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## **Long-Term Exposure to Ambient Fine Particulate Matter and Renal Function in Older Men: The VA Normative Aging Study**

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**Running title:** Long-term PM<sub>2.5</sub> exposure and renal function

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## Abstract

**Background:** It is unknown if ambient fine particulate matter (PM<sub>2.5</sub>) is associated with lower renal function, a cardiovascular risk factor.

**Objective:** We investigated if long-term PM<sub>2.5</sub> exposure was associated with estimated glomerular filtration rate (eGFR) in a cohort of older men living in the Boston Metropolitan area.

**Methods:** This longitudinal analysis included 669 participants from the Veterans Administration Normative Aging Study with up to four visits between 2000 and 2011 (n=1,715). Serum creatinine was measured at each visit and eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation. One-year exposure to PM<sub>2.5</sub> prior to each visit was assessed using a validated spatiotemporal model which utilized satellite remote sensing aerosol optical depth data. eGFR was modeled in a time-varying linear mixed-effects regression model as a continuous function of 1-year PM<sub>2.5</sub> adjusting for important covariates.

**Results:** 1-year PM<sub>2.5</sub> exposure was associated with lower eGFR level; a 2.1 µg/m<sup>3</sup> interquartile range higher 1-year PM<sub>2.5</sub> was associated with a 1.87 mL/min/1.73 m<sup>2</sup> lower eGFR (95%CI: -2.99, -0.76). A 2.1 µg/m<sup>3</sup> higher 1-year PM<sub>2.5</sub> was also associated with an additional annual decrease in eGFR of 0.60 mL/min/1.73 m<sup>2</sup> per year (95%CI: -0.79, -0.40).

**Conclusions:** In this longitudinal sample of older men, the findings support the hypothesis that long-term PM<sub>2.5</sub> exposure negatively affects renal function and renal function decline.

## Introduction

Chronic exposure to ambient fine particulate matter (PM<sub>2.5</sub>) is a well-known risk factor for cardiovascular-related morbidity and mortality (Brook et al. 2010). While the underlying mechanisms are not fully elucidated, there is evidence suggesting that pathways at the molecular level including inflammation (Ostro et al. 2014; R uckerl et al. 2014) and oxidative stress (S orensen et al. 2003), and at the function level including arterial blood pressure (BP) (Fuks et al. 2014; Liang et al. 2014) and vascular/endothelial function (Krishnan et al. 2012; Wilker et al. 2014), may have a role in PM<sub>2.5</sub>-related cardiovascular morbidity and mortality.

It is also hypothesized that renal function impairment may be mediating factor of the cardiovascular effects of long-term PM<sub>2.5</sub> exposure, as the kidney is a vascularized organ susceptible to large vessel atherosclerotic disease and microvascular dysfunction (Lue et al. 2013). Impaired renal function, as determined from the estimated glomerular filtration rate (eGFR), is also associated with cardiovascular events and mortality (Fox et al. 2012; Go et al. 2004; Sarnak et al. 2003). There is limited experimental evidence which suggests that particles exposure affects the kidney; in-vivo studies in rats have shown that controlled exposure to urban or diesel exhaust particles to be associated with increased cytokine expression in the kidney (Thomson et al. 2013), and to aggravate acute renal failure (Nemmar et al. 2010). A recent cross-sectional study of stroke patients living in the Boston Metropolitan Area found that living near a major roadway was associated with lower eGFR (Lue et al. 2013). To our knowledge, there is no longitudinal population study to date that has directly evaluated if long-term PM<sub>2.5</sub> exposure is associated with lower renal function or higher age-related decline in renal function.

We investigated whether 1-year averaged exposure to  $PM_{2.5}$  was associated with lower renal function and renal function decline over time in an ongoing prospective cohort of older men living in the Boston Metropolitan Area. This study takes advantage of a longitudinal sample with serum creatine measured in multiple visits, where renal function was characterized by creatine-based eGFR defined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey et al. 2009), as well as a validated spatially and temporally-resolved prediction model of annual outdoor exposure to  $PM_{2.5}$  at each participant's home address (Kloog et al. 2011; Kloog et al. 2014). We also investigated whether the association between  $PM_{2.5}$  and eGFR was mediated via a change in BP.

## **Methods**

Participants included in this analysis were enrolled in the VA Normative Aging Study, an ongoing longitudinal study of aging established by the Veterans Administration in 1963, details of which have been published previously (Bell et al. 1972). Briefly, the Veterans Administration Normative Aging Study is a closed cohort of 2,280 male volunteers from the greater Boston area (Massachusetts), aged 21 to 80 years at study entry, who enrolled after an initial health screening determined that they were free of known chronic medical conditions. The study population is predominantly White; less than 2 percent of all participants are Black. Participants have been reevaluated every 3–5 years by using detailed, onsite physical examinations and questionnaires. Visits took place in the morning, after an overnight fast and smoking abstinence. The present study was approved by the human research committees of the Harvard School of Public Health and the Veterans Affairs Boston Healthcare System, and written informed consent was obtained from subjects prior to participation.

Eligibility for this study required continued participation between May 2000 and December 2011 when satellite-derived aerosol optical depth (AOD) measurements were available, and 756 participants had at least one scheduled visit during this time period (Figure 1). Of the 756 participants, we excluded 58 (7.7%) for not continuing to live within the coverage area of the prediction model, 11 (1.5%) for not having serum creatinine measured at visit, and 18 (2.3%) for having incomplete information on covariates of interest. Thus, a total of 669 participants were included in this longitudinal repeated-measures analysis and presented for a total of 1,715 visits during the study period.

### *Exposure assessment*

We assessed long-term PM<sub>2.5</sub> exposure using satellite-based spatiotemporal models that predicts daily ambient concentrations of PM<sub>2.5</sub> at each participant's residence. We applied our recently published (Kloog et al. 2014) high resolution 1x1 km exposure model for the years we had prediction data for (2003-2011), and applied a slightly lower resolution 10x10 km model (Kloog et al. 2011) for the years where new model predictions were unavailable (2000-2002). The 1x1 km exposure assessment is based on a new Multi-Angle Implementation to Atmospheric Correction (MAIAC) algorithm developed by the National Aeronautics and Space Administration (NASA) (Lyapustin et al. 2011), while the 10x10 km exposure assessment is based on the older NASA Moderate Resolution Imaging Spectroradiometer (MODIS) algorithm. The MAIAC algorithm provides finer resolution AOD data which allows us to use high resolution 1x1 km *versus* the MODIS 10x10 km AOD data.

Both the 1x1 km and 10x10 km models use very similar methodology. We use a mixed-effects model approach by regressing daily PM<sub>2.5</sub> mass concentration ( $\mu\text{g}/\text{m}^3$ ) from the U.S.

Environmental Protection Agency Air Quality System and Interagency Monitoring of Protected Visual Environments network against AOD, spatial predictors, and temporal predictors. For days when AOD data are not available for some grid cells, we regressed predicted PM<sub>2.5</sub> for each gridcell against the PM<sub>2.5</sub> at the nearest monitor within 60 km of the cell and a thin plate spline term of latitude and longitude. We used this model to fill in the missing gridcell-days. The mean out-of-sample R<sup>2</sup> from 10-fold cross validation was 0.88 and 0.83 for the 1x1 km and 10x10 km models, respectively, showing excellent prediction ability. Further details can be found in previously published papers (Kloog et al. (2011 and 2014)). For each participant, we calculated address-specific exposure of 1-year averaged PM<sub>2.5</sub> concentrations prior to examination visit.

#### *Outcome assessment*

Serum samples were drawn after overnight fasting, and serum creatinine concentration (Scr, mg/dl) was determined by a computerized automatic analyzer [Technicon SAM models (Technicon Corp., Tarrytown, NY) from 1979 to 1993; Boehringer Mannheim/Hitachi 747 analyzer (Boehringer-Mannheim Corp, Indianapolis, IN) from 1993 and onward] at each examination. The analyzer measures creatinine based on the Jaffe procedure (Jaffe 1886) and demonstrated excellent reproducibility. This method of analysis has an intraassay coefficient of variation (CV) of 1.3% at 1.2 mg/dL and interassay CV of 3.3% at 1.1 mg/dL. We calculated eGFR at each visit using the CKD-EPI equation ( $eGFR = 141 \times \min(Scr/0.9, 1)^{-0.411} \times \max(Scr/0.9, 1)^{-1.209} \times 0.993^{Age} \times 1.159[\text{if black}]$ ) (Levey et al. 2009). The calculated intraclass correlation coefficient of 0.7 for eGFR indicated had a high degree of stability over time.

### *Ascertainment of covariates*

At each examination, participants were followed up by physical examination, updating of medical history, and measurement of biomarkers from serum samples including fasting glucose and serum cholesterol. Serum cholesterol was assayed over the course of the study period using standard enzymatic methods and reagents (SCALVO Diagnostics, Wayne, NJ). Weight and height were measured with participants wearing only socks and underpants, from which body mass index (BMI) ( $\text{weight} / \text{height}^2$ ) was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured once in each arm while the subject was seated, using a standard cuff; the mean of right and left arm values were used for analysis. At each visit, participants were also asked to bring their current medical prescriptions; antihypertensive medication use included any of the following classes: ace-inhibitors, diuretics, beta-blockers, angiotensin receptor blockers, calcium channel blockers, and alpha-blockers. As a proxy measure of childhood socioeconomic status, parental homeownership during the participant's childhood was ascertained by questionnaire at the baseline survey. As a proxy measure of adult socioeconomic status, maximum years of education, was ascertained by questionnaire at the early visits. Year 2000 census data were obtained from the US Bureau of the Census Summary File (III) at the census tract level. For this analysis, we used the proportion of the population within in census tract living below poverty as an area-based measure of socioeconomic position.

### *Statistical analysis*

All statistical analyses were carried out using SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina). We used time-varying linear mixed-effects regression models with random intercepts accounting for the correlation of repeated measures (Fitzmaurice et al. 2004)

to model eGFR ( $\text{ml}/\text{min}/1.73 \text{ m}^2$ ) as a continuous function of 1-year  $\text{PM}_{2.5}$  scaled per interquartile range (IQR) and adjusting for age at first visit and time since first visit (years). To evaluate if 1-year  $\text{PM}_{2.5}$  was associated with annual change in eGFR, we added an interaction between 1-year  $\text{PM}_{2.5}$  and time since first visit. We additionally adjusted for the following covariates ascertained at each visit including BMI ( $\text{kg}/\text{m}^2$ ), total cholesterol ( $\text{mg}/\text{dL}$ ), coronary heart disease (no as reference), diabetes (physician-diagnosed or fasting blood glucose  $\geq 126$   $\text{mg}/\text{dL}$ , no as reference), angiotensin receptor blocker (ARB) use (no as reference), ace inhibitor (ACEI) use (no as reference), other antihypertensive medication use (no as reference), years of education ( $< 12$  years, 12 years, 13 to 15 years, 16 or more years as reference), percent of population living in census tract living below poverty, parental homeownership (no as reference), smoking status (current, former, never as reference), cumulative pack years smoked, and daily alcohol intake ( $\geq 2$  drinks/day,  $< 2$  drinks/day as reference). Normality of the residuals in the linear mixed-effects model of eGFR and 1-year  $\text{PM}_{2.5}$  was demonstrated in a preliminary analysis. We also evaluated the following participant characteristics as potential effect modifiers of the association between 1-year  $\text{PM}_{2.5}$  exposure and eGFR by constructing multiplicative interaction terms between each potential modifier and 1-year  $\text{PM}_{2.5}$ , and evaluated each separately in linear mixed-effects regression models: smoking status (current or former, never), high BP (SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg), diabetes mellitus, obesity (BMI  $\geq 30$   $\text{kg}/\text{m}^2$ ), and coronary heart disease, and use of ARB and ACEI medications. All tests for main associations and interactions where  $p < 0.05$  were considered statistically significant.

### *Secondary analyses*

Because approximately 26% of the study participants did not have a repeat visit in this analysis, we conducted a baseline cross-sectional analysis of eGFR using multiple linear regression, excluding the available repeat visits from participants. We additionally adjusted for distance to nearest major roadway, with major roadway defined as those roads having US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access), as in previous studies (Auchincloss et al. 2008; Lue et al. 2013). We additionally adjusted for eGFR measured at first visit to evaluate its influence on the interaction between 1-year  $PM_{2.5}$  and time since first visit. There are 152 participants (~23%) that began the study period with  $eGFR \leq 60 \text{ mL/min/1.73 m}^2$ , presenting for a total of 331 visits during the study period. We also examined if the association between 1-year  $PM_{2.5}$  and eGFR level was modified by presence of impaired renal function ( $eGFR \leq 60 \text{ ml/min/1.73 m}^2$ ) at first visit by including an interaction term in the model.

There were 223 deaths (33%) and 254 non-death drop-outs (38%) during the study period (Figure 1). To account for potential selection bias by age-dependent censoring from death and from non-death drop-out prior to next visit, we applied stabilized inverse probability weights analogous to methods previously applied in the NAS cohort (Power et al. 2013). Estimation of stabilized inverse probability weights for each censoring mechanism required two logistic regression models, which predicted the probability of not being censored (death, non-death drop-out) at the next visit. The first logistic regression was to model death (non-death drop-out) prior to next visit as a function of 1-year  $PM_{2.5}$ . The second logistic regression was to model death (non-death drop-out) as a function of 1-year  $PM_{2.5}$ , eGFR, age, and education, adjusting for an

array of clinical and sociodemographic factors that might be associated with death and/or morbidity. Given the large number of potential predictors of censoring available in this study, we used forward step-wise selection to choose variables for inclusion in these logistic regression models, setting the maximum number of variables chosen to the number of participants who died or dropped out prior to each visit divided by ten, while forcing in 1-year  $PM_{2.5}$ , renal function, age, and education-related variables. Additional variables in the models to predict censoring due to death prior to next visit include: the interaction between age and years of education, exclusion from pulmonary function testing for health reasons, physician's diagnosis of emphysema, coronary heart disease, white blood cell count, smoking status, and pack years smoked. Additional variables in the models to predict censoring due to non-death drop-out prior to next visit include: the interaction between age and years of education, parental homeownership, calendar year of visit, systolic blood pressure, ace inhibitors medication use, calcium channel blocker, statin medication use, cholesterol, serum hematocrit, fasting blood glucose, waist circumference, white blood cell count, diabetes mellitus, and current cancer diagnosis. Subsequently, we estimated stabilized inverse probability weights for censoring (death, non-death drop-out) prior to next visit by taking the ratio of the probabilities estimated from the first and second logistic regression models. All weighted models met the necessary condition for correct model specification such that the mean value for the stabilized weights approximated one (Hernán et al. 2000). To compute a summary weight which combines the censoring by death and non-death drop-out, we simply multiplied the inverse probability weights for censoring by death and by non-death drop-out together.

Considering the evidence which supports an association between long-term  $PM_{2.5}$  and BP (Fuks et al. 2014; Liang et al. 2014), and the association between BP and eGFR decline (Young

et al. 2002), we hypothesized that the association between long-term PM<sub>2.5</sub> and lower renal function is mediated through an increase in BP. We previously found that 1-year PM<sub>2.5</sub> was associated with higher DBP in the NAS cohort (unpublished). Using methods previously developed and applied in the NAS cohort (Bind et al. 2014; Bind et al. 2016), we conducted a mediation analysis and calculated the estimated mediated effect of 1-year PM<sub>2.5</sub> on eGFR level through an increase in DBP. We fit simultaneously two time-varying linear mixed-effects models:

$$M_{ij} = (\gamma_0 + u_i) + \gamma_1 X_{ij} + \sum_k \gamma_{2k} C_{kij} + \varepsilon_{ij} \text{ with } \varepsilon_{ij} \sim N(0, \sigma^2) \text{ and } u_i \sim N(0, \sigma_u^2) \quad [1]$$

$$Y_{ij} = (\beta_0 + g_i) + \beta_1 X_{ij} + \beta_2 M_{ij} + \sum_k \beta_{3k} C_{kij} + \sum_k \beta_{4k} + \eta_{ij} \text{ with } \eta_{ij} \sim N(0, \sigma^2), \text{ and } g_i \sim N(0, \sigma_g^2) \quad [2]$$

where  $i, j, k$ , are defined as individuals, visits, and covariates, respectively;  $M, X$ , and  $Y$ , represent the DBP, 1-year PM<sub>2.5</sub>, and eGFR, respectively;  $C$  represents the set of covariates for which we adjusted, and  $g$  represents the random intercept for  $M$ . The estimated mediated effect is given by the product formula  $\gamma_1 \beta_2$ . The delta method allowed us to approximate the variance of the estimated mediated effect by  $\text{Var}(\beta_2) \gamma_1^2 + 2 \text{Cov}(\gamma_1, \beta_2) \gamma_1 \beta_2 + \text{Var}(\gamma_1) \beta_2^2$ . The mediation formulae we derive are valid if four identification assumptions are met, if there is no time-varying confounding with respect to the 1-year PM<sub>2.5</sub> and DBP (which can be achieved in situations with exogenous exposure and mediator depending only on recent values of the exposure and confounders). The four identification assumptions include: (1) no unmeasured 1-year PM<sub>2.5</sub> – eGFR confounding at time  $j$  given the covariates and random effects, (2) no unmeasured DBP – eGFR confounding, (3) no unmeasured 1-year PM<sub>2.5</sub> – DBP confounding, and (4) no DBP – eGFR confounder affected by 1-year PM<sub>2.5</sub>. Since the measurements of the mediator and outcome are taken at the same time (cross-sectionally), this implies that the

mediator does not necessarily precede the measurement of the outcome, and we cannot rule out that the outcome could be the mediator and the mediator the outcome.

## Results

We summarized the characteristics of the participants at the first visit and over all visits in Table 1. The mean age of participants was 73.5 years, and the majority was former smokers and using anti-hypertensive medication at the first visit. Compared with participants at the first visit, the mean eGFR was lower in participants over all visits, while the prevalences of coronary heart disease, hypertension, and of using anti-hypertensive medications were higher.

The mean 1-year average PM<sub>2.5</sub> concentrations at participant addresses at the first visit was 11.4 µg/m<sup>3</sup> (Table 1). This estimate was lower in participant addresses over all visits; the mean was 10.5 µg/m<sup>3</sup>. All yearly averages from 2000 to 2011 were below the US annual fine particle standard, which was recently revised downward to 12 µg/m<sup>3</sup> in 2013 (Federal Register 2013), and the mean and median 1-year PM<sub>2.5</sub> concentrations closely approximated each other (Table 2). In all person-visits by calendar year, the mean yearly average PM<sub>2.5</sub> concentrations increased from 10.5 µg/m<sup>3</sup> in 2000 to its highest level at 11.8 µg/m<sup>3</sup> in 2002, and decreased to levels below 9.0 µg/m<sup>3</sup> in 2010 and 2011.

The associations between 1-year PM<sub>2.5</sub> and eGFR level in all participants, after various adjustments, are summarized in Figure 2. 1-year averaged exposure to PM<sub>2.5</sub> was statistically significantly ( $p < 0.05$ ) associated with lower eGFR level in the overall sample. In the age-adjusted model, a 2.1 µg/m<sup>3</sup> IQR higher 1-year PM<sub>2.5</sub> was associated with a 2.13 mL/min/1.73 m<sup>2</sup> lower eGFR (95% CI: -3.25, -0.76). Relative to the age-adjusted model, the association between 1-year PM<sub>2.5</sub> and eGFR level in the fully-adjusted model was slightly attenuated; a 2.1

$\mu\text{g}/\text{m}^3$  IQR higher 1-year  $\text{PM}_{2.5}$  was associated with a 1.87 mL/min/1.73  $\text{m}^2$  lower eGFR (95% CI: -2.99, -0.76) after adjustment for all other covariates. However, the association from the fully-adjusted model was robust to additional adjustment for distance to roadway, and inverse probability of censoring weights for death and non-death drop-out and the combined weight of both censoring mechanisms.

There was no statistically significant effect modification by participant characteristics on the association between 1-year  $\text{PM}_{2.5}$  and eGFR level (Figure 3). Higher 1-year  $\text{PM}_{2.5}$  was at least marginally significantly ( $p < 0.10$ ) associated with lower eGFR level for the majority of subgroups, and the 95% confidence intervals of the effect estimates for the subgroups of each modifier widely overlapped each other. However, the negative association between 1-year  $\text{PM}_{2.5}$  and eGFR level in the overall sample, as shown in Figure 2, was observed mainly for individuals not using ARB medication ( $\beta$ : -2.10 mL/min/1.73  $\text{m}^2$ , 95%CI: -3.25, -0.95); a null association was observed for individuals using ARB medication ( $\beta$ : -0.28 mL/min/1.73  $\text{m}^2$ , 95%CI: -2.54, -1.98). A similar pattern was observed for diabetes; the negative association between 1-year  $\text{PM}_{2.5}$  and eGFR level was more pronounced for non-diabetic individuals ( $\beta$ : -2.11 mL/min/1.73  $\text{m}^2$ , 95%CI: -3.26, -0.97) than diabetic individuals ( $\beta$ : -0.64 mL/min/1.73  $\text{m}^2$ , 95%CI: -2.46, -0.93) ( $P_{\text{interaction}} = 0.09$ ). After additional adjustment for the 1-year  $\text{PM}_{2.5}$ -ARB interaction in the model, there was less contrast in the 1-year  $\text{PM}_{2.5}$ -eGFR association between diabetic ( $\beta$ : -1.00 mL/min/1.73  $\text{m}^2$ , 95%CI: -2.91, 0.90) and non-diabetic subgroups ( $\beta$ : -2.27 mL/min/1.73  $\text{m}^2$ , 95%CI: -3.44, 1.10) ( $P_{\text{interaction}} = 0.16$ ). In contrast to the observations for diabetes, the negative associations between 1-year  $\text{PM}_{2.5}$  and eGFR level were more pronounced for individuals present with obesity ( $\beta$ : -2.64 mL/min/1.73  $\text{m}^2$ , 95%CI: -4.25, -1.03) and high BP ( $\beta$ : -2.71 mL/min/1.73  $\text{m}^2$ , 95%CI: -4.36, -1.05) than for individuals who did not present with obesity ( $\beta$ : -1.63

mL/min/1.73 m<sup>2</sup>, 95%CI: -2.80, -0.46) and high BP ( $\beta$ : -1.62 mL/min/1.73 m<sup>2</sup>, 95%CI: -2.77, -0.46) ( $P_{\text{interaction}} = 0.20$  and  $P_{\text{interaction}} = 0.17$  for obesity and high BP, respectively).

1-year PM<sub>2.5</sub> was associated with a higher rate of decline in eGFR over time; an interaction was identified between time since first visit and 1-year PM<sub>2.5</sub> ( $P_{\text{interaction}} < 0.0001$ ) (Figure 4). After adjustment for all covariates, a 2.1  $\mu\text{g}/\text{m}^3$  higher 1-year PM<sub>2.5</sub> was associated with an additional annual decrease in eGFR of 0.60 mL/min/1.73 m<sup>2</sup>/yr (95% CI: -0.79, -0.40). This association was robust to additional adjustments for distance to roadway and for eGFR measured at the first visit, and to inverse probability of censoring weights by death and non-death drop-out and the combined weight of both censoring mechanisms.

### *Secondary analyses*

A similar finding was observed for the association between 1-year PM<sub>2.5</sub> and eGFR level from the baseline cross-sectional analysis; in the fully-adjusted model, a 2.1  $\mu\text{g}/\text{m}^3$  higher 1-year PM<sub>2.5</sub> was associated with a 1.63 mL/min/1.73 m<sup>2</sup> lower eGFR (95%CI: -3.78, 0.51). No significant effect modification ( $P_{\text{interaction}} = 0.27$ ) was observed by impaired renal function at the first visit on the association between 1-year PM<sub>2.5</sub> and eGFR level; negative associations between 1-year PM<sub>2.5</sub> and eGFR level was observed for both individuals who began the study period with impaired renal function ( $\beta$ :-2.40 mL/min/1.73 m<sup>2</sup>, 95%CI: -4.11, -0.61) and without ( $\beta$ :-1.41 mL/min/1.73 m<sup>2</sup>, 95%CI: -2.47, -0.35). Similarly, age-related decline in eGFR associated with 1-year PM<sub>2.5</sub> was observed for both individuals who began the study period with impaired renal function ( $\beta$ :-0.53 mL/min/1.73 m<sup>2</sup>/yr, 95%CI: -0.74, -0.33) and without ( $\beta$ :-0.65 mL/min/1.73 m<sup>2</sup>/yr, 95%CI: -0.84, -0.46). For the mediation analysis, we observed that a 2.1  $\mu\text{g}/\text{m}^3$  increase in 1-year PM<sub>2.5</sub> was associated with an estimated 0.14 mL/min/1.73 m<sup>2</sup> lower eGFR (95%CI: -0.28,

-0.01) through a 1 mmHg increase in DBP, assuming that the identification assumptions were met, and that there was no time-varying confounding with respect to 1-year  $PM_{2.5}$  and DBP.

## Discussion

The novel findings from this prospective cohort study of older men indicate that 1-year  $PM_{2.5}$  exposure is associated with lower eGFR level and a higher rate of eGFR decline over time. These associations were robust to various sensitivity analyses. There was no statistically significant effect modification by participant characteristics on the association between 1-year  $PM_{2.5}$  and eGFR level, but the associations were null for ARB users and for diabetics. The association between 1-year  $PM_{2.5}$  and eGFR level was also mediated by an increase in DBP, although this finding is based on some unverifiable assumptions.

There has been limited research to date on the topic of long-term exposure to particulate matter air pollution and renal-related outcomes. A recent cross-sectional study of 1,103 stroke patients in the Boston Metropolitan Area found that participants living near a major roadway, by less than 50 meters had a 3.9 mL/min/1.73 m<sup>2</sup> lower eGFR (95%CI: -1.0, -6.7) compared with participants living more than 1,000 meters away (Lue et al. 2013). An earlier longitudinal analysis of 3,901 participants within the Multi-Ethnic Study of Atherosclerosis reported that chronic exposures to  $PM_{2.5}$  and  $PM_{10}$ , which were averaged over 20 years, were not associated with urinary albumin/creatinine ratio, although there was an elevated risk of microalbuminuria associated with chronic  $PM_{10}$  exposure that was of marginal statistical significance (O'Neill et al. 2008).

While we did not identify a statistically significant interaction between 1-year  $PM_{2.5}$  and ARB use, it is of interest that the association between 1-year  $PM_{2.5}$  and eGFR level was null for

ARB users. ARBs, alone or in combination with ACEIs, have been shown to slow the progression of chronic kidney disease in individuals with or without diabetes, independent of their blood-pressure lowering effect (Palmer et al. 2015). Findings from experimental in-vivo and in-vitro studies also suggest that ARBs may minimize the oxidative stress and vasoconstrictive effects of PM (Ghelfi et al. 2010; Li et al. 2005). We also observed that the negative association between 1-year PM<sub>2.5</sub> and eGFR level was stronger for obese participants, but weaker for diabetic participants, which was unexpected. The pattern of effect modification by diabetes was similar to ARB use, and in this study, the prevalence of ARB use was two-fold greater in diabetic (36%) than in non-diabetic participants (18%).

The underlying biological mechanism(s) that may explain the novel association between long-term PM<sub>2.5</sub> exposure and lower eGFR and eGFR decline are not known. We hypothesized that the negative association between 1-year PM<sub>2.5</sub> exposure and eGFR level was mediated by an increase in DBP, and the result from the mediation analysis appears consistent with that hypothesis. If the assumptions of the causal mediation analysis hold, the small magnitude of the estimated mediated effect for PM<sub>2.5</sub> also suggests that the association between 1-year PM<sub>2.5</sub> and eGFR level is likely only partially mediated by DBP, and that there may be non-hemodynamic pathways to consider. Previous studies have demonstrated associations between long-term PM<sub>2.5</sub> exposures and vascular/endothelial dysfunction (Hoffmann et al. 2007; Krishnan et al. 2012; Wilker et al. 2014). There is also observational evidence which supports the associations between markers of vascular/endothelial dysfunction and serum creatinine-derived eGFR decline (Foster et al. 2013; Perticone et al. 2010). Taking these findings together, we also hypothesize that the associations between 1-year PM<sub>2.5</sub> and eGFR, and eGFR decline, are possibly mediated by pathways associated with vascular/endothelial dysfunction.

The clinical relevance of the present findings merits further discussion. The difference in eGFR level for a  $2.1 \mu\text{g}/\text{m}^3$  increase in 1-year  $\text{PM}_{2.5}$  is comparable in magnitude to the reduction in eGFR observed for a 2-year increase in age in this cohort ( $\beta$ :  $-1.8 \text{ mL}/\text{min}/1.73 \text{ m}^2$ , 95%CI:  $-2.1, -1.5$ ). In the context of eGFR decline, a rapid decline in creatinine-based eGFR of  $\geq 3 \text{ mL}/\text{min}/1.73 \text{ m}^2$  per year in older adults has been shown to be associated with a 70% higher risk in cardiovascular mortality (Rifkin et al. 2008). Extrapolating our findings for a  $10 \mu\text{g}/\text{m}^3$  increase, which may be more appropriate in more polluted settings, may result in a more clinically meaningful estimate of association for eGFR decline, particularly in older population settings.

This study has a number of strengths including a prospective design to investigate the role of  $\text{PM}_{2.5}$  exposure on repeated measures of serum-creatinine derived eGFR, the use of validated spatio-temporal models for assessment of  $\text{PM}_{2.5}$ , advanced methods to address potential bias from age-dependent censoring by death and non-death drop-out, and adjustment for multiple potential confounders and individual-level risk factors. However, there are limitations to consider in this study. While the CKD-EPI equation for estimating eGFR has demonstrated clinical utility in risk prediction of end stage renal disease and cardiovascular outcomes (Matsushita et al. 2010), there is an inherent physiologic limitation to using serum creatinine as a marker of kidney filtration (Shemesh et al. 1985). Non-GFR determinants of eGFR including muscle mass or diet may lead to overestimation of serum creatinine, particularly for individuals with preserved renal function, and future studies should consider using alternative agents for estimation of eGFR including cystatin C (Fan et al. 2014). We hypothesize that any measurement error of eGFR is likely independent of 1-year  $\text{PM}_{2.5}$  predictions assigned to participants in this study, and would result in bias of the true association between 1-year  $\text{PM}_{2.5}$  and eGFR toward

the null. The potential for reverse causation, particularly between DBP and eGFR, is not theoretical and is also a limitation of our mediation findings; there is limited observational evidence which suggests that lower eGFR may precede elevation in blood pressure and onset of hypertension (Kestenbaum et al. 2008; Takase et al. 2012). Potential risk factors or confounding variables included in our models, such as diabetes status and BMI, may also be intermediate variables. Additionally, there may be some unmeasured confounding from other factors associated with eGFR which may be correlated with PM<sub>2.5</sub> exposure in this study, such as environmental noise. Traffic, aircraft, and railway noise has been shown to be associated with markers of cardiovascular disease (Münzel et al. 2014), but whether environmental noise is associated with renal function is unknown. However, our association persisted after control for distance to major roadway, which is a marker for traffic-related pollution including noise. Lastly, this study also consists of older men who are predominantly White that reside in a lightly polluted area. The observed findings may not be generalizable to women, younger individuals, other racial and ethnic groups, or people living in other areas, due to differential environmental and physiological factors.

In summary, we found that long-term PM<sub>2.5</sub> exposure was associated with lower eGFR and higher age-related eGFR decline in this longitudinal sample of predominantly older White men. These findings support the hypothesis that long-term PM<sub>2.5</sub> exposure negatively affects renal function and renal function decline. These findings should be verified in other study populations with longitudinal follow-up.

## References

- Auchincloss AH, Diez Roux AV, Dvorchak JT, Brown PL, Barr RG, Davignus ML, et al. 2008. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect.* 116:486-91.
- Bell B, Rose C, Damon A. 1972. The Normative Aging Study: an interdisciplinary and longitudinal study of health and aging. *Int J Aging Hum Dev* 3:5-17.
- Bind MA, Lepeule J, Zanobetti A, Gasparrini A, Baccarelli A, Coull BA, et al. 2014. Air pollution and gene-specific methylation in the Normative Aging Study: association, effect modification, and mediation analysis. *Epigenetics.* 9:448-458.
- Bind MA, Vanderweele TJ, Coull BA, Schwartz JD. 2016. Causal mediation analysis for longitudinal data with exogenous exposure. *Biostatistics.* 17:122-134.
- Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation.* 121:2331-2378.
- Federal Register. National Ambient Air Quality Standards for Particulate Matter; Final Rule. 2013. 40 CFR parts 50, 51, 52, 53 and 58. 78:3086-3287.
- Fitzmaurice GM, Laird NM, Ware JH. 2004. *Applied Longitudinal Analysis* Hoboken, NJ: Wiley-Interscience.
- Foster MC, Ghuman N, Hwang SJ, Murabito JM, Fox CS. 2013. Low ankle-brachial index and the development of rapid estimated GFR decline and CKD. *Am J Kidney Dis.* 61:204-210.

Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. 2012.

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 380:1662-1673.

Fuks KB, Weinmayr G, Foraster M, Dratva J, Hampel R, Houthuijs D, et al. 2014. Arterial Blood Pressure and Long-Term Exposure to Traffic-Related Air Pollution: An Analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environ Health Perspect*. 122:896-905.

Ghelfi E, Wellenius GA, Lawrence J, Millet E, Gonzalez-Flecha B. 2010. Cardiac oxidative stress and dysfunction by fine concentrated ambient particles (CAPs) are mediated by angiotensin-II. *Inhal Toxicol*. 22(11):963-972.

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. 2004. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 351:1296-1305.

Hernan MA, Brumback B, Robins JM. 2000. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 11:561-70.

Hoffmann B, Moebus S, Möhlenkamp S, Stang A, Lehmann N, Dragano N, et al. 2007. Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation*. 116:489-496.

Jaffe M. 1886. Ueber den Niederschlag, welchen Pikrinsäure in normalem harn erzeugt und über eine neue reaction des kreatinins. *Zeitschrift für Physiologische Chemie*. 10:391-400.

Kestenbaum B, Rudser KD, de Boer IH, Peralta CA, Fried LF, Shlipak MG, et al. 2008.

Differences in kidney function and incident hypertension: the multi-ethnic study of atherosclerosis. *Ann Intern Med.* 148:501-8.

Kloog I, Chudnovsky AA, Just AC, Nordio F, Koutrakis P, Coull BA et al. 2014. A new hybrid spatio-temporal model for estimating daily multi-year PM<sub>2.5</sub> concentrations across northeastern USA using high resolution aerosol optical depth data. *Atmos Environ.* 95:581-590.

Kloog I, Koutrakis P, Coull BA, Lee HJ, Schwartz J. 2011. Assessing temporally and spatially resolved PM<sub>2.5</sub> exposures for epidemiological studies using satellite aerosol optical depth measurements. *Atmos Environ.* 45:6267-6275.

Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, et al. 2012.

Vascular responses to long- and short-term exposure to fine particulate matter: MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). *J Am Coll Cardiol.* 60:2158-2166.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. 2009. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 150:604–612.

Li Z, Carter JD, Dailey LA, Huang YC. 2005. Pollutant particles produce vasoconstriction and enhance MAPK signaling via angiotensin type I receptor. *Environ Health Perspect.* 113:1009-14.

Liang R, Zhang B, Zhao X, Ruan Y, Lian H, Fan Z. 2014. Effect of exposure to PM<sub>2.5</sub> on blood pressure: a systematic review and meta-analysis. *J Hypertens.* 32:2130-2141.

Lue SH, Wellenius GA, Wilker EH, Mostofsky E, Mittleman MA. 2013. Residential proximity to major roadways and renal function. *J Epidemiol Community Health.* 67:629-634.

Lyapustin A, Martonchik J, Wang Y, Laszlo I, Korkin S. 2011. Multiangle implementation of atmospheric correction (MAIAC): 1. Radiative transfer basis and look-up tables. *J Geophys Res Atmos.* 116:1984–2012.

Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. 2010. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis.* 55:648-659.

Münzel T, Gori T, Babisch W, Basner M. 2014. Cardiovascular effects of environmental noise exposure. *Eur Heart J.* 35:829-836.

Nemmar A, Al Salam S, Zia S, Yasin J, Al Husseni I, Ali BH. 2010. Diesel exhaust particles in the lung aggravate experimental acute renal failure. *Toxicol Sci.* 113:267-277.

O'Neill MS, Diez-Roux AV, Auchincloss AH, Franklin TG, Jacobs DR Jr, Astor BC, et al. 2008. Airborne particulate matter exposure and urinary albumin excretion: the Multi-Ethnic Study of Atherosclerosis. *Occup Environ Med.* 65:534-540.

Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, et al. 2014. Chronic PM<sub>2.5</sub> exposure and inflammation: determining sensitive subgroups in mid-life women. *Environ Res.* 132:168-75.

Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, et al. 2015. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet.* 385:2047-2056.

Perticone F, Maio R, Perticone M, Sciacqua A, Shehaj E, Naccarato P, et al. 2010. Endothelial dysfunction and subsequent decline in glomerular filtration rate in hypertensive patients.

*Circulation*. 122:379-84.

Power MC, Tchetgen EJ, Sparrow D, Schwartz J, Weisskopf MG. 2013. Blood pressure and cognition: factors that may account for their inconsistent association. *Epidemiology*. 24:886-93.

Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, et al. 2008. Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med*. 168:2212-2218.

Rückerl R, Hampel R, Breitner S, Cyrys J, Kraus U, Carter J, et al. 2014. Associations between ambient air pollution and blood markers of inflammation and coagulation/fibrinolysis in susceptible populations. *Environ Int*. 70:32-49.

Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culeton B, Hamm LL, et al. 2003. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 108:2154–2169.

Shemesh O, Golbetz H, Kriss JP, Myers BD. 1985. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int*. 28:830-838.

Sørensen M, Daneshvar B, Hansen M, Dragsted LO, Hertel O, Knudsen L, et al. 2003. Personal PM<sub>2.5</sub> exposure and markers of oxidative stress in blood. *Environ Health Perspect*. 111:161-166.

Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H, et al. 2012. Evaluation of risk for incident hypertension using glomerular filtration rate in the normotensive general population. *J Hypertens*. 30:505-12.

Thomson EM, Vladisavljevic D, Mohottalage S, Kumarathasan P, Vincent R. 2013. Mapping acute systemic effects of inhaled particulate matter and ozone: multiorgan gene expression and glucocorticoid activity. *Toxicol Sci*. 135:169-81.

Wilker EH, Ljungman PL, Rice MB, Kloog I, Schwartz J, Gold DR, et al. 2014. Relation of long-term exposure to air pollution to brachial artery flow-mediated dilation and reactive hyperemia. *Am J Cardiol*. 113:2057-2063.

Young JH, Klag MJ, Muntner P, Whyte JL, Pahor M, Coresh J. 2002. Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). *J Am Soc Nephrol*. 13:2776-2782.

Zanobetti A, Coull BA, Gryparis A, Kloog I, Sparrow D, Vokonas PS, et al. 2014. Associations between arrhythmia episodes and temporally and spatially resolved black carbon and particulate matter in elderly patients. *Occup Environ Med*. 71:201-207.

**Table 1** Characteristics of participants at first visit and over all visits [mean  $\pm$  SD or n (%)]

<b>Characteristics</b>	<b>First visit n=669</b>	<b>All visits n=1,715</b>
Age, yr	73.5 $\pm$ 6.8	75.9 $\pm$ 6.8
eGFR (CKD-EPI), mL/min/1.73 m <sup>2</sup>	71.0 $\pm$ 15.7	68.0 $\pm$ 16.2
Body mass index, kg/m <sup>2</sup>	28.2 $\pm$ 4.1	27.9 $\pm$ 4.2
Serum creatinine, mg/dl	1.1 $\pm$ 0.5	1.1 $\pm$ 0.5
Total cholesterol, mg/dl	195.5 $\pm$ 38.5	183.8 $\pm$ 38.3
Years of education	15.0 $\pm$ 3.0	15.1 $\pm$ 2.9
Percent below poverty level (census tract 1999)	6.1 $\pm$ 5.6	6.0 $\pm$ 5.4
PM <sub>2.5</sub> (1-year average) ( $\mu$ g/m <sup>3</sup> )	11.4 $\pm$ 1.0	10.5 $\pm$ 1.4
Smoking status		
Current	31 (5)	55 (3)
Former	450 (67)	1,160 (68)
Never	188 (28)	500 (29)
Daily alcohol intake		
$\geq$ 2 drinks/day	124 (19)	315 (18)
< 2 drinks/day	545 (81)	1,400 (82)
Parents owned home	250 (37)	643 (37)
Obese ( $\geq$ 30 kg/m <sup>2</sup> )	175 (26)	438 (26)
Diabetes	117 (17)	332 (19)
Coronary heart disease	204 (30)	597 (35)
Hypertension diagnosis	474 (71)	1,298 (76)
High blood pressure (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90)	186 (28)	402 (23)
Angiotensin receptor blocker medication use	31 (5)	144 (8)
Ace-inhibitor medication use	188 (28)	625 (36)
Other antihypertensive medication use (calcium channel blockers, $\beta$ -blockers, or $\alpha$ -blockers)	378 (57)	1,097 (64)

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; Estimated glomerular filtration rate; PM<sub>2.5</sub> - Particulate matter  $\leq$  2.5  $\mu$ m in diameter

**Table 2** Distribution of 1-year PM<sub>2.5</sub> concentrations over all visits by calendar year

<b>Year</b>	<b>N visits</b>	<b>Mean (SD)</b>	<b>Median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile)</b>
2000	141	10.5 (0.8)	10.5 (9.9, 11.0)
2001	245	11.8 (0.7)	11.7 (11.3, 12.3)
2002	173	11.8 (0.6)	11.9 (11.5, 12.2)
2003	106	11.7 (0.8)	11.7 (11.4, 12.2)
2004	169	10.8 (0.9)	10.8 (10.4, 11.3)
2005	193	10.8 (1.0)	11.0 (10.4, 11.4)
2006	126	10.2 (0.9)	10.2 (9.7, 10.8)
2007	116	9.3 (0.9)	9.3 (9.0, 9.8)
2008	147	10.1 (0.9)	10.2 (9.7, 10.7)
2009	104	9.0 (0.9)	9.0 (8.6, 9.5)
2010	93	8.0 (1.0)	8.0 (7.5, 8.5)
2011	102	8.4 (0.8)	8.5 (8.1, 9.0)

PM<sub>2.5</sub> - Particulate matter  $\leq 2.5$   $\mu\text{m}$  in diameter

## Figure Legends

**Figure 1** Flowchart describing inclusion of participants in analysis

**Figure 2** Adjusted differences in eGFR per  $2.1 \mu\text{g}/\text{m}^3$  interquartile range increase in 1-year  $\text{PM}_{2.5}$ . Associations were estimated in time-varying linear mixed-effect models of eGFR with random intercept for study participant. Age-adjusted models included adjustment for time since first visit, and age at first visit. Fully-adjusted models included additional adjustment for BMI, total cholesterol, diabetes, coronary heart disease, ARB medication, ACEI medication, other anti-hypertensive medication, years of education, percentage below poverty in census tract, parental homeownership, smoking status, cumulative pack-years smoked, and daily alcohol intake. For the fully-adjusted model, we additionally adjusted for distance to roadway, and applied stabilized IPW for censoring by death and non-death drop-out and by the combination of both censoring mechanisms. Abbreviations: eGFR, estimated glomerular filtration rate; IPW, inverse probability weight;  $\text{PM}_{2.5}$ , fine particulate matter  $\leq 2.5 \mu\text{m}$  in diameter.

**Figure 3** Adjusted differences in eGFR per  $2.1 \mu\text{g}/\text{m}^3$  interquartile range increase in 1-year  $\text{PM}_{2.5}$  in subgroups according to participant characteristics. Associations were estimated in time-varying linear mixed-effect models of eGFR with random intercept for study participant after adjustment for time since first visit, age at first visit, BMI, total cholesterol, diabetes, coronary heart disease, ARB medication, ACEI medication, other anti-hypertensive medication, years of education, percentage below poverty in census tract, parental homeownership, smoking status, cumulative pack-years smoked, and daily alcohol intake. Effect estimates presented for each subgroup were estimated from the nested interaction model. Abbreviations: ACEI, ace-inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate;  $P_{\text{int}}$  = p-value for interaction  $\text{PM}_{2.5}$ , fine particulate matter  $\leq 2.5 \mu\text{m}$  in diameter.

**Figure 4** Adjusted difference in annual change in eGFR since first visit ( $\text{mL}/\text{min}/1.73 \text{ m}^2/\text{yr}$ ) per  $2.1 \mu\text{g}/\text{m}^3$  interquartile range increase in 1-year  $\text{PM}_{2.5}$ . Associations were estimated in time-varying linear mixed-effect models of eGFR with random intercept for study participant. Age-adjusted models included adjustment for time since first visit, and age at first visit. Fully-adjusted models included additional adjustment for BMI, total cholesterol, diabetes, coronary

heart disease, ARB medication, ACEI medication, other anti-hypertensive medication, years of education, percentage below poverty in census tract, parental homeownership, smoking status, cumulative pack-years smoked, and daily alcohol intake. For the fully-adjusted model, we additionally adjusted for distance to roadway and baseline eGFR, and applied stabilized IPW for censoring by death and non-death drop-out and by the combination of both censoring mechanisms. The effect estimates presented for each model is estimated from the interaction between time since first visit and 1-year PM<sub>2.5</sub>. Abbreviations: eGFR, estimated glomerular filtration rate; IPW, inverse probability weight; PM<sub>2.5</sub>, fine particulate matter  $\leq 2.5$   $\mu\text{m}$  in diameter.

**Figure 1.**

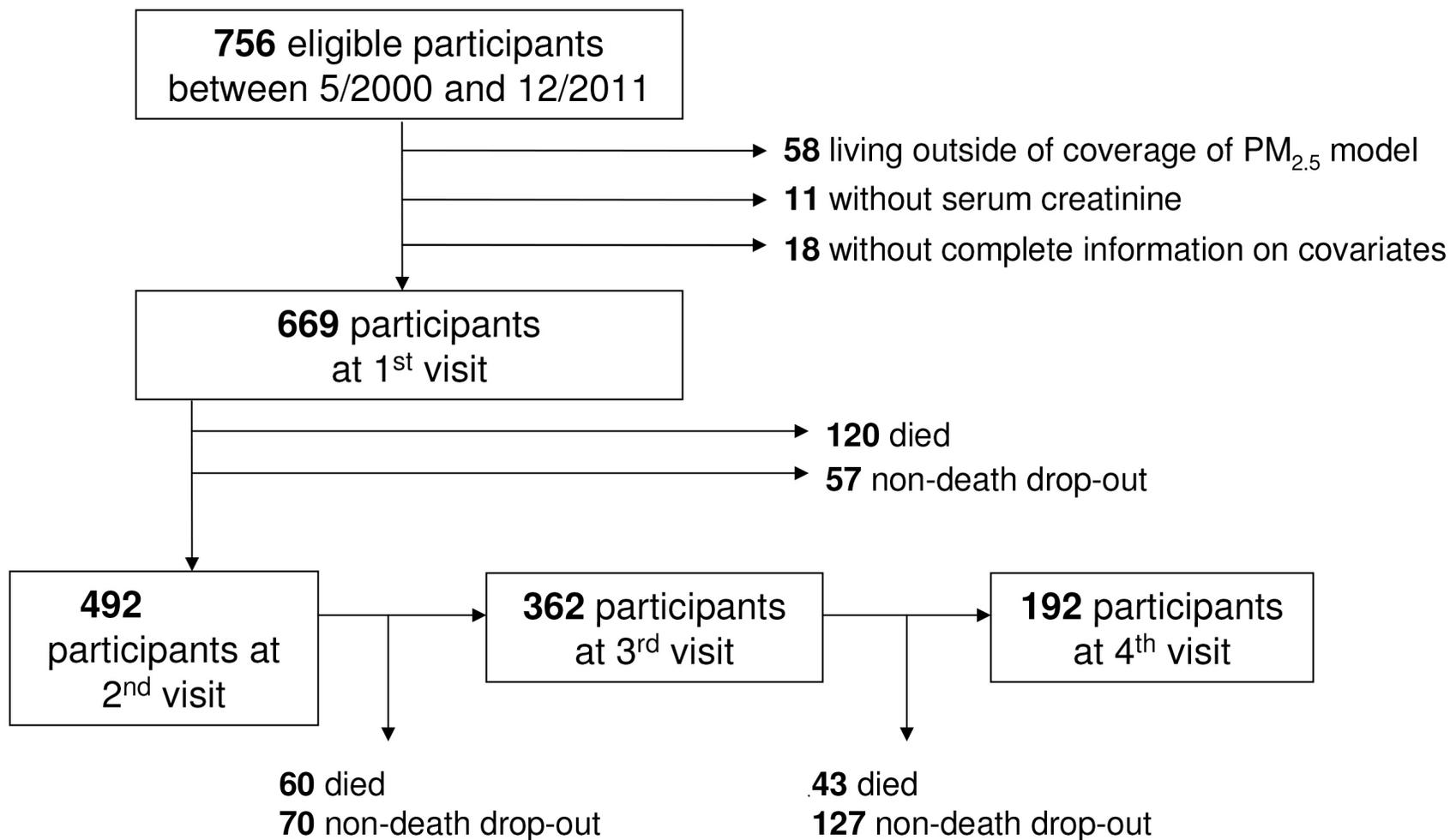


Figure 2.

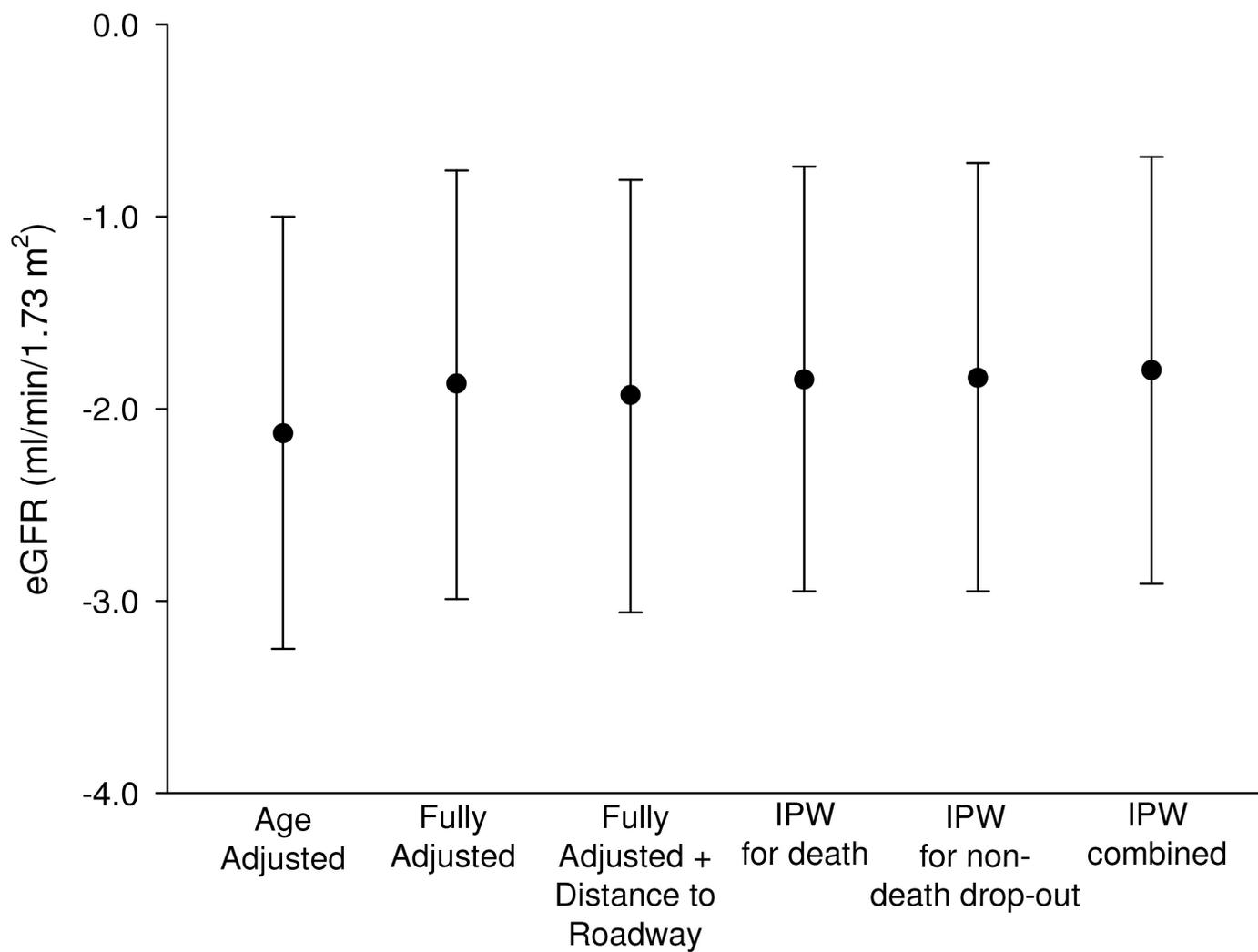


Figure 3.

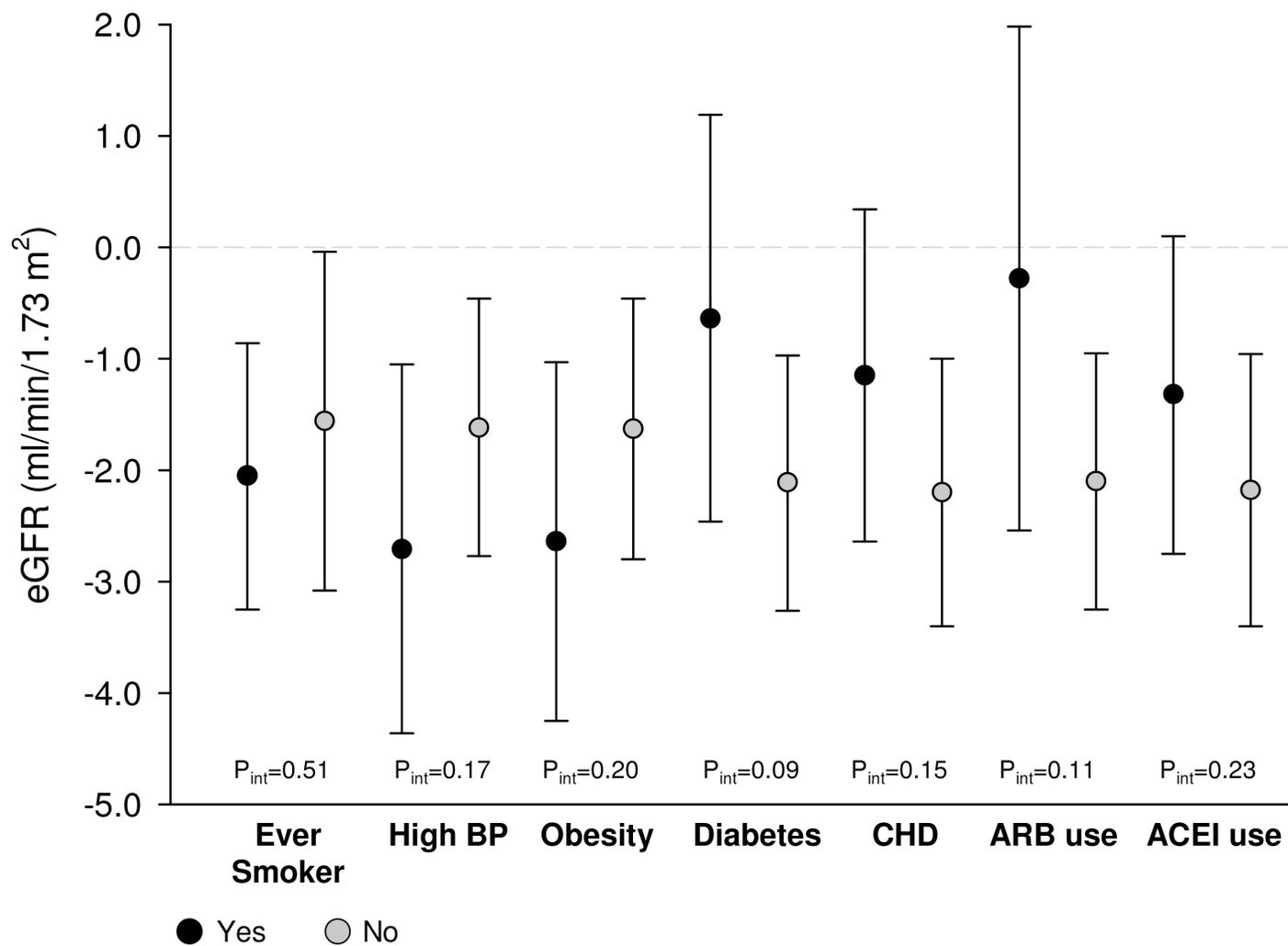


Figure 4.

