Long-Term Exposure to Ambient PM$_{2.5}$ and Increased Risk of CKD Prevalence in China

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ABSTRACT

Background Fine particulate matter (PM$_{2.5}$) is an important environmental risk factor for cardiopulmonary diseases. However, the association between PM$_{2.5}$ and risk of CKD remains under-recognized, especially in regions with high levels of PM$_{2.5}$, such as China.

Methods To explore the association between long-term exposure to ambient PM$_{2.5}$ and CKD prevalence in China, we used data from the China National Survey of CKD, which included a representative sample of 47,204 adults. We estimated annual exposure to PM$_{2.5}$ before the survey date at each participant’s address, using a validated, satellite-based, spatiotemporal model with a 10 km×10 km resolution. Participants with eGFR <60 ml/min per 1.73 m$^2$ or albuminuria were defined as having CKD. We used a logistic regression model to estimate the association and analyzed the influence of potential modifiers.

Results The 2-year mean PM$_{2.5}$ concentration was 57.4 µg/m$^3$, with a range from 31.3 to 87.5 µg/m$^3$. An increase of 10 µg/m$^3$ in PM$_{2.5}$ was positively associated with CKD prevalence (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.22 to 1.35) and albuminuria (OR, 1.39; 95% CI, 1.32 to 1.47). Effect modification indicated these associations were significantly stronger in urban areas compared with rural areas, in males compared with females, in participants aged <65 years compared with participants aged ≥65 years, and in participants without comorbid diseases compared with those with comorbidities.

Conclusions These findings regarding the relationship between long-term exposure to high ambient PM$_{2.5}$ levels and CKD in the general Chinese population provide important evidence for policy makers and public health practices to reduce the CKD risk posed by this pollutant.

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The most advanced stage of CKD, ESKD, requires costly dialysis or transplantation and results in reduced quality of life and enormous socioeconomic burden. Furthermore, CKD is regarded as an important risk factor for cardiovascular disease (CVD). It has been reported that the cardiovascular mortality rate is much higher in patients with CKD than in those with normal kidney function.

Ambient PM$_{2.5}$ is suggested to be a novel potential environmental risk factor for CKD. However, studies on the relationships between ambient PM$_{2.5}$ exposure and risk of CKD are still limited, and almost all of the evidence comes from countries or regions with low levels of PM$_{2.5}$. The only available evidence is limited to the elderly, such as US veterans, those enrolled in the US Medicare program (aged ≥65 years), or cohorts or populations in a single city or region, where PM$_{2.5}$ levels are much lower than those in mainland China. Minimal data exist on the association between PM$_{2.5}$ and the risk of CKD in areas with high levels of PM$_{2.5}$, and epidemiologic studies in areas with high PM$_{2.5}$ pollution should be a research priority.

Considering ambient PM$_{2.5}$ pollution is an environmental issue worldwide, especially in China, where high levels of PM$_{2.5}$ remain a tremendous challenge, and CKD prevalence has rapidly increased in recent years, the associations between long-term ambient PM$_{2.5}$ exposure and the risk of CKD in the general Chinese population were investigated in this study. This study used a representative sample from the China National Survey of CKD, and used a validated, satellite-based spatiotemporal model for estimation of long-term ambient PM$_{2.5}$ exposure. Furthermore, the relationships between ambient PM$_{2.5}$ exposure and albuminuria were also explored, because albuminuria is a well-established kidney damage indicator that reflects the high risk of progression or poor prognosis of CKD. The results of this study will contribute to the evidence of the relationship between high levels of ambient PM$_{2.5}$ and CKD risk in the general population.

**METHODS**

**Study Population and Health Measurements**

A multistage, stratified, sampling method was used to obtain a representative sample of the general population aged ≥18 years in China. In the China National Survey of CKD from September 2009 to September 2010, 13 provinces from different regions were selected by probability-proportional-to-size sampling.

A questionnaire was distributed to the participants to collect information, including urban or rural area residence, demographic status (e.g., age, sex, family income, and education), personal and family health history (e.g., hypertension, diabetes, and kidney disease), lifestyle factors (e.g., smoking and alcohol consumption), comorbidities (e.g., diabetes mellitus or hypertension), history of CVD (including myocardial infarction or stroke), nephrotoxic medications, and medical insurance. Anthropometric measurements, including weight and height, were obtained by the study investigators and staff members using standard instruments.

The eGFR was measured from venipuncture blood samples, and the eGFR was calculated using an equation developed by adapting the Modification of Diet in Renal Disease equation on the basis of data from Chinese patients with CKD. Albuminuria was measured with immunoturbidimetric tests. The urinary albumin-creatinine ratio (milligrams per gram creatinine) was calculated. Participants with a urinary albumin-creatinine ratio ≥30 mg/g were defined as having albuminuria. Participants with an eGFR <60 ml/min per 1.73 m$^2$ or albuminuria were defined as having CKD, according to the 2012 Clinical Practice Guideline for the Evaluation and Management of CKD.

A training program was provided for all study investigators, and a strict quality-control procedure was performed during the whole process. The details of the survey have been described elsewhere. The ethics committee of Peking University First Hospital approved the study. All the participants provided written informed consent before data collection.

**Ambient PM$_{2.5}$ Exposure Assessment**

Annual exposure to PM$_{2.5}$ before the survey date was assessed at each participant’s address, which was geocoded into latitude and longitude data. The participants in the survey were defined as residents who lived in the investigated region for at least 1 year. Considering the survey design in this study and the main exposure metric used in a previous study, the annual average PM$_{2.5}$ concentration before the survey date and the annual average for the previous year (2-year mean PM$_{2.5}$) was calculated as the primary exposure variable in our main analysis. A validated, spatiotemporal model that combined ground-level PM$_{2.5}$ monitoring data measured in China and satellite-derived data were used to estimate ambient PM$_{2.5}$ concentrations.

Daily, average, ground PM$_{2.5}$ concentrations in 2013 in China were obtained from the China Environmental Monitoring Center. Satellite, remote-sensing, aerosol optical depth (AOD) data retrieved by the Moderate Resolution Imaging
Spectroradiometer (http://modis.gsfc.nasa.gov), which was launched by the US National Aeronautics and Space Administration, were used in this study.

A 0.1°×0.1° grid (approximately 10 km×10 km) was created for data integration and model development. Ground PM$_{2.5}$ data from multiple monitors in each grid cell were averaged. The percentage of forest cover and urban areas in each grid cell and the daily total counts for Moderate Resolution Imaging Spectroradiometer fire spots for each grid cell, using a 75-km radius buffer, were calculated. Finally, all of the variables in 2013 were matched by grid cell and day of year for model fitting.

A two-stage statistical model was developed to calibrate the spatiotemporal relationships between PM$_{2.5}$ and AOD.

The first-stage, linear, mixed-effects model included day-specific random intercepts, slopes for AOD, and season-specific random slopes for meteorologic variables. The dependent variable in the first-stage model was the daily PM$_{2.5}$ concentration.

The second-stage, generalized, additive model was constructed as follows:

$$PM_{2.5\text{-resid}_{it}} = \mu_0 + s(X, Y) + s(\text{ForestCover}) + s(\text{UrbanCover}) + \epsilon_{it}$$

In this equation, $PM_{2.5\text{-resid}_{it}}$ is the residual from the first-stage model in grid cell $s$ on day $t$; $\mu_0$ is the intercept term; $s(X, Y)$ is the smooth term of the coordinates of the centroid of grid cell $s$; $s(\text{ForestCover})$ and $s(\text{UrbanCover})$ are the smooth functions of the percentage of forest cover and urban areas for grid cell $s$, respectively; and $\epsilon_{it}$ is the error term.

The historical daily ambient PM$_{2.5}$ concentrations (2005–2010) in China were estimated using the two-stage model developed on the basis of 2013 data, assuming that the daily relationship between PM$_{2.5}$ and AOD was constant for the same day of year in each year. The full-model fitting $R^2$ value of the historical PM$_{2.5}$ predictions on monthly and seasonal scales were 0.73 and 0.79, respectively, suggesting that PM$_{2.5}$ predictions are accurate representations of the ground measurements, with relatively low bias, and can serve as reasonable exposure estimates to study the health effects of long-term PM$_{2.5}$ exposure in China. This study used the predicted PM$_{2.5}$ concentrations from a study by Ma et al. in exactly the same study period and study area. This model was validated to minimize bias in assessment of long-term PM$_{2.5}$ concentrations.

**Statistical Analyses**

We used a logistic regression model to estimate the associations between increases in the annual average PM$_{2.5}$ exposure and the dichotomous outcomes of CKD and albuminuria, with adjustment for covariates in the following equation:

$$\text{log odds}(Y_i = 1|x) = b_0 + b_1 x_1 + \ldots + b_p x_p + \beta PM_{2.5}$$

In this model, $Y_i$ is the status of CKD or albuminuria (yes or no), $b_0$ is the intercept, $x_1$–$x_p$ are the covariates, $b_1$–$b_p$ are the coefficients of the covariates, $\beta$ is the coefficient (log odds ratio [OR]) of PM$_{2.5}$. Model covariates included urban or rural area, age (as a continuous variable), sex (male or female), body mass index (BMI; as a continuous variable), current smoker (yes or no), alcohol consumption (never, one to three times a month to three to five times a week, almost once a day), education ($\geq$ high-school education or $<$ high-school education), family income index (low income, middle income, and high income), history of CVD (yes or no), diabetes mellitus (yes or no), hypertension (yes or no), nephrotoxic medications (yes or no), and medical insurance (yes or no). Study province was adjusted as a factor. The OR and 95% confidence interval were calculated to estimate the associations between ambient PM$_{2.5}$ exposure and the prevalence of CKD and albuminuria.

Spline functions were widely used to characterize the exposure–response curves of the estimate effects of air pollution in environmental epidemiologic studies, and they can flexibly capture the linear or nonlinear relationship between environmental exposure and health outcomes. Thus, the linear variable PM$_{2.5}$ was replaced by cubic regression spline functions of PM$_{2.5}$ to explore the possible curve shape between long-term PM$_{2.5}$ exposure and the prevalence of CKD and albuminuria in our analysis.

Analysis of the within- and between-city analysis was performed using a logistic regression model for the associations of CKD prevalence and albuminuria with PM$_{2.5}$ exposure. For PM$_{2.5}$ exposure, the site average PM$_{2.5}$ and individual PM$_{2.5}$ exposure minus the site mean PM$_{2.5}$ were used as between-site and within-site exposure variables, respectively.

In addition, models were stratified by urban or rural area residence, sex (male or female), age ($\geq$65 years and $<$65 years), current smoker (yes or no), and in participants with a normal weight (BMI $<$25 kg/m$^2$) or those who were overweight (BMI $\geq$25 kg/m$^2$). The influences of comorbidities, including diabetes mellitus, hypertension, and CVD history, were also estimated. Effect modification analysis was performed by adding an interaction term $PM_{2.5} \times$ the testing variable in the full model.

**Sensitivity Analysis**

Sensitivity analyses were performed to examine whether the results were robust to changes in the parameters, including using the 1-year mean PM$_{2.5}$ as an exposure assessment and controlling for different covariates in the models, such as adding the medical insurance status (yes or no) as a potential confounder in the model.

All of the analyses were performed using R software (version 3.1.2; R Core Team), and statistical significance was defined as a two-sided $P$ value of $<$0.05. A Bonferroni-corrected $P$ value of 0.006 was used as the significance threshold for the eight interaction analyses.
RESULTS

In total, 55,550 study participants aged ≥18 years in China were invited to participate in the China National Survey of CKD, and 47,204 participants who completed the questionnaire and health examination were enrolled in the study, with a response rate of 93% (Supplemental Figure 1).

The 2-year mean PM$_{2.5}$ concentration, on the basis of AOD data, was 57.4 µg/m$^3$ (with an SD of 15.6 µg/m$^3$) at participants’ addresses, with a range from 31.3 to 87.5 µg/m$^3$ (Figure 1). The study sites were distributed in both urban and rural areas (Supplemental Figure 2), and the 2-year mean PM$_{2.5}$ concentration was 58.3 µg/m$^3$ (SD of 17.5 µg/m$^3$) in urban areas, which was higher than the mean concentration of 53.9 µg/m$^3$ (SD of 12.0 µg/m$^3$) in rural areas. The percentage of study participants in each PM$_{2.5}$ level was shown in Supplemental Table 1. Table 1 shows the baseline characteristics of the study population, stratified by the 2-year mean PM$_{2.5}$ concentration.

An increase of 10 µg/m$^3$ in the 2-year mean ambient PM$_{2.5}$ was positively associated with the prevalence of CKD, with an OR of 1.28 (95% CI, 1.22 to 1.35). In addition, a significant association was also found for albuminuria, with an OR of 1.39 (95% CI, 1.32 to 1.47). The results were robust to changes in parameters in the models (Table 2).

There were increasing trends in concentration-response curves for long-term PM$_{2.5}$ exposure and the prevalence of CKD and albuminuria, and the curves suggest a generally positive, linear relationship between PM$_{2.5}$ exposure and CKD risk (Figure 2). Furthermore, the risk started to increase at a relatively low concentration of PM$_{2.5}$ that was well below the grade-2 criteria set by the Chinese ambient air-quality standards (35 µg/m$^3$).

The difference in the PM$_{2.5}$ effects on CKD prevalence between urban and rural areas was analyzed, and a significantly higher effect was found in the urban areas (OR, 1.27; 95% CI, 1.21 to 1.34) than in rural areas (OR, 1.17; 95% CI, 1.07 to 1.27) (interaction P=0.004).

Effect modification of ambient PM$_{2.5}$ exposure and CKD prevalence showed that the estimated effects were significantly higher in males (OR, 1.34; 95% CI, 1.26 to 1.41) than in females (OR, 1.27; 95% CI, 1.20 to 1.34) (interaction P=0.005), and significantly higher in people <65 years (OR, 1.34; 95% CI, 1.27 to 1.41) than in older people (OR, 1.17; 95% CI, 1.11 to 1.25) (interaction P<0.001).

Furthermore, the association was stronger in participants without diabetes than in participants with diabetes. Specifically, the multivariable-adjusted OR was 1.31 (95% CI, 1.25 to 1.38) in participants without diabetes, which was higher than that of 1.20 (95% CI, 1.12 to 1.28) in participants with diabetes (interaction P=0.002). The associations also showed a stronger trend in participants without hypertension or CVD history than in those with hypertension or CVD history, although no statistical significance was found.

The results for the associations between ambient PM$_{2.5}$ exposure and albuminuria showed the same trend as that for between ambient PM$_{2.5}$ and the prevalence of CKD, except the association was significantly higher in participants without diabetes.
CVD history (OR, 1.40; 95% CI, 1.32 to 1.48) than in those with CVD history (OR, 1.29; 95% CI, 1.20 to 1.39) (interaction \( P = 0.001 \)) (Table 3).

The within-city effects were significant, whereas the between-city effects were nonsignificant (Supplemental Table 2), suggesting no significant differences in the magnitude of risk within major metropolitan areas were found in our study. Sensitivity analyses showed the results were robust to adjustment for potential confounders in the model (Supplemental Table 3), and the association of the 1-year mean PM\(_{2.5}\) with the prevalence of CKD and albuminuria showed the same trend as the 2-year mean PM\(_{2.5}\) (Supplemental Figure 3, Supplemental Tables 4 and 5).

### Table 1. Baseline characteristics of the study population stratified above and below 2-yr mean PM\(_{2.5}\) concentrations in China between 2007 and 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(&lt;\text{2-Yr Mean Concentration})</th>
<th>(\geq\text{2-Yr Mean Concentration})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (%)</td>
<td>25,188 (53.36)</td>
<td>22,016 (46.64)</td>
</tr>
<tr>
<td>CKD, (n) (%)</td>
<td>3205 (12.72)</td>
<td>3108 (14.12)</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m(^2))</td>
<td>101.04 ± 26.69</td>
<td>101.40 ± 28.28</td>
</tr>
<tr>
<td>eGFR category, (n) (%)</td>
<td>24,563 (97.52)</td>
<td>21,456 (97.46)</td>
</tr>
<tr>
<td>(&lt;60) mL/min per 1.73 m(^2)</td>
<td>625 (2.48)</td>
<td>560 (2.54)</td>
</tr>
<tr>
<td>uACR (mg/g), mean (range)</td>
<td>6.67 (3.24–13.58)</td>
<td>6.60 (2.91–13.77)</td>
</tr>
<tr>
<td>uACR category, (n) (%)</td>
<td>22,430 (89.05)</td>
<td>19,302 (87.67)</td>
</tr>
<tr>
<td>Age (yr), mean ± SD</td>
<td>49.71 ± 15.54</td>
<td>49.47 ± 14.83</td>
</tr>
<tr>
<td>Sex, (n) (%)</td>
<td>10,445 (41.47)</td>
<td>9703 (44.07)</td>
</tr>
<tr>
<td>Education, (n) (%)</td>
<td>14,743 (58.53)</td>
<td>12,313 (55.93)</td>
</tr>
<tr>
<td>Family income, (n) (%)</td>
<td>14,372 (57.24)</td>
<td>11,763 (53.53)</td>
</tr>
<tr>
<td>Region, (n) (%)</td>
<td>13,629 (54.11)</td>
<td>11,716 (53.22)</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), mean ± SD</td>
<td>23.86 ± 3.66</td>
<td>23.91 ± 3.72</td>
</tr>
<tr>
<td>BMI category, (n) (%)</td>
<td>17,048 (68.41)</td>
<td>13,370 (60.73)</td>
</tr>
<tr>
<td>Smoking, (n) (%)</td>
<td>19,748 (78.4)</td>
<td>16,362 (74.32)</td>
</tr>
<tr>
<td>Alcohol consumption, (n) (%)</td>
<td>19,728 (78.32)</td>
<td>16,046 (72.88)</td>
</tr>
<tr>
<td>History of CVD, (n) (%)</td>
<td>641 (2.90)</td>
<td>579 (2.86)</td>
</tr>
<tr>
<td>Diabetes mellitus, (n) (%)</td>
<td>1752 (6.96)</td>
<td>1736 (7.89)</td>
</tr>
<tr>
<td>Hypertension, (n) (%)</td>
<td>8364 (33.45)</td>
<td>8240 (37.52)</td>
</tr>
<tr>
<td>Nephrotoxic medication, (n) (%)</td>
<td>915 (3.63)</td>
<td>621 (2.82)</td>
</tr>
</tbody>
</table>

There are missing values for some of the variables (numbers that do not add up to the total because of missing values), and the percentage of each category was calculated excluding the missing data. uACR, urinary albumin creatinine ratio.
We found that long-term exposure to ambient PM\textsubscript{2.5} was associated with an increased risk of CKD and albuminuria in the general Chinese population. The results were robust after adjustment for multiple covariates and individual-level risk factors, including age, sex, BMI, smoking, alcohol consumption, education, family income, urban or rural area residence, comorbidities (including diabetes mellitus, hypertension, and CVD history), nephrotoxic medication use, and medical insurance status. Although the effect estimates of ambient PM\textsubscript{2.5} were modest compared with other traditional risk factors, such as CVD, considering its ubiquitous existence, PM\textsubscript{2.5} could have a substantial effect on CKD risk in the general population. Furthermore, increasing trends in exposure-response curves were found between PM\textsubscript{2.5} and CKD prevalence and albuminuria, with the risk increasing at PM\textsubscript{2.5} concentrations below the current PM\textsubscript{2.5} standards in China. These results may lead to a greater impetus to encourage public-health efforts to offer greater protection to the general population in lowering the risk of CKD associated with ambient PM\textsubscript{2.5}, and provides evidence for stricter air quality control of ambient PM\textsubscript{2.5}.

In this study, we used the estimated ground-level PM\textsubscript{2.5} from satellite-retrieved AOD data, which is a promising and new method that has rapidly advanced in recent years.\textsuperscript{27,28} Satellite-based, spatiotemporal models have the potential to fill the spatiotemporal PM\textsubscript{2.5} gaps left by ground monitors with high-quality predictions, and the model applied in our study was validated to provide reliable historical PM\textsubscript{2.5} concentration estimates in China.\textsuperscript{20} The 2-year mean PM\textsubscript{2.5} concentration was 57.4 µg/m\textsuperscript{3}, which was relatively higher than that in previous studies, and had a broad range from 31.3 to 87.5 µg/m\textsuperscript{3}.

Current literature on ambient PM\textsubscript{2.5} exposure and CKD remain relatively limited. The available studies have mainly been conducted in countries or regions with low levels of PM\textsubscript{2.5}, and the results have been inconsistent.\textsuperscript{7–15} For example, a positive association was observed between county-level PM\textsubscript{2.5} concentrations and CKD diagnoses in adults ≥65 years old enrolled in the US Medicare program, with an adjusted prevalence ratio of 1.03 (95% CI, 1.02 to 1.05) for an increase of 4 µg/m\textsuperscript{3} in PM\textsubscript{2.5}.\textsuperscript{9} Another study demonstrated that an increase of 10 µg/m\textsuperscript{3} in the annual average PM\textsubscript{2.5} was associated with an increased incidence of CKD in United States veterans with a hazard ratio of 1.27 (95% CI, 1.17 to 1.38).\textsuperscript{8} Each increase of 1 µg/m\textsuperscript{3} in the annual average PM\textsubscript{2.5} concentration was associated with a significantly higher risk of incident CKD in a community-based cohort in the United States (hazard ratio, 1.05; 95% CI, 1.01 to 1.10).\textsuperscript{10} Nevertheless, a study conducted in elderly residents in Taipei city found an interquartile range increase in PM\textsubscript{2.5} was not significantly associated with CKD prevalence, with an OR of 1.01 (95% CI, 0.96 to 1.06).\textsuperscript{5}

The effect estimation of the OR between long-term exposure to ambient PM\textsubscript{2.5} and CKD prevalence was 1.28 (95% CI, 1.22 to 1.35) for every increase of 10 µg/m\textsuperscript{3} in PM\textsubscript{2.5} in our

### Table 2. Estimated effects of an increase of 10 µg/m\textsuperscript{3} in 2-yr mean PM\textsubscript{2.5} exposure on CKD and albuminuria in China between 2007 and 2010

<table>
<thead>
<tr>
<th>Models</th>
<th>CKD</th>
<th></th>
<th></th>
<th></th>
<th>Albuminuria</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>N</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1a</td>
<td>47,204</td>
<td>1.28 (1.22 to 1.35)</td>
<td>&lt;0.001</td>
<td>47,204</td>
<td>1.39 (1.32 to 1.47)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2b</td>
<td>47,204</td>
<td>1.29 (1.23 to 1.26)</td>
<td>&lt;0.001</td>
<td>47,204</td>
<td>1.40 (1.32 to 1.48)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Model 1: age, sex, education, family income, and urban/rural areas were adjusted in the model.

*b* Model 2: model 1 plus health-related factors, including BMI, smoking history, alcohol consumption, history of CVD, diabetes mellitus, hypertension, and nephrotoxic medications were adjusted in the model.

**Figure 2.** The linear exposure-response curves of ambient PM\textsubscript{2.5} exposure and the prevalence of CKD and albuminuria in China between 2007 and 2010. The PM\textsubscript{2.5} exposure level was calculated as the 2-year mean concentration. (A) CKD; (B) albuminuria.

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DISCUSSION

We found that long-term exposure to ambient PM\textsubscript{2.5} was associated with an increased risk of CKD and albuminuria in the general Chinese population. The results were robust after adjustment for multiple covariates and individual-level risk factors, including age, sex, BMI, smoking, alcohol consumption, education, family income, urban or rural area residence, comorbidities (including diabetes mellitus, hypertension, and CVD history), nephrotoxic medication use, and medical insurance status. Although the effect estimates of ambient PM\textsubscript{2.5} were modest compared with other traditional risk factors, such as CVD, considering its ubiquitous existence, PM\textsubscript{2.5} could have a substantial effect on CKD risk in the general population. Furthermore, increasing trends in exposure-response curves were found between PM\textsubscript{2.5} and CKD prevalence and albuminuria, with the risk increasing at PM\textsubscript{2.5} concentrations below the current PM\textsubscript{2.5} standards in China. These results may lead to a greater impetus to encourage public-health efforts to offer greater protection to the general population in lowering the risk of CKD associated with ambient PM\textsubscript{2.5}, and provides evidence for stricter air quality control of ambient PM\textsubscript{2.5}.

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Current literature on ambient PM\textsubscript{2.5} exposure and CKD remain relatively limited. The available studies have mainly been conducted in countries or regions with low levels of PM\textsubscript{2.5}, and the results have been inconsistent.\textsuperscript{7–15} For example, a positive association was observed between county-level PM\textsubscript{2.5} concentrations and CKD diagnoses in adults ≥65 years old enrolled in the US Medicare program, with an adjusted prevalence ratio of 1.03 (95% CI, 1.02 to 1.05) for an increase of 4 µg/m\textsuperscript{3} in PM\textsubscript{2.5}.\textsuperscript{9} Another study demonstrated that an increase of 10 µg/m\textsuperscript{3} in the annual average PM\textsubscript{2.5} was associated with an increased incidence of CKD in United States veterans with a hazard ratio of 1.27 (95% CI, 1.17 to 1.38).\textsuperscript{8} Each increase of 1 µg/m\textsuperscript{3} in the annual average PM\textsubscript{2.5} concentration was associated with a significantly higher risk of incident CKD in a community-based cohort in the United States (hazard ratio, 1.05; 95% CI, 1.01 to 1.10).\textsuperscript{10} Nevertheless, a study conducted in elderly residents in Taipei city found an interquartile range increase in PM\textsubscript{2.5} was not significantly associated with CKD prevalence, with an OR of 1.01 (95% CI, 0.96 to 1.06).\textsuperscript{5}

The effect estimation of the OR between long-term exposure to ambient PM\textsubscript{2.5} and CKD prevalence was 1.28 (95% CI, 1.22 to 1.35) for every increase of 10 µg/m\textsuperscript{3} in PM\textsubscript{2.5} in our
study, suggesting the association of CKD risk with PM$_{2.5}$ may vary geographically. However, the results may not be directly comparable, because the average concentrations of ambient PM$_{2.5}$ in the aforementioned studies (ranging from 5.0 to 27.1 μg/m$^3$) were much lower than the average level of PM$_{2.5}$ in our study (57.4 μg/m$^3$). Thus, our results add to the current evidence on the associations between high levels of PM$_{2.5}$ exposure and the increased risk of CKD prevalence in the general population. In addition, we found a significant association between PM$_{2.5}$ and the prevalence of albuminuria, which is a well-established indicator of kidney damage in the prognosis of CKD. Nevertheless, a previous study did not find an association between chronic PM$_{2.5}$ exposure and albuminuria, which was probably due to the low mean PM$_{2.5}$ (16.5 μg/m$^3$).

There are plausible biologic mechanisms linking PM$_{2.5}$ exposure and increased CKD risk. The kidney is a vascularized organ, susceptible to vascular dysfunction. Experimental evidence has shown that exposure to diesel exhaust particles, which are a major source for urban ambient PM$_{2.5}$, exacerbated vascular damage in rats and facilitated progression to tubular damage. In addition, diesel exhaust particles also induced nephrotoxicity in vitro and in vivo through autophagy, endoplasmic-reticulum stress, and apoptosis in kidney tissues. Furthermore, various chemical components in PM$_{2.5}$ could have adverse consequences on renal function through inflammation, oxidative stress, and endothelial dysfunction, thus contributing to progressive, cumulative renal injury and increased risk of CKD over a long time. Nevertheless, research on renal toxicity of ambient PM$_{2.5}$ exposure remains limited, and the underlying mechanisms need to be further elucidated.

The association of PM$_{2.5}$ exposure with CKD risk was significantly higher in urban areas than in rural areas. Previous studies also found that higher urbanicity may lead to an additional increase in the health risk associated with particulate matter exposure. The 2-yr mean PM$_{2.5}$ concentrations were used in the models. The analysis was performed for an increase of 10 μg/m$^3$ in PM$_{2.5}$.

### Table 3. The associations between long-term PM$_{2.5}$ exposure and CKD and albuminuria in participants with different characteristics in China between 2007 and 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Eligible Participants</th>
<th>CKD OR (95% CI)</th>
<th>Interaction P Value</th>
<th>Albuminuria OR (95% CI)</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>25,345</td>
<td>1.27 (1.21 to 1.34)</td>
<td>0.004</td>
<td>1.37 (1.29 to 1.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Rural</td>
<td>21,859</td>
<td>1.17 (1.07 to 1.27)</td>
<td></td>
<td>1.23 (1.12 to 1.36)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20,148</td>
<td>1.34 (1.26 to 1.41)</td>
<td>0.005</td>
<td>1.45 (1.37 to 1.54)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>27,056</td>
<td>1.27 (1.20 to 1.34)</td>
<td></td>
<td>1.36 (1.29 to 1.44)</td>
<td></td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>7915</td>
<td>1.17 (1.11 to 1.25)</td>
<td>&lt;0.001</td>
<td>1.25 (1.17 to 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &lt;65 yr</td>
<td>39,289</td>
<td>1.34 (1.27 to 1.41)</td>
<td></td>
<td>1.44 (1.36 to 1.53)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥25 kg/m$^2$</td>
<td>16,453</td>
<td>1.28 (1.21 to 1.35)</td>
<td>0.30</td>
<td>1.39 (1.31 to 1.47)</td>
<td>0.49</td>
</tr>
<tr>
<td>BMI &lt;25 kg/m$^2$</td>
<td>30,418</td>
<td>1.31 (1.24 to 1.38)</td>
<td></td>
<td>1.41 (1.33 to 1.49)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncurrent smoker</td>
<td>36,110</td>
<td>1.28 (1.22 to 1.35)</td>
<td>0.14</td>
<td>1.39 (1.31 to 1.47)</td>
<td>0.19</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11,094</td>
<td>1.33 (1.25 to 1.41)</td>
<td></td>
<td>1.43 (1.34 to 1.53)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43,671</td>
<td>1.31 (1.25 to 1.38)</td>
<td>0.002</td>
<td>1.38 (1.31 to 1.46)</td>
<td>0.11</td>
</tr>
<tr>
<td>Yes</td>
<td>3488</td>
<td>1.20 (1.12 to 1.28)</td>
<td></td>
<td>1.32 (1.23 to 1.42)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30,357</td>
<td>1.30 (1.24 to 1.36)</td>
<td>0.03</td>
<td>1.42 (1.34 to 1.51)</td>
<td>0.02</td>
</tr>
<tr>
<td>Yes</td>
<td>16,604</td>
<td>1.25 (1.18 to 1.31)</td>
<td></td>
<td>1.36 (1.28 to 1.45)</td>
<td></td>
</tr>
<tr>
<td>History of CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41,114</td>
<td>1.30 (1.23 to 1.36)</td>
<td>0.03</td>
<td>1.40 (1.32 to 1.48)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>1220</td>
<td>1.23 (1.16 to 1.32)</td>
<td></td>
<td>1.29 (1.20 to 1.39)</td>
<td></td>
</tr>
</tbody>
</table>

Model 2 adjustment (as illustrated in the Table 2 footnote) was used for the stratified analyses. The 2-yr mean PM$_{2.5}$ concentrations were used in the models.
rural areas, which needs to be further explored in future studies.

The results in our study showed the association between PM$_{2.5}$ exposure and the prevalence of CKD and albuminuria was higher in males than in females, which was possibly due to more outdoor time in males (236 min/d) than in females (209 min/d) and could result in longer exposure to ambient PM$_{2.5}$ in males in China, thus increasing the adverse influence of ambient PM$_{2.5}$ exposure.

Furthermore, the associations were significantly stronger in the young (<65 years) than in the elderly (≥65 years). The effects of PM$_{1.5}$ on CKD prevalence were significantly higher in participants without diabetes than in those with diabetes, whereas the effects on albuminuria were significantly higher in participants without CVD history than in those with CVD history. These results were consistent with the results of some previous studies. For instance, Mehta et al. also reported that the inverse association between PM$_{2.5}$ and renal function, as reflected by eGFR, was significantly stronger in participants without diabetes than in participants with diabetes, and was stronger in participants without coronary heart disease than in those with coronary heart disease. In our study, individuals who were elderly or had comorbidities were more likely to take medications, such as antihypertensive drugs and angiotensin receptor blockers. The medication-use proportions were 4.82%, 3.91%, and 8.20% in the elderly, those with diabetes, and those with CVD history, respectively, which were relatively higher than the proportions of 2.94%, 3.20%, and 2.96%, respectively, in the young, those without diabetes, and those without CVD history. Medication use may attenuate the oxidative stress and vasoconstrictive effects of PM$_{2.5}$ exposure, and the age or comorbidity status may dominate the main effect on renal dysfunction, thus reducing their susceptibility to the adverse renal effects of PM$_{2.5}$. If the relationship between PM$_{2.5}$ and CKD risk is truly independent, it would manifest more strongly in groups with lower baseline risk, such as younger individuals and individuals without diabetes or CVD history. Nevertheless, further studies to elucidate the susceptibility of the population to kidney disease related to ambient PM$_{2.5}$ exposure are warranted.

To the best of our knowledge, this is the first study to comprehensively evaluate long-term high levels of ambient PM$_{2.5}$ exposure on CKD risk in Chinese adults, on the basis of the China National Survey of CKD, using a standard, multistage, stratified sampling method and strict quality-control procedures. The response rate of the participants was 93% in this study. This rate was relatively high compared with previous studies. Thus, this analysis could provide convincing results and could be extrapolated to the general Chinese population. In addition, a major strength of this study is that it was a nationwide survey in a developing country with high levels of ambient PM$_{2.5}$ and, thus, provided us with a unique opportunity to explore the exposure-response relationship between high levels of ambient PM$_{2.5}$ exposure and CKD prevalence and albuminuria. Our results will contribute to evidence of a relationship between high levels of PM$_{2.5}$ exposure and the risk of CKD. Third, this study revealed a significantly higher effect in urban areas than in rural areas, which provides insights for target PM$_{2.5}$ pollution control. Furthermore, the use of a validated, spatiotemporal model to assess PM$_{2.5}$, and the adjustment for multiple covariates and individual-level risk factors, strengthened the credibility of the results in our study.

Our study also had several limitations. First, causal inferences between long-term ambient PM$_{2.5}$ exposure and the prevalence of CKD could not be made because this study was cross-sectional. Second, single measurements of indicators were used to define CKD, which may have led to misclassification of CKD due to acute kidney disease or other diseases. Nevertheless, repeated measurements were poorly feasible in such a large-scale, national survey. Third, we did not evaluate the effects of gaseous pollutants. Nevertheless, ambient PM$_{2.5}$ and gaseous pollutants are generally highly correlated with each other, and the lack of data on gaseous pollutants is unlikely to affect our conclusion. In addition, considering that PM$_{2.5}$ is a heterogeneous mixture, the integration of information about the relative distribution of major PM$_{2.5}$ components into health risk assessments of CKD needs to be investigated in future studies. This study did not account for some potentially important confounders, including indoor air pollution and second-hand smoke, due to data availability. Furthermore, the relatively low resolution of the model of a 10-km grid in our study would make the exposure assessment nondifferential, probably leading to an underestimation of the potential effects.

In conclusion, this study assessed the long-term effects of high levels of ambient PM$_{2.5}$ on CKD risk in the general Chinese population and revealed a significant association between ambient PM$_{2.5}$ and the prevalence of CKD and albuminuria. A significantly higher effect was found in urban areas than in rural areas. In addition, the risk started to increase at PM$_{2.5}$ concentrations well below the Chinese ambient air quality standards, suggesting that air quality control should be more stringent in China. Furthermore, the association was stronger in younger participants than in older participants, and in participants without comorbidities than in those with comorbidities, providing novel insights for target population protection. These findings offer important evidence to inform policy makers and public-health practices in lowering the risk of CKD associated with exposure to ambient PM$_{2.5}$ pollution.

DISCLOSURES

J. Wang reports being a member of a speakers bureau for Boehringer-Ingelheim. L. Zhang reports being a scientific advisor or member of the American Journal of Kidney Disease and receiving research funding from AstraZeneca. M. Zhao reports being an executive member of the Asian Pacific
Society of Nephrology; receiving honoraria from the Asian Pacific Society of Nephrology, Chinese Medical Association, Chinese Society of Nephrology, and International Society of Nephrology; being the vice president of the Chinese Society of Internal Medicine and the Chinese Society of Nephrology; and having consultancy agreements with Roche. All remaining authors have nothing to disclose.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020040517/-/DCSupplemental.

Supplemental Table 1. The percentage of study participants in each PM$_{2.5}$ level in China between 2007 and 2010.

Supplemental Table 2. Within-city effects and between-city effects of ambient PM$_{2.5}$ exposure on CKD and albuminuria in China between 2007 and 2010.

Supplemental Table 3. Estimated effects of an increase of 10 $\mu$g/m$^3$ in 2-year mean PM$_{2.5}$ exposure on CKD and albuminuria in China between 2007 and 2010 when controlling for different potential confounders.

Supplemental Table 4. Estimated effects of an increase of 10 $\mu$g/m$^3$ in 1-year mean PM$_{2.5}$ exposure on CKD and albuminuria in China between 2007 and 2010.

Supplemental Table 5. The associations between 1-year mean PM$_{2.5}$ exposure on CKD and albuminuria in participants with different characteristics in China between 2007 and 2010.

Supplemental Figure 1. CONSORT diagram of study participants recruitment in the analysis.

Supplemental Figure 2. Distribution of the study sites in both urban and rural areas. Note: Triangle indicates the urban sites, and circular indicates the rural sites.

Supplemental Figure 3. Exposure-response curves of 1-year mean PM$_{2.5}$ exposure and the prevalence of chronic kidney disease (A) and albuminuria (B) in China between 2007 and 2010.

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Correction: Long-Term Exposure to Ambient PM$_{2.5}$ and Increased Risk of Chronic Kidney Disease Prevalence in China


In Table 2, the OR (95% CI) for CKD in model 2 should be 1.29 (95% CI: 1.23, 1.36) instead of 1.29 (95% CI: 1.23, 1.26).

In Supplemental Table 3, the OR (95% CI) for CKD in model 2 should be 1.29 (95% CI: 1.23, 1.36) instead of 1.29 (95% CI: 1.23, 1.26), as well.

See related original article, “Long-Term Exposure to Ambient PM$_{2.5}$ and Increased Risk of Chronic Kidney Disease Prevalence in China,” in Vol. 32, Iss. 2, on pages 448-458.