al were used to calculate the annual-average concentrations of $PM_{2.5}$, O_3 , and NO_2 after adjusting for several important geographical factors, including land use and population density [38-40]. In addition to satellite-derived estimates of air pollution levels, the daily measurements of air pollutants at all Air Quality System (AQS) monitoring sites from U.S. Environmental Protection Agency data repository were used to build the IEG regression models [39]. The air pollutant estimates can be obtained from the Center for Air, Climate, and Energy Solutions (https://www.caces.us/data). Further details on the estimation method and model building are explained elsewhere [39]. The annual mean concentrations of ambient $PM_{2.5}$, O_3 and NO_2 from 2001 to 2015 were assigned to each individual based on residential ZIP codes using geographical information system software (GIS). Yearly levels of ambient air pollutants were assigned based on changing attained-age risk sets. These estimates were then merged with USRD data for each subject.

2.4 Potential Confounding Variables

The USRDS database encompasses a wealth of information on several important factors used to adjust for potential confounding effects, including demographics, lifestyle factors, medical history, and transplant-related factors. Covariates were added to the models with a-priori specification and included age; gender; race; primary cause of ESRD (diabetes, hypertension, primary glomerulonephritis, polycystic kidney disease, other factors); length in years from first ESRD services to first transplant (0-1, 2 -5, 6 - 10, 10+ years); donor type (deceased/living); ESRD network categories (low, medium, high transplant ratio); BMI categories (< 18.5, 18.5 - <25, 25 - <30 , 30+); types of anti-rejection medications (e.g., cyclosporine [yes/no] or tacrolimus [yes/no]); history of hypertension (yes/no), and history of diabetes (yes/no). Anti-rejection medications were

evaluated on an intention-to-treat basis. ESRD regional networks were classified based on their standardized transplant ratio [41].

2.5 Statistical Analysis

Descriptive statistics for demographic and health characteristics in the overall study cohort were calculated according to quartiles of annual average $PM_{2.5}$ levels (ug/m^3) and given as mean ± standard deviation for continuous variables, and a number with valid percentages for categorical variables. Pearson Chi-square and one-way ANOVA were performed to evaluate the associations between these demographic and health characteristics and $PM_{2.5}$ quartiles after assessing the assumptions of these statistical tests.

Time-dependent Cox-proportional hazard regression models with attained age as the time variable and left truncation by age at time of transplant were used to estimate the association between $PM_{2.5}$ and risk of total CVD, CHD, stroke, sudden cardiac arrest and CHF mortality after adjusting for covariates. Ambient air pollutant levels were assigned within Cox regression models as a 1-year average incrementing yearly for each risk set.

The baseline Cox regression model was developed based on an a-priori specification that included $PM_{2.5}$, gender, race and years since first transplant. Primary cause of ESRD (diabetes, hypertension, primary glomerulonephritis, polycystic kidney disease, other factors), length in years from first ESRD services and first transplant (0-1, 2 -5, 6 - 10, + 10 years), donor type, ESRD Network categories (low, medium, and high STR), BMI categories (< 18.5, 18.5 - <25, 25 - <30, 30 +), and immunosuppressive medications (cyclosporine and tacrolimus) were added to the final model.

Considering the change in the ambient levels of $PM_{2.5}$ in the last few decades, $PM_{2.5}$ categories were created by calculating the medians of 25^{th}, 50^{th} and 75^{th} percentiles for the annual $PM_{2.5}$ concentrations from 2001 through 2015. The linearity assumption for the main exposure variable with mortality outcomes was assessed graphically by plotting the estimated coefficients of $PM_{2.5}$ quartiles; this was met for all outcomes except CHF.

Additionally, we assessed the relationship between $PM_{2.5}$ quartiles and mortality outcomes. Time-dependent variables were included in the final model if the proportionality assumption was not met, and the effects were reported at an average age of 60 years as indicated in Table 1 and Table 2.

Sensitivity Analysis was also done where we included the 9,269 who were excluded at baseline because of prevalent CVD. We assessed each of the mortality outcomes using the same single-pollutant full model as was used in the analytic population (Table 1)

SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA) was used to perform the main analyses of the study. ArcGIS Desktop (release 10.6; Esri, Redlands, CA, USA) was used to geocode air pollutant levels and create maps.

Table 1 Multivariable adjusted hazard ratios for CVD fatal events per 10 ug/m^3 increment of $PM_{2.5}$: Single pollutant model.

	Basic Model* N= 92,965		Single Pollutant Full Model** N=85,171	
Outcome (Mortality)	# events	HR (95%CI)	# events	HR (95%CI)
Total CVD	3,000	2.48 (2.13, 2.90)	2,783	1.85 (1.57, 2.17)[¥]
CHD	607	3.17 (2.27, 4.43)	564	2.20 (1.53, 3.17)
Stroke	385	2.77 (1.81, 4.25)	358	1.82 (1.15, 2.89)
Cardiac arrest	1,768	2.42 (1.98, 2.96)	1,643	1.77 (1.42, 2.19)[¥]
CHF	240	1.28 (0.73, 2.25)	218	0.85 (0.50, 1.44)

[*]Adjusted for all of the following variables: sex, race, and years after transplant.

[**]Adjusted for all of the following variables: sex, race, years after transplant, primary cause of ESRD, length in years from first ESRD services and first transplant, donor type, ESRD network categories, BMI categories, and immunosuppressive medications; [¥] Effect estimates at attained age of 60 yrs. using time-dependent variables.

Table 2 Multivariable adjusted hazard ratios for CVD fatal events per 10 ug/m^3 increment of $PM_{2.5}$: Two pollutant models with Ozone and NO_2.

	Full model adjusted for O_3 N=85,171		Full model adjusted for NO_2 N=85,171	
Outcome (Mortality)	# events	HR (95%CI)	# events	HR (95%CI)
Total CVD	2,783	2.05 (1.71, 2.45) [¥]	2,783	2.30 (1.87, 2.82) [¥]
CHD	564	2.19 (1.45, 3.31)	564	2.95 (1.86, 4.67)
Stroke	358	2.07 (1.23, 3.47)	358	3.20 (1.76, 5.81)
Cardiac arrest	1,643	1.95 (1.55, 2.45) [¥]	1,643	2.02 (1.54, 2.63) [¥]
CHF	218	1.27 (0.70, 2.28)	218	0.95 (0.46, 1.35)

[*]Adjusted for all of the following variables: sex, race, years after transplant, primary cause of ESRD, length in years from first ESRD services and first transplant, donor type, ESRD network categories, BMI categories, and immunosuppressive medications; [¥] effect estimates at attained age of 60 yrs. using time-dependent variables.

3. Results

3.1 Study Population

The study population included 93,857 non-smoking renal transplant recipients from across the entire continental U.S. (Figure 1) who had lived at the same ZIP code during the entire follow-up period. During a median follow-up of 14.91 years, 3,082 fatal CVD cases were reported, of which 624 were due to CHD; 245 to CHF; 1,810 were cardiac arrests, and 403 were due to stroke. The annual levels of ambient air pollutants are displayed in Table 3. When comparing demographics and health characteristics of the study cohort across differing categories of ambient $PM_{2.5}$, significant differences in some of these factors were observed, especially among those in the highest quartile of $PM_{2.5}$ (> 12 ug/m^3). Transplant recipients in the highest quartile were more likely to be non-white; female; underweight (BMI<18.5); have received a kidney from a cadaveric

donor; have ESRD attributed to diabetes or hypertension; have a longer period between first ESRD service and first transplant procedure, and to be registered within the ESRD network with a low or medium transplant ratio (Table 4). On the other hand, there was no significant difference in years since the first transplant between the $PM_{2.5}$ quartiles (Table 4).

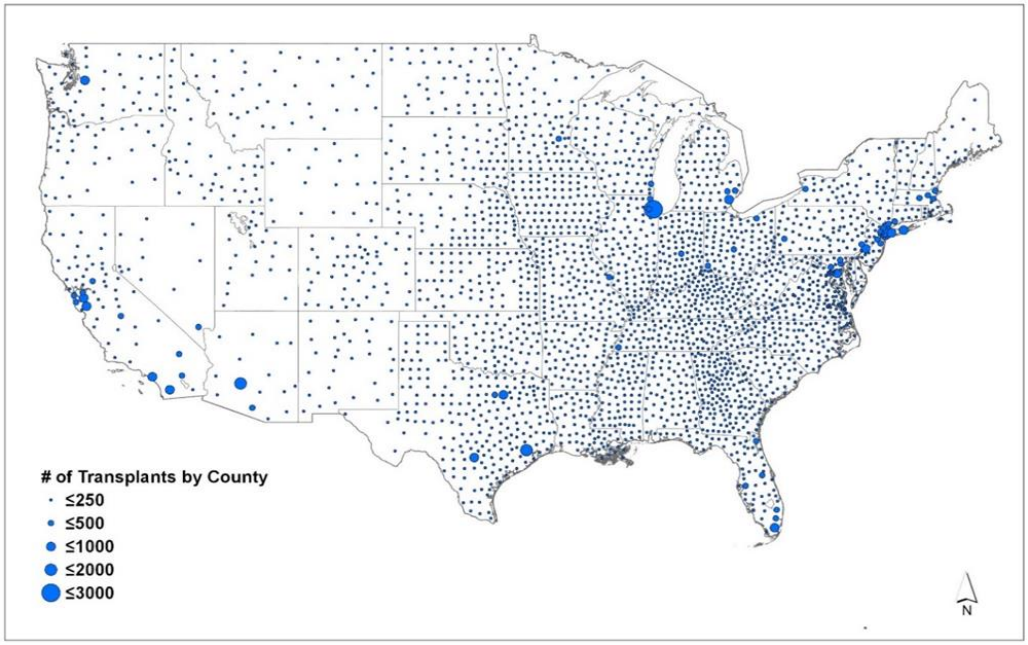

Figure 1 Distribution of renal transplant recipient cohort subjects (age >18 years and transplanted between Jan 2001 – Jan 2015) by county.

Table 3 Annual levels of $PM_{2.5}$, O_3, and NO_2 by calendar year.

	$PM_{2.5}$(ug/m^3)	O_3(ppb)	NO_2 (ppb)
Year	Median (Min – Max) *	Median (Min – Max) *	Median (Min – Max) *
2001	12.57 (01.78, 27.38)	51.21 (27.27, 66.84)	11.66 (01.13, 36.79)
2002	12.26 (02.20, 26.34)	53.81 (27.87, 65.14)	11.80 (00.26, 37.66)
2003	11.94 (02.53, 25.65)	49.00 (25.29, 64.50)	10.99 (01.00, 37.12)
2004	11.75 (01.81, 23.84)	46.32 (27.35, 63.51)	09.76 (00.17, 35.87)
2005	12.66 (01.42, 20.48)	50.69 (24.14, 63.42)	10.36 (00.08, 36.21)
2006	11.55 (01.52, 18.81)	49.53 (31.46, 63.45)	09.29 (00.19, 34.36)
2007	11.83 (01.77, 20.73)	49.74 (28.16, 64.81)	08.78 (00.39, 32.72)
2008	10.63 (01.82, 21.23)	48.03 (28.13, 60.32)	08.01 (00.26, 31.37)
2009	09.39 (02.30, 18.27)	43.25 (28.42, 57.16)	06.92 (00.23, 35.31)
2010	09.56 (01.82, 15.21)	46.79 (19.92, 60.26)	06.96 (00.69, 31.34)
2011	09.60 (02.18, 14.94)	47.52 (24.25, 62.14)	07.08 (00.36, 31.50)
2012	09.02 (02.52, 13.37)	49.78 (24.36, 63.41)	06.67 (00.34, 28.63)
2013	08.64 (02.34, 19.06)	44.42 (25.62, 58.09)	06.30 (00.01, 25.84)
2014	08.63 (02.14, 19.27)	44.17 (27.59, 56.94)	06.08 (00.20, 25.03)
2015	08.19 (01.94, 15.67)	45.18 (27.12, 58.35)	05.92 (00.41, 24.26)

*Median (Minimum – Maximum); ppb = part per billion)

Table 4 Demographic and health characteristics of overall study cohort according to quartile of annual average of $PM_{2.5}$ (ug/m^3).

Characteristic	Q1 Median (Min – Max) 7.7 (2.1 – 9.0)	Q2 Median (Min – Max) 9.94 (>9.0 – 10.6*)*	Q3 Median (Min – Max) 11.3 (>11.6 – 12.0*)*	Q4 Median (Min – Max) 12.7 (>12.0 – 18.4*)*	Standardized Difference
Age at transplant: (years (mean ±SD)) *β	52.7 ± 13.0	52.2 ± 12.9	52.4 ± 13.0	51.8 ± 13.3	0.054
Years since 1st transplant: (mean ±SD)) *	6.7 ± 3.7	6.7 ± 3.7	6.7 ± 3.7	6.7 ± 3.8	<0.001
Gender: n (%) **β					0.010
Male	16,153 (60.6)	15,446 (59.9)	14,570 (59.6)	8,855 (59.2)	
Female	10,501(39.4)	10,325 (40.1)	9,869 (40.4)	6,112 (40.8)	
Race: n (%) **β					0.181
White	21,690 (81.5)	18,498 (71.9)	15,966 (65.5)	9,508 (63.7)	
Black	2,808 (10.5)	5,577 (21.7)	6,783 (27.8)	4,313 (28.9)	
Other	2,133 (08.0)	1,667 (06.5)	1,645 (06.7)	1,096 (07.4)	
Donor type: n (%) **β					0.048
Cadaveric	14,866 (55.8)	14,918 (58.0)	14,822 (60.7)	9,275 (62.1)	
Living	11,772 (44.2)	10,826 (42.0)	9,583 (39.3)	5,669 (37.9)	
BMI categories: n (%) **β					0.033
< 18.5	688 (02.7)	738 (03.0)	689 (03.0)	431 (03.1)	
18.5 - < 25.0	8,504 (33.1)	7,595 (30.9)	7,266 (31.4)	4,764 (33.8)	
25.0 - < 30.0	8,614 (33.5)	8,029 (32.6)	7,491 (32.4)	4,593 (32.6)	
30.0 +	7,915 (30.8)	8,239 (33.5)	7,679 (33.2)	4,311 (30.6)	
Elapsed time between first ESRD service and transplantation: n (%) **β					0.105
0 - 1 Year	16,438 (61.7)	15,334 (59.5)	14,004 (57.3)	7,518 (50.2)	
2 - 5 Year	8,637 (32.4)	8,569 (33.3)	8,352 (34.2)	5,404 (36.1)	
6 - 10 Year	1,446 (05.4)	1,703 (06.6)	1,918 (07.9)	1,877 (12.5)	

+ 10 Year	139 (0.5)	166 (0.6)	166 (0.7)	173 (01.2)	
Transplant network ratio groups: n (%)**β					0.202
Low	6,407 (24.1)	10,211 (39.6)	8,535 (34.9)	5,924 (39.6)	
Medium	8,846 (33.2)	6,198 (24.1)	8,973 (36.7)	5,934 (39.6)	
High	11,407 (42.8)	9,363 (36.3)	6,932 (28.4)	3,114 (20.8)	
Primary cause of ESRD: n (%) **β					0.107
Diabetes	7,639 (30.2)	7,194 (29.6)	6,710 (29.4)	4,255 (30.7)	
Hypertension	3,697 (14.6)	4,706 (19.4)	5,041 (22.1)	3,531 (25.5)	
Glomerulonephritis	7,047 (27.8)	6,447 (26.6)	5,848 (25.6)	3,432 (24.8)	
Cystic kidney	3,773 (14.9)	3,088 (12.7)	2,686 (11.8)	1,288 (09.3)	
Other urologic	570 (02.3)	486 (02.0)	399 (01.8)	211 (01.5)	
Other cause	2,583 (10.2)	2,348 (09.7)	2,165 (09.5)	1,142 (08.2)	

*ANOVA; **Chi-square

β P-value <0.05

3.2 Total CVD Mortality Risk

3.2.1 Single-Pollutant Models

The basic model showed a strong and significant association between each 10 ug/m^3 incremental increase in ambient $PM_{2.5}$ and total CVD mortality (HR=2.48, 95% CI: 2.13 – 2.90). The estimate was slightly attenuated in the multivariable-adjusted full model with time-interaction adjusting for demographics and transplant-related factors (HR=1.85, 95% CI: 1.57 – 2.17) (Table 1).

3.2.2 Two-Pollutant Models

Compared with the single-pollutant full model, the hazard ratio for each 10 ug/m^3 increase in $PM_{2.5}$ for total CVD mortality, after adjusting for O_3 and NO_2 in two separate models, was somewhat strengthened, with HR=2.30 adjusting for NO_2 HR=2.05 in the model with O_3 (Table 2).

3.2.3 Models with $PM_{2.5}$ Quartiles

In the single multivariable-adjusted full model with quartiles of $PM_{2.5}$ as the exposure variable, the hazard ratio for the fourth quartile was 40% higher compared to the first quartile (HR=1.40, 95% CI: 1.24 – 1.59) (Table 5).

In the two-pollutant models, the hazard ratios for the fourth quartile were higher than the first quartile also after adjusting for O_3 and NO_2, 47% and 55%, respectively (Table 5).

3.3 CHD Mortality Risk

The strongest associations between ambient $PM_{2.5}$ and mortality outcomes were found for CHD, except when adjusted for NO_2, where the association with stroke was somewhat stronger (Table 1 and 2).

3.3.1 Single-Pollutant Models

The basic model showed that for each 10 ug/m^3 increase in ambient $PM_{2.5}$, CHD mortality increased three-fold (HR=3.17, 95% CI: 2.27 – 4.43), but was somewhat attenuated to 120% increase in the multivariable-adjusted full model (HR=2.20, 95% CI: 1.53 – 3.17) (Table 1).

3.3.2 Two-Pollutant Models

Compared with the single-pollutant full model, the strength of association between a 10 ug/m^3 increase in ambient $PM_{2.5}$ levels and risk of CHD mortality was further strengthened after adjusting for NO_2 (HR=2.95) (Table 2), but remained virtually unchanged in the two-pollutant model with O_3 (HR=2.19).

3.3.3 Models with $PM_{2.5}$ Quartiles

In the single multivariable-adjusted full model with $PM_{2.5}$ as a categorical variable, the hazard ratio for the fourth quartile was 86% higher than for the first quartile (Table 5).

In the two-pollutant models, comparing Q4 with Q1, the association with fatal CHD after adjusting for O_3 was somewhat attenuated (HR=1.87) (Table 5) while the association was virtually the same after adjusting for NO_2 (HR=2.22) (Table 5).

Table 5 Multivariable-adjusted hazard ratios for CVD fatal events per quartile of $PM_{2.5}$: Single and two pollutant models.

	Quartiles of $PM_{2.5}$ Level (ug/m^3)				
	Q1 (1.4 - <9.0) *	Q2 (9.0 - <10.6) *	Q3 (10.6 - <12.0) *	Q4 (12.0 - <27.4) *	*p*-trend
Outcome (Mortality)	HR (95%CI) **	HR (95%CI) **	HR (95%CI) **	HR (95%CI) **	
Total CVD[¥]					
Model 1	1.00	1.13 (1.03, 1.23)	1.37 (1.22, 1.54)	1.40 (1.24, 1.59)	<0.001
Model 2 [β]	1.00	1.15 (1.05, 1.26)	1.41 (1.26, 1.59)	1.47 (1.29, 1.68)	<0.001
Model 3 [α]	1.00	1.17 (1.06, 1.29)	1.46 (1.29, 1.66)	1.55 (1.34, 1.80)	<0.001
CHD					
Model 1	1.00	1.03 (0.84, 1.28)	1.54 (1.19, 2.00)	1.86 (1.44, 2.40)	<0.001
Model 2 [β]	1.00	1.04 (0.84, 1.28)	1.55 (1.19, 2.02)	1.87 (1.41, 2.48)	<0.001
Model 3 [α]	1.00	1.11 (0.98, 1.39)	1.72 (1.30, 2.28)	2.22 (1.65, 2.98)	<0.001
Stroke					
Model 1	1.00	1.22 (0.95, 1.56)	1.47 (1.06, 2.05)	1.32 (0.91, 1.92)	0.029
Model 2 [β]	1.00	1.25 (0.96, 1.62)	1.53 (1.09, 2.16)	1.42 (0.95, 2.11)	0.017
Model 3 [α]	1.00	1.37 (1.06, 1.79)	1.77 (1.25, 2.52)	1.77 (1.14, 2.75)	0.001
Cardiac arrest[¥]					
Model 1	1.00	1.12 (1.00, 1.26)	1.33 (1.15, 1.55)	1.30 (1.10, 1.53)	<0.001
Model 2 [β]	1.00	1.14 (1.01, 1.29)	1.37 (1.17, 1.59)	1.36 (1.14, 1.62)	<0.001
Model 3 [α]	1.00	1.14 (1.00, 1.29)	1.36 (1.16, 1.60)	1.35 (1.11, 1.64)	<0.001
CHF					
Model 1	1.00	1.15 (0.85, 1.57)	0.91 (0.58, 1.42)	0.76 (0.45, 1.28)	0.360
Model 2[β]	1.00	1.27 (0.93, 1.74)	1.05 (0.67, 1.63)	0.98 (0.57, 1.69)	0.844
Model 3[α]	1.00	1.17 (0.84, 1.62)	0.93 (0.58, 1.51)	0.80 (0.43, 1.48)	0.548

**Adjusted for all of the following variables: sex, race, years after transplant, primary cause of ESRD, length in years from first ESRD services and first transplant, donor type, ESRD network categories, BMI categories, and immunosuppressive medications; ¥ effect estimates at attained age of 60 yrs. using time-dependent variables; [β]adjusted for O_3; [α] Adjusted for NO_2.

* Range (Min -Max)

3.4 Stroke Mortality Risk

3.4.1 Single-Pollutant Models

The basic model showed a strong association between each 10 ug/m^3 increase in ambient $PM_{2.5}$ levels and stroke mortality (HR=2.77, 95% CI: 1.81 – 4.25) and remained significant, but somewhat attenuated, in the multivariable-adjusted full model (HR=1.82, 95% CI: 1.15 – 2.89) (Table 1).

3.4.2 Two-Pollutant Models

Compared to the single-pollutant full model, the association between a 10 ug/m^3 increase in ambient $PM_{2.5}$ and the risk of stroke mortality increased to a HR of 3.20 (95%CI: 1.76 – 5.81) and 2.07 (95% CI: 1.23 – 3.47) when also controlling for NO_2 and O_3, respectively (Table 2).

3.4.3 Models with $PM_{2.5}$ Quartiles

In the single multivariable-adjusted full model with $PM_{2.5}$ as a categorical variable, the risk of stroke mortality for the fourth quartile was 32% higher than the hazard ratio for the first quartile (Table 5), but it was not statistically significant.

In the two-pollutant models, comparing Q4 with Q1, the hazard ratios were somewhat attenuated (Table 5).

3.5 Cardiac Arrest Mortality Risk

3.5.1 Single-Pollutant Models

Similar to the findings for CHD and stroke, the basic model showed a very strong association between each 10 ug/m^3 increase in ambient $PM_{2.5}$ and cardiac arrest mortality (HR=2.42, 95% CI: 1.98 – 2.96), which was somewhat attenuated in the multivariable-adjusted full model (HR=1.77, 95% CI: 1.42 – 2.19) (Table 1).

3.5.2 Two-Pollutant Models

As for the previous outcomes, the hazard ratios were strengthened to 2.02 and 1.95, respectively, when also controlling for NO_2 and O_3 (Table 2).

3.5.3 Models with $PM_{2.5}$ Quartiles

In the single multivariable-adjusted full model with $PM_{2.5}$ as a categorical variable, the risk was lower, but still statistically significant when comparing the fourth quartile with the first quartile (HR=1.30) (Table 5).

In the two-pollutant models, adjusting for O_3 and NO_2, respectively, the association remained more or less the same as in the continuous model (Table 5).

3.6 CHF Mortality Risk

Unlike the other mortality outcomes, there was no clear association found between ambient $PM_{2.5}$ and CHF mortality in any of the basic, multivariable or two-pollutant models (Tables 3 and 4), nor in models when we used $PM_{2.5}$ as a categorical variable (Table 5).

3.7 Sensitivity Analysis

The HR for all outcomes stayed virtually unchanged when including the 9,269 subjects with prevalent CVD who were excluded at baseline. The HR for CVD mortality was 1.90, for CHD 2.18, for stroke 1.95, for sudden death 1.83 and for CHF 1.02 with the 95% confidence intervals almost

completely overlapping those for the single-pollutant full model in the analytic population (Table 1).

4. Discussion

To the best of our knowledge, this is the first study to explore the relationship between ambient $PM_{2.5}$ and the risk of premature death due to CVD and its subcategories among this highly sensitive population of renal transplant recipients. Because of the large number of subjects, we were able to study several subcategories of CVD mortality, namely CHD, stroke, cardiac arrest, and CHF mortality. We were also able to eliminate one of the major risk factors for CVD in that we excluded all current smokers. The results from this large retrospective cohort study support the hypothesis that ambient levels of $PM_{2.5}$ is an independent risk factor for fatal CVD among the renal transplant population. We found detrimental effects on CVD mortality even for $PM_{2.5}$ levels below the current EPA standard. In our previous study among renal transplant recipients, Spencer-Hwang et al. found significant positive associations between ambient O_3 levels and the risk of CHD mortality, but not with ambient PM_{10} levels [18]. Due to the limited number of $PM_{2.5}$ air quality monitors in the nation at that time, the researchers were not able to assess the relationship between ambient $PM_{2.5}$ and the risk of CHD mortality [18]. In other populations, several studies have shown a stronger association between $PM_{2.5}$ and CVD mortality than for PM_{10} [11, 23]. The possible explanation is that the smaller particle size of $PM_{2.5}$ can penetrate deeper into the lungs and then enter the blood stream, resulting in greater health effects [34].

Our current study was designed to reduce the gap in the literature on the CVD effects of increasing levels of ambient $PM_{2.5}$ among renal transplant recipients. As we anticipated, the findings of this study provide strong evidence for adverse effects of ambient particulate air pollution on human health, especially among this vulnerable group. Positive associations were found between $PM_{2.5}$ and all CVD mortality outcomes, except CHF mortality, in both single- and two-pollutant multivariable adjusted models. It is not clear why the association with CHF is lower, but the etiology of CHF is multifactorial and some of them may have no association with ambient air pollution. In addition, it is possible that for CHF, it is the immediate short-term particulate air pollution that is most important, not the average annual levels. This is supported by the meta-analyses of Shah, et al. [42], who found an increased risk of CHF associated with same-day ambient $PM_{2.5}$ levels. In a recent ecologic cross-sectional study on CHF mortality, Bennett, et al. found a negative association with the particulate matter indicator [43]. However, the PM indicator was PM less than 10 $\mu g/m^3$ and they were contrasting rural versus urban areas. The levels of the PM indicator were slightly higher in the rural areas, where the CHF mortality was lower. It is hard to evaluate these findings, as they will be influenced by both the size and composition of the particles. The urban areas had higher levels of NO_x, indicating higher traffic pollution, and thus, likely higher levels of fine PM. Also, as an ecologic study, there was no subject-specific information on lifestyle differences between those living in rural versus urban areas, although it is likely that the rural population had a better diet and more physical activity, which could have contributed to the lower rates in the rural areas. As a result of these findings, the team recommended that patients' living condition (rural vs. urban) should be considered when assessing associations between particulate matter exposure and morbidity and mortality due to heart failure [43].

Our results are consistent, but stronger, than the findings of most previous cohort studies among the general population as well as among potentially sensitive subpopulations. However, similar to our findings, Chen et al., reporting from the earlier Adventist Health and Smog Study (AHSMOG 1) found a positive association of similar magnitude between $PM_{2.5}$ and fatal CHD among non-smoking, mostly never smoking, non-Hispanic, white adult females during 22 years of follow up (RR=2.00, 95% CI: 1.51 – 2.64) [23].

Weaker associations have been reported by others from populations that were not limited to non- or never-smokers. In a study of 8,096 white subjects from the Harvard Six Cities study, Laden, et al. found that ambient $PM_{2.5}$ levels were positively associated with an increase in CVD mortality (RR=1.28, 95% CI: 1.13 – 1.44) [28]. Additionally, the reduction in ambient $PM_{2.5}$ emissions in the second period of the study (between 1990 and 1998) was associated with lower CVD mortality risk [28]. Moreover, Turner, et al.[44], studying 669,046 participants from the Cancer Prevention Study II, found positive associations between ambient $PM_{2.5}$ and total CVD mortality (HR=1.07, 95% CI: 1.04 – 1.10); ischemic heart disease (HR=1.07; 95% CI, 1.04 – 1.10); dysrhythmias, heart failure, and cardiac arrest (HR=1.06, 95%CI: 1.00 – 1.13), and cerebrovascular disease (HR=1.13, 95% CI:1.06 – 1.21). These associations were much stronger when ambient air levels were restricted to near-source $PM_{2.5}$ [44].

After adjusting for ecological covariates (median household income; percentage of people with < 125% of poverty-level income; percentage of unemployed individual aged ≥ 16 years; percentage of adults with < 12th grade education; and percentage of the population who were black or Hispanic), Pope III and colleagues [45] observed positive relations between ambient levels of $PM_{2.5}$ and CVD mortality risk (HR=1.12; 95% CI, 1.10 – 1.15). In addition, pre-existing cardiometabolic risk factors were not significant effect modifiers of the association between $PM_{2.5}$ and CVD mortality. Furthermore, $PM_{2.5}$ was associated with increased mortality risks of type II diabetes (HR=1.25: 95% CI, 1.17 – 1.33) and hypertension (HR=1.26, 95% CI: 1.18 – 1.36) [45].

Among elderly white male veterans, Mehta, et al. found a significant association between one-year higher ambient levels of $PM_{2.5}$ and a decline in renal function [46]. A 2.1 $\mu g/m^3$-higher 1-year ambient $PM_{2.5}$ was linked with an additional annual reduction in the glomerular filtration rate (eGFR) of 0.60-mL/min/1.73 m^2 per year (95% CI: –0.79, –0.40) [46].

Also, in a recent study, Malik et al. found a significant association between ambient $PM_{2.5}$ and total mortality among myocardial infarction survivors (HR =1.13). However, no significant association was detected with ambient O_3 (HR=1.01) [47].

Comparing our results with these previous investigations among various populations, we found stronger effects, which may be explained by the unique characteristics of this vulnerable population. Declining kidney function, prevalence of hypertension, diabetes, and use of immunosuppressive medications are factors that, compared to non-diseased subjects, may make non-smoking, renal transplant recipients more sensitive to ambient air pollutants and its effect on risk factors for cardiovascular disease.

4.1 Possible Biological Mechanism

Over the years, several biological mechanisms have been proposed to explain the relationship between ambient levels of air pollution and CVD morbidity and mortality. One of the possible explanations of the adverse effects of particulate matter on human health is that exposure to air

pollutants have been linked to increased levels of pulmonary oxidative stress and inflammation, which leads to the release of inflammatory factors and free radicals into the bloodstream, causing cell injury [48-50]. Vascular inflammation has been associated with the development of atherosclerosis after transplantation, which leads to a higher number of CVD events [51, 52]. The second common explanation is the translocation of small air pollution particles (PM2.5 and ultrafine) into blood circulation, and their ability to pass through the plasma membrane of different body cells and interact with them. These interactions may contribute to thrombosis and atherosclerotic plaque formations that eventually lead to changes in the cardiovascular system [10, 49, 50]. Additionally, sudden exposure to high levels of $PM_{2.5}$ have been found to be associated with a significant change in the stability of atherosclerotic plaque and the thrombogenic process, which may trigger CVD events [53]. Furthermore, researchers have found significant relationships between $PM_{2.5}$ exposure and the occurrence of ventricular arrhythmias, especially among patients with coronary heart disease [54, 55] and with diabetes or impaired glucose tolerance [56].

4.2 Strengths and Limitations

There are several strengths to this study. All health care professionals in the US are required by law to report all patient information for subjects who receive a diagnosis of chronic kidney disease as well as all who receive a renal transplant to USRD. The availability of this large database ensures that we are studying all US renal transplant recipients. In addition, this database includes a large number of important variables, allowing for the adjustment of several confounding effects. Another strength is our ability to adjust for ambient O_3 and NO_2 in two-pollutant models, allowing us to see how these modify the effect of $PM_{2.5}$. Using this database assures generalizability from our study population of non-smoking renal transplant patients to the non-smoking renal transplant population at large. Furthermore, ZIP code-specific annual-average concentrations of air pollutants were assigned using previously available integrated empirical geographic (IEG) regression models, adjusting for several geographical factors that had high cross-validation statistics. Our findings are robust as demonstrated with the relatively narrow 95% CIs and the fact that the estimates stayed virtually unchanged even when the 9,269 subjects with prevalent CVD at baseline were included in the sensitivity analyses.

However, this study also has some limitations. Only annual ambient concentrations of $PM_{2.5}$, Ozone and NO_2 at the ZIP code level of the place of residence, rather than the subjects' physical address, were available as exposure variables. In addition, place of work is not included in this database, preventing us from including such data in our exposure estimates. However, renal transplant recipients are likely live and work in close proximity, and thus with similar $PM_{2.5}$ concentrations; these limitations are therefore unlikely to greatly influence their mean annual level of ambient air pollutants. Additionally, as a result of using the adjusted annual averages of ambient $PM_{2.5}$ levels, we could not adjust for seasonal variations, which could explain the low levels of $PM_{2.5}$. Yet, significant adverse health effects of $PM_{2.5}$ at concentrations below EPA standards of 12 ug/m^3 have been reported for both morbidity and mortality in other cohort studies [46, 47, 57] .

Another limitation is the lack of more specific classification on the death certificate, especially for stroke and cardiac arrest death. Moreover, no information on dietary factors and physical

activity is available in the dataset. However, we were able to control for BMI, which partially accounts for such lifestyle factors.

5. Conclusions

In conclusion, this study is one of very few epidemiological studies to explore the association between ambient fine-particulate air pollution and risk of fatal CVD events among renal transplant recipients. Our findings demonstrate detrimental health effects even at $PM_{2.5}$ levels below the EPA standard and thus begs the question of whether these standards need revision. More studies are needed to confirm our strong findings and to assess the potential association among other sensitive subgroups within this and other populations. Further research is also needed to explore the association between the various $PM_{2.5}$ compositions and health outcomes. Ultimately, our findings may contribute to the development of preventive strategies to lessen the impact of air pollution on health outcomes in renal transplant recipients, and to reduce healthcare costs for patients with cardiovascular diseases. Our research findings may also help renal transplant recipients in making informed decisions to reduce personal exposure to ambient air pollution, particularly in highly polluted areas. Finally, managing modifiable CVD factors, including air pollution exposure, may eventually reduce the risk of graft loss and improve the quality of life for this vulnerable population.

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The authors declare that they have no relevant financial interests.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: ESRD death notification codes used for CVD mortality outcomes.
2. Table S2: Smoking status and prevalent CVS cases according to quartiles of annual average of $PM_{2.5}$ (ug/m^3).

Author Contributions

Salem Dehom: Conception, Study Design, Data Acquisition, Data Management, GIS, Data Analysis, Interpretation, Drafted Manuscript, Final Approval; Synnove Knutsen: Conception, Study Design, Data Analysis, Interpretation, Drafted Manuscript, Final Approval; David Shavlik: Conception, Study Design, Data Management, GIS, Data Analysis, Interpretation, Drafted Manuscript, Final Approval; Khaled Bahjri: Conception, Study Design, Data Acquisition, Data Analysis, Interpretation, Drafted Manuscript, Final Approval; Hatem Ali: Data Management, Drafted Manuscript, Final Approval; Lance Pompe: GIS, Final Approval; Rhonda Spencer-Hwang:

Conception, Study Design, Data Acquisition, Data Management, Data Analysis, Interpretation, Drafted Manuscript, Final Approval.

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Competing Interests

The authors have not published or submitted any related papers from this study. The authors have no financial conflict of interest.

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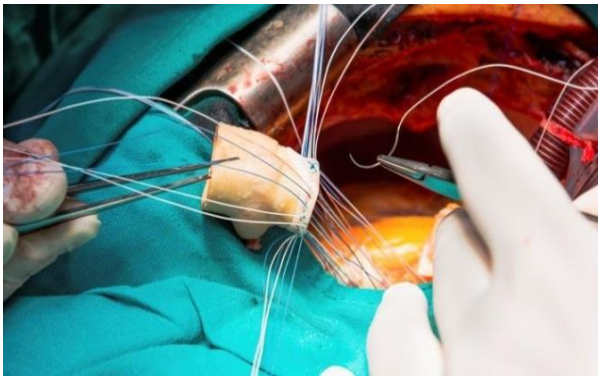

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