

# Female Renal Transplant Recipients Potentially at Increased Risk of Fatal Coronary Heart Disease Associated with Ambient Air Pollutants

Rhonda Spencer-Hwang<sup>1,2</sup>, Synnove Fonnebo Knutsen<sup>1</sup>, Mark Ghamsary<sup>1</sup>, W. Lawrence Beeson<sup>1</sup>, Keiji Oda<sup>1</sup>, David Shavlik<sup>1</sup>, Navin Jaipaul<sup>3</sup> and Sam Soret<sup>2</sup>

<sup>1</sup>Department of Epidemiology and Biostatistics, Loma Linda University, Loma Linda, California, USA

<sup>2</sup>Department of Environmental and Occupational Health, Loma Linda University, Loma Linda, California, USA

<sup>3</sup>Division of Nephrology, Jerry L. Pettis Memorial VA Medical Center and Loma Linda, University School of Medicine, Loma Linda, California, USA

## Abstract

**Background:** There is increasing evidence that specific ambient air pollutants are associated with coronary heart disease (CHD) morbidity and mortality and risks may differ by gender. Renal transplant recipients have previously been identified as a potentially sensitive subgroup. The purpose of this study was to evaluate the possible effect of long-term ambient pollutant ozone (O<sub>3</sub>) and particulate matter (PM<sub>10</sub>) on risk of coronary heart disease (CHD) mortality and determine if gender differences exist among renal transplant recipients.

**Methods:** This retrospective cohort study included 38,101 (22,276 males and 15,825 females) subjects identified through the US Renal Data System (USRDS), which included adult, renal transplant recipients, transplanted between 1997-2003, and living in the continental U.S.A. Air pollution statistics collected over the national ambient monitoring network, were extracted from US Environmental Protection Agency (EPA) Air Quality System (AQS). Mean monthly concentrations of O<sub>3</sub> and PM<sub>10</sub> calculated from ambient monitoring data and interpolated to ZIP code centroids according to residence of the subjects. Cox proportional hazard models used to estimate effect of air pollutants on mortality (CHD) risks, while adjusting for potential confounders. All analyses conducted were gender-specific.

**Results:** In both the age- and multivariable adjusted models, there was a significant association between risk of fatal CHD and O<sub>3</sub> for females (HR=1.56, 95%CI: 1.06-2.30), no significant association found for males. O<sub>3</sub> displayed the strongest association with CHD mortality among females with a HR=1.57 (95%CI: 1.07-2.30) after adjustment for PM<sub>10</sub> in the two pollutant multivariable model. For both pollutants and across all models, females consistently experienced greater risk than males. No significant association identified for PM<sub>10</sub> for either gender.

**Conclusions:** The findings from our study have potential implications for policies and regulations of air pollution. Gender, as a higher risk category, may be relevant in developing individual CHD risk reduction strategies for renal transplant recipients to ultimately improve long-term survival.

**Keywords:** Air pollution; Coronary heart disease; Epidemiology; Renal transplantation; Survival analysis

**Abbreviations:** AHSMOG: Adventist Health Study On The Health Effects Of Smog; AQS: Air Quality System; EPA: Environmental Protection Agency; CDC: Centers for Disease Control; CHD: Coronary Heart Disease; CMS: Centers for Medicare and Medicaid Services; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; EPA: Environmental Protection Agency; ESRD: End-Stage Renal Disease; GIS: Geographical Information System; GFR: Glomerular Filtration Rate; HRV: Heart Rate Variability; ICU: Intensive Care Unit; IDW: Inverse Distance Weight; MI: Myocardial Infarction; NIDDK: National Institute of Diabetes and Digestive and Kidney Disease; OPO: Organ Procurement Organization; O<sub>3</sub>: Ozone; PM<sub>10</sub>: Particulate Matter ≤10μm in diameter; PM<sub>2.5</sub>: Particulate Matter ≤2.5μm in diameter; UNOS: United Network for Organ Sharing; USRDS: United States Renal Data System

## Background

Substantial epidemiological research has identified a potential link between ambient air pollutants and a number of adverse cardiovascular (CVD) health outcomes [1-10]. Subpopulations with states of chronic inflammation such as diabetes and hypertension experience enhanced susceptibility to adverse cardiovascular conditions associated with ambient air pollution [11-14]. Both gaseous and particulate ambient air pollutants, including ozone and particulate matter have been identified as potential agents capable of instigating inflammatory response associated with exposure, with some of the greatest risks identified for individuals with compromised health status. Across a

number of air pollution studies researchers have identified potential gender differences in risk [10,15-17]. Recently, we have identified renal transplant recipients as potentially another sensitive subgroup experiencing enhanced susceptibility associated with air pollution and the identified associated risks may not be gender equal [18]. Both traditional risk factors (including diabetes and hypertension) and nontraditional risk factors (e.g. inflammatory markers and immunosuppressive medications) are prevalent in renal transplant recipients [19, 20].

Numerous epidemiological studies have provided evidence indicating that women may be at increased risk of adverse health events associated with air pollution, however it remains to be determined if female transplant recipients are at greatest risk. Chen et

**\*Corresponding author:** Rhonda Spencer-Hwang, DrPH, MPH, Department of Environmental and Occupational Health, Loma Linda University, School of Public Health, Nichol Hall, Loma Linda, CA 92354, USA, Tel: 909-558-8750; Fax: 558-0326; E-mail: [rspencer@llu.edu](mailto:rspencer@llu.edu)

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al. have previously reported gender-based differences for risk of fatal CHD with women experiencing a higher risk associated with chronic ambient particulate pollution [10]. The observed differences between men and women may be due to biological factors (i.e. lung volume, hormonal activity...etc), environmental activity exposure patterns (i.e. job related...etc.) or a combination of both [21]. It is important to determine if risk of CHD mortality associated with chronic ambient air pollution differs by gender among renal transplant recipients, as identification of risk reduction opportunities could ultimately reduce CHD morbidity and mortality and positively influence longevity.

The purpose of this study was to evaluate the potential association between long-term ambient air pollutants ( $O_3$  and  $PM_{10}$ ) and the risk of CHD mortality and determine if any gender differences exist among renal transplant recipients.

## Materials and Methods

### Study population

Study subjects were identified through the US Renal Data System (USRDS). The USRDS is a national data repository containing extensive demographic (including updated residential information) and diagnostic data (including extensive transplantation information), biochemical values, dialysis claims and information on treatment history, hospitalizations, physician/supplier services and mortality data for all persons living with end-stage renal disease (ESRD) and renal transplant recipients. The USRDS is funded directly by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and collaborates with other agencies including CMS (Centers for Medicare and Medical Services), UNOS (United Network for Organ Sharing), the Centers for Disease Control (CDC), and ESRD Networks to share datasets and work to improve the accuracy of patient information contained within the USRDS database. All data derived through the USRDS database has been validated [22]. Our study population included all primary renal transplant recipients, 18 years and older, transplanted between 1997-2003, with at least one year of graft survival, and living within the continental U.S.A. Only subjects residing within the same ZIP-code during the entire follow-up study period were included in analysis. Subjects were followed until date of event (CHD mortality) or censoring which occurred at the end of the study period (10/31/2003). Censoring included death from non-CHD causes or the end of the study. Those who smoked cigarettes (N=2,502) at the time of transplant were excluded. Thus a total of 38,101 (22,276 males, and 15,825 females) non-smoking, renal transplant recipients met the inclusion criteria and were included in this study.

### Pollution exposure assignment

Air pollution statistics collected over the national ambient monitoring network from 1997-2003, as well as the geographic coordinates of each fixed monitoring station, were extracted from the US Environmental Protection Agency (EPA) Air Quality System (AQS). The detailed methods for assigning air pollutant estimates for each individual subject have been previously described in detail [18]. Briefly, hourly  $O_3$  and  $PM_{10}$  data were collected for each monitoring location and were used to create monthly average values for each site. ArcGIS 9.3 (ESRI, www.esri.com) was used for all spatial data manipulations and implementation of exposure models in order to estimate air pollutant concentrations for each subject. Estimates of monthly concentrations of ambient  $O_3$  and  $PM_{10}$  were created for each of the study subjects according to their residential address at the time of transplant. Residential ZIP codes were used to geo-reference the

study population. Using GIS-based Inverse-Distance weighted (IDW) interpolations (power = 2; # neighbors = 3), multiple monthly pollution surfaces were created in order to predict  $O_3$  and  $PM_{10}$  concentrations at each ZIP-code centroid. Employing overlay geo processing tools, we linked the residential ZIP-code locations with the air pollution surfaces containing the ZIP-code specific exposure estimates modeled from ambient air pollution data. GIS-derived monthly exposure averages were used to cumulate and assign a moving average exposure for each subject from the time of transplant through the follow-up period, with exclusion of the month prior to death to avoid any short term induced effects in assigning exposure. Subjects were only included in the analysis if they resided within 50 Km of an air pollutant monitor.

### Ascertainment of Deaths

Our main outcome of interest was death from CHD. CHD death was defined as the primary cause of death as it was coded within the USRDS database and this information has been previously validated [22]. If the primary cause of death listed was acute MI or atherosclerotic heart disease then it was determined that a fatal CHD event has occurred.

### Potential confounding variables

All identified potential confounders available within the USRDS database, were assessed for confounding in the base model by adding and removing each potential confounder one at a time to the base model and determining if they individually changed the air pollution main effect by 10% or more. The potential confounders investigated included: race (White, Black, Other); body mass index (<18.5, 18.5-29.9, 30+); duration of pre-transplant dialysis (months); causes of renal failure (diabetes, hypertension, primary glomerulonephritis, polycystic kidney disease, miscellaneous factors and unknown factors); UNOS region (eleven regions divide the US for administration), serum creatinine level prior to post-transplant hospital discharge (0.1-1.2, 1.3-1.7, 1.7-2.7, and 2.8+mg/dl); hypertension independent of the cause of renal failure (yes/no); diabetes independent of the cause of renal failure (yes/no); educational level at the time of transplant (<=high school, college+); pre-transplant blood transfusion (yes/no); delayed graft function defined as the need for dialysis within the first week post-transplantation or the lack of urine output in the first 24 hours after transplantation (yes/no); total number of kidney transplants performed throughout the follow-up period (1 only, 2 or more); organ donor type (deceased/living); organ donor age (<30, 30-44, >44-60, 60+years); and organ donor gender. Immunosuppressant medication was evaluated on an intention- to-treat basis and included the following variables: cyclosporine (yes/no), tacrolimus (yes/no), other (rapamycin, leflunomide, deoxyspergualin, sang Cy A) (yes/no), azathioprine (yes/no), mycophenolate mofetil (yes/no), steroid (prednisone, methylprednisolone, solumedrol, medrol, decadron) (yes/no).

### Statistical analysis

Gender-specific comparison of recipient baseline and follow-up demographics were made utilizing Student t-test or Chi-square test for univariate analysis. Correlation of air pollutants estimated using Pearson correlation coefficient. The specific health outcome analyzed included death from CHD as previously defined. Subjects were followed from time of transplant until event or censoring as previously defined. Cox proportional hazard models were used to estimate the effect of ambient air pollutants on risk of CHD. We further adjusted for change in the air pollutant compositions over time by adding year of transplant as a covariate.

A basic model was developed which included the air pollutant, gender, age, the year of transplant and presence of heart disease at the time of transplant. Subjects with a history prior to transplantation of ischemic heart disease and peripheral vascular disease were coded as having prevalent heart disease at the time of transplant. All potential confounders available within the USRDS database were assessed for confounding in this base model. None of the candidate variables changed the main effect 10% or more. However, because of the strong predictive effect of primary cause of renal disease and length of dialyses before transplant on mortality among renal transplant subjects, these were added to the final model. Tests of interactions between the various patient demographics and air pollutants were assessed utilizing the log likelihood ratio chi-square test comparing the reduced Cox model (without interaction terms) with the full Cox model (with interaction terms). None of the interaction terms were statistically significant. All variables in the final model were assessed with respect to meeting the requirements of proportional hazard assumptions by checking the log  $[-\log(\text{survival})]$  curves against the log time variable and they all met the assumption. Additionally, all variables were assessed for multicollinearity. All Cox regression analyses conducted were gender-specific. Results are reported per 10  $\mu\text{g}/\text{m}^3$  increase for  $\text{PM}_{10}$  and 10 ppb increase for  $\text{O}_3$ . A sandwich variance estimate was added to the final model to adjust for potential correlation that might exist between observations within a localized area [23]. Additional sensitivity analyses were conducted which included only subjects residing within 30 km of the nearest monitor to compare with overall study results. No large differences were observed when utilizing a cohort of subjects residing within 30km compared with subjects residing within 50km. All analyses were performed utilizing SAS version 9.2 (SAS Institute, www.sas.com). University IRB approval was obtained prior to conducting this research.

## Results

### Study population

The transplant cohort consisted of subjects residing across the continental U.S. (Figure 1). A total of 379 CHD deaths occurred during the 7-year follow-up period (257 CHD deaths among males and 122 among females). For males, deaths from CHD accounted for 15.7% of 1,637 total deaths from natural causes and, for females 10.7% of 1,138 total deaths. Among the transplants that died from CHD, the median time from transplantation to death from CHD was 35.7 months (mean =  $37.1 \pm 17.6$  months) for men and 35.4 months (mean =  $36.6 \pm 17.0$ ) for women. A total of 5,863 subjects (3,773 males and 2,090 females) had prevalent heart disease at the time of transplant. Cases and non-cases differed on a number of baseline demographic and other variables (Table 1). For the entire transplant cohort the average pollutant level for  $\text{PM}_{10}$  and  $\text{O}_3$  was  $25.3 \mu\text{g}/\text{m}^3$  ( $\pm 6.4 \mu\text{g}/\text{m}^3$ ) and 25.5 ppb ( $\pm 4.4$  ppb) respectively. The correlation between  $\text{O}_3$  and  $\text{PM}_{10}$  was low, but statistically significant ( $p < 0.0001$ ).

### Risk of fatal CHD

#### Single pollutant models

In the age-adjusted model, there was a significant association between risk of fatal CHD and  $\text{O}_3$  for females with the strongest association found for the multivariable adjusted model (HR=1.56, 95%CI: 1.06-2.30,  $p$  value=0.02). Among males a weaker association was found for  $\text{O}_3$ , within the age- and multivariable adjusted models (HR=1.14 and 1.13, respectively), however the results did not attain statistical significance.  $\text{PM}_{10}$  also exhibited a higher point estimate for

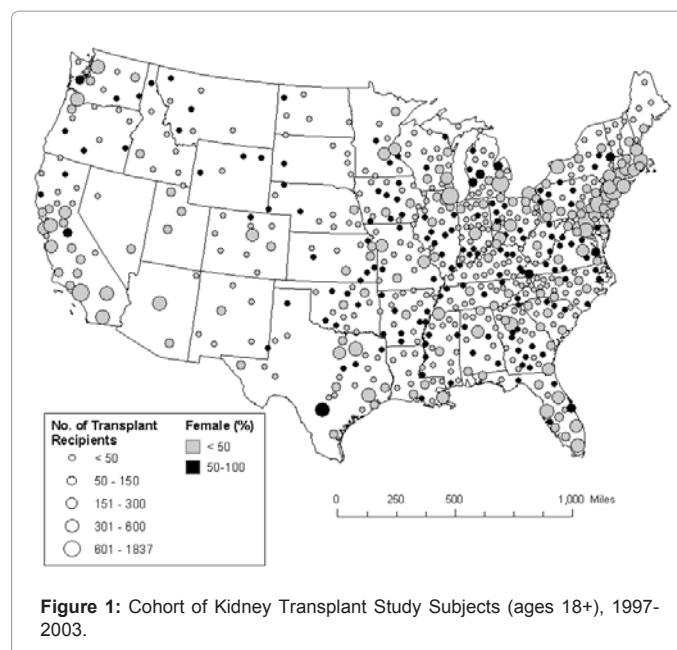


Figure 1: Cohort of Kidney Transplant Study Subjects (ages 18+), 1997-2003.

females within the age- and multivariable adjusted models compared with males. The point estimates for  $\text{O}_3$  and  $\text{PM}_{10}$  changed very little from the age adjusted to the multivariate adjusted models. Overall there were no statistically significant differences identified between males and females for either  $\text{PM}_{10}$  or  $\text{O}_3$  and risk of CHD mortality (Table 2).

#### Two-pollutant models

For females, a consistent and strong association was seen between fatal CHD and  $\text{O}_3$  across all the models and after adjustment for  $\text{PM}_{10}$ . After adjustment for  $\text{PM}_{10}$ , the relative risk of CHD mortality for  $\text{O}_3$  among females was 45% higher than the corresponding risk found for males (HR=1.57 and HR=1.12, respectively). Comparing the relative risk estimates for  $\text{O}_3$  between males and females, females consistently had a higher risk value after adjustment for  $\text{PM}_{10}$ . The strongest relative risk associated with  $\text{O}_3$  was found for females with a HR= 1.55 (95%CI: 1.06-2.26,  $p$ value=0.02) in the age adjusted and a HR=1.57 (95%CI: 1.07-2.30,  $p$ value =0.02) in the multivariable adjusted models after adjustment of both models for  $\text{PM}_{10}$ . For males the corresponding point estimate for  $\text{O}_3$  adjusted for  $\text{PM}_{10}$  in the age adjusted model is 1.13 (95%CI: 0.86-1.49,  $p$ value=0.39) and a HR=1.12 (95%CI: 0.84-1.49,  $p$ value=0.61) in the multivariable adjusted model.  $\text{PM}_{10}$  did not show any statistically significant relationship for either males or females, however the point estimates were consistently stronger for females compared with males (Table 3).

### Discussion

Overall our results revealed, for females, a consistent and significant increased risk of fatal CHD for increasing levels of ambient  $\text{O}_3$ , across all models from age- to multivariable-adjusted and in both single and two pollutant models. For  $\text{O}_3$ , in age-and multivariable adjusted and single-and two pollutant models, females consistently displayed a higher risk of CHD mortality than males although the differences were not statistically significant. For both  $\text{O}_3$  and  $\text{PM}_{10}$  females consistently experienced a greater risk. The findings from this cohort study provides support to the hypothesis that air pollution exacerbates the atherosclerotic process and may increase the risk especially among

Characteristics	Males (N=22,276)		Females (N=15,825)	
	Cases (N=257)	Noncases (N=22,019)	Cases (N=122)	Noncases (N=15,703)
Age at Transplant[years(mean+SD)]	54.2+9.5**	47.6+12.3		52.0+10.1** 47.2+12.3
Race				
White	172(66.9)	15,554(70.6)	73(59.8)	10,620(67.6)
Black	70(27.2)	5,185(23.5)	44(36.1)	4,003(25.5)
Asian/Indian/Other	15(5.8)	1,274(5.8)	5(4.1)	1,077(6.9)
College Education	94(36.6)	8,220(37.3)	30(24.6)	5,474(34.9)
	BMI			
<18.5	4(1.6)	375(1.7)	2(1.6)	662(4.2)
18.5-29.9	125(48.6)	12,170(55.3)	52(42.6)	8,116(51.7)
30+	39(15.2)	3,899(17.7)	21(17.2)	2,943(18.7)
	Primary Cause of ESRD			
Diabetes	121(47.1)	5,483(24.9)	62(50.8)	3,549(22.6)
Hypertension	53(20.6)	4,359(19.8)	21(17.2)	2,524(16.1)
Primary nephritis	43(16.7)**	6,063(27.5)	12(9.8)**	3,825(24.4)
PKD	9(3.5)	2,211(10.0)	6(4.9)	1,829(11.6)
Miscellaneous	19(7.4)	2,563(11.6)	16(13.1)	2,978(19.0)
Unknown factor	12(4.7)	1,340(6.1)	5(4.1)	998(6.4)
Hypertension	107(41.6)	10,800(49.0)	53(43.4)	7,505(47.8)
	(independent of cause of ESRD)			
	Time on dialysis (months)			
0-12	88(34.2)	9,074(41.2)	35(28.7)	6,596(42.0)
13-24	48(18.7)	4,440(20.2)	29(23.8)	2,962(18.9)
>24	121(47.1)	8,505(38.6)	58(47.5)	6,145(39.1)
	Creatinine level at discharge			
0.1-1.2 (mg/dL)	35(13.6)	2,932(13.3)	33(27.0)	5,919(37.7)
1.3-1.7	53(20.6)	5,782(26.3)	21(17.2)*	3,367(21.4)
1.8-2.7	66(25.7)	5,728(26.0)	17(13.9)	2,474(15.8)
2.8+	99(38.5)	7,042(32.0)	45(36.9)	3,573(22.8)
Living Donor type	66(25.7)**	8,882(40.3)	33(27.0)*	6,447(41.1)
Female Donor sex	127(49.4)	10,645(48.3)	56(45.9)	7,389(47.1)
Delayed graft function	64(24.9)**	4,400(20.0)	43(35.2)**	2,735(17.4)
Pretransplant blood transfusion	83(32.3)**	5,184(23.5)	46(37.7)	4,956(31.6)

Values are presented as no. (%) or mean ± SD

Some columns do not add to 100% because of missing data

\*p < 0.01, \*\*p < 0.001

\*For continuous outcomes, comparison by Student t test. For categorical outcomes, comparison by chi square test

Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ , x76.26

**Table 1:** Baseline Characteristics of the Study Population.

Gender	Pollutant	Increment	Age adjusted		Multivariable adjusted <sup>a</sup>		Multivariable adjusted <sup>b</sup>	
			Cases	HR(95%CI)	Cases	HR(95%CI)	Cases	HR(95%CI)
Males	PM <sub>10</sub>	10 $\mu\text{g}/\text{m}^3$	257	0.95 (0.78-1.15)	252	0.92 (0.75-1.11)	252	0.92 (0.75-1.12)
	O <sub>3</sub>	10 ppb	257	.14 (0.86-1.50)	252	1.13 (0.86-1.50)	252	1.13 (0.86-1.49)
Females	PM <sub>10</sub>	10 $\mu\text{g}/\text{m}^3$	122	1.11 (0.86-1.44)	121	1.07 (0.83-1.40)	121	1.07 (0.88-1.33)
	O <sub>3</sub>	10 ppb	122	1.54 (1.05-2.26)	121	1.56 (1.06-2.30)	121	1.56 (1.06-2.31)

<sup>a</sup>Multivariable model is adjusted for all of the following variables: race (White, Black, Other), age, year of transplant (1997-2003), primary cause of ESRD (diabetes, hypertension, primary glomerulonephritis, polycystic kidney disease, miscellaneous, and unknown factor), time on dialysis prior to transplantation (0-12, 13-24, 24+ months), and prevalent heart disease at time of transplant (yes/no)

<sup>b</sup>Multivariable model with inclusion of sandwich variance estimate to adjust for potential spatial autocorrelation.

**Table 2:** Age and Multivariable Adjusted Relative Risks of Fatal CHD: SINGLE POLLUTANT MODELS.

female renal transplant recipients for fatal CHD events. To the best of our knowledge, no other studies have been conducted to assess if gender differences exist for risk of CHD mortality associated with chronic air pollution exposures among organ transplant recipients.

The identification of potential gender difference within this study

is further supported by findings from a number of additional published epidemiological studies identifying a greater risk among females for adverse health outcomes associated with ambient air pollution. The Adventist Health Study on the Health Effects of Smog (AHSMOG) cohort study with 22 years of follow-up found a positive association with three fractions of PM (<2.5, 2.5-10, and  $\leq 10\mu\text{g}/\text{m}^3$ ) for increased



Gender	Pollutant	Increment	Adjusted	Age adjusted		Multivariable adjusted <sup>a</sup>		Multivariable adjusted <sup>b</sup>	
				Cases	HR(95%CI)	Cases	HR(95%CI)	Cases	HR(95%CI)
Male	PM <sub>10</sub>	10 ug/m <sup>3</sup>	O <sub>3</sub>	257	0.96 (0.79-1.16)	252	0.92 (0.76-1.12)	252	0.92 (0.76-1.12)
	O <sub>3</sub>	10 ppb	PM <sub>10</sub>	257	1.13 (0.86-1.49)	252	1.12 (0.84-1.49)	252	1.12 (0.85-1.47)
Female	PM <sub>10</sub>	10 ug/m <sup>3</sup>	O <sub>3</sub>	122	1.13 (0.88-1.45)	121	1.10 (0.85-1.42)	121	1.10 (0.91-1.33)
	O <sub>3</sub>	10 ppb	PM <sub>10</sub>	122	1.55 (1.06-2.26)	121	1.57 (1.07-2.30)	121	1.57 (1.08-2.30)

<sup>a</sup>Multivariable model is adjusted for all of the following variables: race (White, Black, Other), age, year of transplant (1997-2003), primary cause of ESRD (diabetes, hypertension, primary glomerulonephritis, polycystic kidney disease, miscellaneous, and unknown factor), time on dialysis prior to transplantation (0-12, 13-24, 24+ months), and prevalent heart disease at time of transplant (yes/no).

<sup>b</sup>Multivariable model with inclusion of sandwich variance estimate to adjust for potential spatial autocorrelation

**Table 3:** Age and Multivariable Adjusted Relative Risks of Fatal CHD: TWO- POLLUTANT MODELS.

risk of CHD mortality among women, but not for men [10]. The Public Health and Air Pollution in Asia (PAPA) study found for women strong associations between a number of ambient air pollutants including PM<sub>10</sub> and O<sub>3</sub> and increased risk of daily total mortality [15]. A Spanish study assessed 2,305 adults in Spain and found a greater increase in both all cause and cardiovascular related mortality associated with ambient air pollutant exposure among women [16]. A US study analyzing deaths in 27 communities across the country identified a larger risk for cardiovascular related deaths among women compared with men [17]. However, there are published studies citing no gender increase risk and others citing males as increased risk, thus the gender results may differ between populations. The findings from this study provide additional support to the growing pool of studies indicating that compared with males, females potentially experience a greater risk of CHD related health events associated with chronic ambient air pollution exposure.

Among the female population, female renal transplant recipients may be one of the most sensitive subpopulations and there may be a number of factors at play enhancing susceptibility placing them at even greater risk than the general public for adverse cardiovascular events associated with chronic ambient air pollution. Hospital admissions and mortality research have implicated diabetes, obesity, hypertension and elderly age as groups with enhanced vulnerability [11-14,24]. Many of these conditions are highly prevalent among renal transplant recipients potentially making them one of the highest risk sensitive subpopulations, with women at even greater risk, for cardiovascular effects associated with air pollution [19]. In addition to the high prevalence of the known CHD risk factors, transplant recipients have additional CHD risk factors as a result of the use of immunosuppressant medications. The medications have been associated with hyperlipidemia, hypertension, and new onset of diabetes post-transplant [25,26]. Together, these various factors may enhance vulnerability among renal transplant recipients, making them one of the most sensitive subpopulations at risk for adverse cardiovascular health effects associated with short- and long-term ambient air pollution exposures.

### Possible biological mechanisms

The basic biological mechanisms as well as any potential gender differences through which air pollution may promote adverse cardiovascular effects remains unclear. One of the supported biological mechanisms is that inhalation of ambient air pollutants promotes a pulmonary inflammatory response that triggers a cascade of events, including subsequent release into circulation of prothrombotic and inflammatory cells and mediators, setting in motion a systemic inflammatory process [27]. Scientific evidence is accumulating that air pollutants may influence a number of blood markers including fibrinogen, platelets, C-reactive protein (CRP) and white cell count ultimately increasing the risk of cardiovascular disease and mortality [28-30]. Researchers have identified that gender differences exist

in the distribution of CRP within the general public with females experiencing higher median CRP levels [31]. Thus the possibility exists that air pollution may exacerbate the already heightened levels of CRP among women enhancing a disruption in the cardiovascular system homeostasis and further promoting heart disease [32]. In addition to inflammation, there may be a number of other sex related biological factors influencing increased susceptibility among females including: smaller lung size, increased deposition of fine particles in the lungs, [33] and increased airway responsiveness and hyper responsiveness [34]. Further research is required to determine which gender specific characteristics potentially increase the risk of CHD mortality for female transplant recipients when exposed to air pollution.

### Strengths and Limitations

Our study design had several strengths as well as limitations. By utilizing the USRDS database we have a nationally representative sample of more than 79,500 first time, renal only, adult transplants, transplanted between 1997 through 2003. This large number of transplant recipients also gives access to a large number of events, providing sufficient strength in determining if these subjects are especially vulnerable with respect to risk of CHD in an environment with higher air pollution levels.

Our study has some limitations that merit discussion. As with other studies on the health effects of air pollution, only ambient pollution concentrations at place of residence was available, which could potentially cause exposure misclassification. However, it is unlikely that there is a directional bias with only cases experiencing misclassification of exposure assignment. Additionally we did not have information on ambient levels of PM<sub>2.5</sub>. As PM<sub>2.5</sub> (≤2.5 μm) is smaller in diameter compared with PM<sub>10</sub> (≤10 μm), it is anticipated that stronger associations will be found for PM<sub>2.5</sub> as the smaller particle more easily penetrates the biological defense mechanisms. Adjusting for this pollutant could potentially alter the effects of O<sub>3</sub> even if adding PM<sub>10</sub> in two pollutant models, did not change the effect of O<sub>3</sub>. However, a number of both animal and human laboratory studies have found harmful effects of O<sub>3</sub> independent of PM<sub>2.5</sub> [35-37]. Lastly, the low number of CHD deaths among renal transplant recipients in this study, may indicate that CHD deaths have been assigned a different cause of death within the database, quite possibly with a cardiovascular disease other than CHD. Further analysis into the association between ambient air pollutants and other cardiovascular related deaths are warranted.

### Conclusion

In summary, we have presented the first epidemiological evidence showing the possibility that female renal transplant recipients may be at greater risk of fatal CHD associated with chronic exposures to ambient air pollutant O<sub>3</sub> when compared to male recipients. More research is needed to confirm our findings among renal transplant recipients and

additionally determine if subjects with renal insufficiency in general have increased risk of fatal CHD associated with ambient air pollution. Findings from this study may thus have implications for policies and regulations of air pollution in protecting the health of a potentially vulnerable segment of our population. Additionally, the findings from our study have implications for development of health information guidelines and patient education targeting exposure reduction for this potentially vulnerable population.

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#### Competing Interests

The authors have submitted a related paper from this same study to the American Journal of Kidney Diseases. The previously submitted paper looked at the overall risk of air pollution for renal transplants, while this article focuses on the risk for males vs. females transplant recipients. The authors have no financial conflict of interest.

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