AAAS
Health Data Science
Volume 2022, Article ID 9846805, 9 pages
https://doi.org/10.34133/2022/9846805

Health Data Science
A SCIENCE PARTNER JOURNAL

Research Article

Association of $PM_{2.5}$ Reduction with Improved Kidney Function: A Nationwide Quasiexperiment among Chinese Adults

Yiqun Han,[1,2] Tao Xue,[3] Frank J. Kelly,[1] Yixuan Zheng,[4] Yao Yao,[5] Jiajianghui Li,[3] Jiwei Li,[6] Chun Fan,[7] Pengfei Li,[8] and Tong Zhu[2]

[1]*Environmental Research Group, MRC Centre for Environment and Health, Imperial College London, London, UK*
[2]*BIC-ESAT and SKL-ESPC, College of Environmental Sciences and Engineering, Center for Environment and Health, Peking University, Beijing 100871, China*
[3]*Institute of Reproductive and Child Health/Ministry of Health Key Laboratory of Reproductive Health and Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China*
[4]*Center of Air Quality Simulation and System Analysis, Chinese Academy of Environmental Planning, 100012 Beijing, China*
[5]*China Center for Health Development Studies, Peking University, Beijing, China*
[6]*College of Computer Science and Technology, Zhejiang University, Hangzhou, China*
[7]*Computer Center, Peking University and Peng Cheng Laboratory, China*
[8]*Advanced Institute of Information Technology, Peking University, China*

Correspondence should be addressed to Tao Xue; xuetaogk_9032@126.com

Received 7 September 2021; Accepted 20 December 2021; Published 18 January 2022

Copyright © 2022 Yiqun Han et al. Exclusive Licensee Peking University Health Science Center. Distributed under a Creative Commons Attribution License (CC BY 4.0).

Background. Increasing evidence from human studies has revealed the adverse impact of ambient fine particles ($PM_{2.5}$) on health outcomes related to metabolic disorders and distant organs. Whether exposure to ambient $PM_{2.5}$ leads to kidney impairment remains unclear. The rapid air quality improvement driven by the clean air actions in China since 2013 provides an opportunity for a quasiexperiment to investigate the beneficial effect of $PM_{2.5}$ reduction on kidney function. *Methods*. Based on two repeated nationwide surveys of the same population of 5115 adults in 2011 and 2015, we conducted a difference-in-difference study. Variations in long-term exposure to ambient $PM_{2.5}$ were associated with changes in kidney function biomarkers, including estimated glomerular filtration rate by serum creatinine (GFR_{scr}) or cystatin C (GFR_{cys}), blood urea nitrogen (BUN), and uric acid (UA). *Results*. For a 10 $\mu g/m^3$ reduction in $PM_{2.5}$, a significant improvement was observed for multiple kidney functional biomarkers, including GFR_{scr}, BUN and UA, with a change of 0.42 (95% confidence interval [CI]: 0.06, 0.78) mL/min/1.73m^2, -0.38 (-0.64, -0.12) mg/dL, and -0.06 (-0.12, -0.00) mg/dL, respectively. A lower socioeconomic status, indicated by rural residence or low educational level, enhanced the adverse effect of $PM_{2.5}$ on kidney function. *Conclusions*. These results support a significant nephrotoxicity of $PM_{2.5}$ based on multiple serum biomarkers and indicate a beneficial effect of improved air quality on kidney function.

1. Introduction

Chronic kidney disease (CKD) has a significant and increasing impact on the world's population (*1*). In 2017, the recorded cases of CKD were 697.5 million with an average prevalence of 9.1% globally, resulting in 35.8 million disability-adjusted life-years (DALYs) (*2*). The symptoms of CKD are usually latent initially, before becoming more apparent manifesting as cardiovascular disease (CVD), edema, bone disease, anemia, and nerve damage. Finally, this leads to kidney failure, known as end-stage kidney disease (ESRD) when regular dialysis treatment or a kidney transplant is the only options for survival (*1*). Declining kidney function is a key characteristic and diagnostic indicator which identifies the onset and development of CKD. Traditional risk factors of CKD and kidney dysfunction, such as

Downloaded from https://spj.science.org on March 20, 2024

diabetes and hypertension (*1*), cannot fully explain the geographic heterogeneity of the disease, and it is suggested that other drivers including air pollution may account for the variation (*3*, *4*).

The air pollutant causing most health concerns is the particulate matter with aerodynamic diameter smaller than 2.5 μm ($PM_{2.5}$) which has been well documented for its adverse cardiorespiratory and metabolic effects (*5*). It has been proposed that the underlying biological mechanisms, such as systemic inflammation, oxidative stress, and vascular endothelial dysfunction, may potentially damage distant organs including the kidneys, which is a highly vascularized organ of the human circulatory system (*6*).

Increasing evidence from human studies has revealed associations between air pollution and declining kidney function indicators such as the prevalence (*7*–*9*), incident and progression of CKD (*8*, *10*), and decreased estimated glomerular filtration rates (eGFR) (*7*, *8*, *11*–*13*); although, the findings remain inconsistent. A study which included 1.1 million adults from the US Medicare program reported that the annual concentration of county-level $PM_{2.5}$ was positively associated with the prevalence of diagnosed CKD (*9*). However, this conclusion has not been repeated in three other large cross-sectional studies (*7*, *8*,*14*). On the other hand, the evidence from cohort studies is consistent that long-term exposure to $PM_{2.5}$ is significantly associated with the incident and progression of CKD (*8*) and the risk of eGFR decline (*10*, *12*). To date, no evidence has been provided to examine if $PM_{2.5}$ reduction could beneficially impact kidney function in human.

The Clean Air Action Plan, initiated in 2013 by the Chinese government, was a bold nationwide policy aiming at tackling the severe air pollution problem in China that was leading to about 1 million premature deaths every year (*15*). The plan consists of ten key measures including some important policies as reducing emissions from industrial facilities and vehicles and improving the efficiency of fuel usage (*16*). As a consequence, annual $PM_{2.5}$ concentrations in mainland China have decreased significantly by 32%, from 67.4 $\mu g/m^3$ in 2013 to 45.5 $\mu g/m^3$ in 2017 (*15*). This rapid change provides an opportunity of designing quasiexperiments to investigate the beneficial effect of air pollution reduction on the human health in the Chinese population (*17*–*19*). Based on repeated nation-scale surveys launched before and after the Clean Air Action Plan in 2011 and 2015 on the same population of 5115 adults, we conducted a difference-in-difference study to investigate the causal relationship between chronic exposure to ambient $PM_{2.5}$ and changes in kidney function.

2. Methods

2.1. Population Data. The population in this study was based on the project "The China Health and Retirement Longitudinal Study (CHARLS)," which provided a public database (http://opendata.pku.edu.cn/) with a wide range of information from socioeconomic status to health conditions in Chinese people aged 45 and over (*20*). To ensure sample representativeness, ~20,000 participants were recruited based on a complex four-stage sampling approach across the country. A detailed introduction and protocol of the project is provided in the CHARLS document (*21*). Briefly, three waves of repeated surveys were launched in the years 2011, 2013, and 2015, and most of the surveys were conducted during summer season (Figure S1). The analysis of this study relied on the data collected from waves 1 and 3, because blood samples were not collected in wave 2. Demographic background and social economic information of all participants were collected using follow-up questionnaire qualified enumerators. Blood samples were also collected by well-trained staff.

2.2. Kidney Function Measurement. The evaluation of kidney function was based on four clinical biomarkers measured in fast blood samples, namely, serum creatinine (SCR), cystatin C (CYS), blood urea nitrogen (BUN), and uric acid (UA). Samples were sent to a central national laboratory and stored -80°C until assay. Strict standards were applied from sample transportation, storage, to the measurement and quality control, with details in supplement (S1.1).

Decline in glomerular filtration rate (GFR) was deemed as the golden standard for the clinical diagnosis of CKD (*1*). In this study, we applied the two equations to calculate eGFR by SCR (GFR_{scr}) or CYS (GFR_{cys}), based on age and sex (details in S1.2) (*22*). In a comparative study (*21*) for Chinese adults, the utilized equations were proofed to outperform other eGFR approaches suggested by the Chronic Kidney Disease Epidemiology Collaboration (*23*). BUN and UA can also be utilized as biomarkers of kidney impairment, because these two biomarkers reflect the concentrations of waste products generated from protein and purine metabolism, respectively. The elevated concentrations of BUN and UA are usually seen in patients with reduced GFR (*24*, *25*). Since BUN and UA may also be indicative for other diseases (e.g., gouty arthritis), in this study, they act as secondary biomarkers for kidney function. Major conclusions from our analyses should be drawn from the eGFR results.

2.3. Exposure Data. Similar to our previous studies, we evaluated the long-term exposure to $PM_{2.5}$ and temperature for CHARLS subjects according to the reanalyzed environmental database (*26*, *27*). Details on exposure assessment are documented in supplement (S1.3).

2.4. Study Design and Statistical Analyses. This study applied a difference-in-difference method to examine the causal effect of $PM_{2.5}$ on kidney function. The same approach has been applied in our previous analyses (*17*, *19*) and briefly introduced in supplement (S1.4). For this study, the difference-in-difference analysis was parameterized using the following equation:

$$\Delta\text{Biomarker}_i = \Delta PM_{2.5,i}\beta + \Delta x_i\gamma_1 + x_i\gamma_2 + \varepsilon_i, \quad (1)$$

where i denotes the individual index; $\Delta PM_{2.5,\ i}$ denotes the temporal change in the exposure level from pre- to postclean air actions for the i -th adults; $\Delta\text{Biomarker}_i$ denotes the corresponding temporal change in a targeted biomarker; Δx_i denotes the temporal changes in the longitudinal covariates

Downloaded from https://spj.science.org on March 20, 2024

(i.e., inconstant variables, including marriage, smoking, drinking, indoor temperature maintenance, cooking energy type, and body weight, as shown in Table 1); x_i denotes the baseline covariates (i.e., constant variables, including residence, sex, and education); and β and $\boldsymbol{\gamma}_1$ and $\boldsymbol{\gamma}_2$ denotes the corresponding regression coefficients. For categorical longitudinal variables, $\Delta \boldsymbol{x}_i$ denotes a new categorical variable, coded by combination of measurements in the two waves (for example, between the two surveys, a person who quit smoking was coded as yes-no, and a person who started to smoke was coded as no-yes); for continuous longitudinal variables, Δx_i denotes the difference between the two measurements. Given the possibility that the studied subjects were not completely randomly distributed along different levels of $\Delta PM_{2.5}$, we applied the inversed probability weights, which were derived using the *R* package *ipw*. The probability of $\Delta PM_{2.5}$ was estimated using a regression model that incorporated covariates of residence, sex, education, age, BMI, temperature variation, body weight change, and an indicator of regional developmental level and gross domestic product per capita. The effect of $PM_{2.5}$ on kidney function was evaluated as $(10 \times \beta)$, i.e., the change in biomarkers for a 10 $\mu g/m^3$ increment of $PM_{2.5}$ in the long-term exposure. $\Delta x_i\ \gamma_1$ aims to control for the potential confounding effects from the longitudinal changes in the study population, such as the lifestyle (drinking and smoking) changes. $x_i\ \gamma_2$ aims to control for the heterogenous temporal trend in the kidney function, which is assumed to progress in temporal patterns different by demographic characteristics (e.g., educational level). Since $\Delta Biomarker_i$ for each of the four biomarkers was distributed in bell shape (Figure S2), there was no clear evidence to model the outcomes in transformed scale.

In sensitivity analyses, we first examined whether the estimated effect varied with model settings: (1) different choices of adjusted covariates and (2) incorporation of the inversed probability weights or not. Second, we explored how the estimated effect was heterogeneous between different subpopulations using interaction analyses. Third, linearity of the effect was tested with details in supplement (S1.5). Fourth, we explored how the estimated effect of $PM_{2.5}$ was varied between subjects with different baselines of kidney function. The baseline-varying model, which is similar to the nonlinear model, has been applied in our previous study (*28*) and is documented in the supplement (S1.5). Fifth, we explored whether the estimated associations were sensitive to the potential heterogeneity between different survey waves or the skewed distributions of the biomarker levels. To test that, we first normalized the measurements (i.e., normalized $biomarker_i = (biomarker_i - mean)/SD$) within each wave and then utilized their differences as new dependent variables to reexamine the effect of $PM_{2.5}$. Sixth, we conducted two sensitivity analyses to evaluate the exposure measurement errors caused by using city-level average to assess the $PM_{2.5}$ exposure. We applied a well-developed bootstrap method (Supplement S1.6), which has been applied in our previous studies, to quantify the exposure measurement error (*17*, *29*). We also further lowered the error by deriving city-level $PM_{2.5}$ concentrations specifically for urban or rural area (Supplement S1.7) and reestimated the associations. Finally, we also conducted post hoc analyses to examine whether the associations were sensitive to the choice of time window for exposure assessment. We repeated our main models using alternative city-level $PM_{2.5}$ concentrations averaged within 1, 2, 3, or 4 years preceding the survey time. All the statistical analyses were performed using *R* (version 3.4.1), and the significance level was set as $p < 0.05$.

3. Results

3.1. Descriptive Statistics. In total, this study involved 5115 eligible adults, who have completed the survey waves 1 and 3 (i.e., pre- and postclean air actions, respectively (Figure S1). Among them, there were 4911, 3841, 5109, or 5113 pairs of valid records on SCR, CYS, BUN, and UA, respectively. Mean age of the studied population at 2011 was 58.8 (standard deviation = 8.9) years old. In the survey wave 1, the mean values of GFR_{scr}, GFR_{cys}, BUN, or UA were 89.1 (9.7) mL/min/1.73 m^2, 82.7 (19.0) mL/min/1.73m^2, 15.6 (4.4) mg/dL, or 4.4 (1.2) mg/dL, respectively. In the wave 3, those values were 86.3 (10.3) mL/min/1.73 m^2, 93.0 (19.5) mL/min/1.73m^2, 15.7 (4.6) mg/dL, or 4.9 (1.4) mg/dL, respectively. Between the two waves, mean body weight slightly increased from 59.3 (11.4) kg to 59.5 (11.9) kg, and the mean exposure concentration of $PM_{2.5}$ decreased from 63.1 (18.9) $\mu g/m^3$ to 54.7 (17.0) $\mu g/m^3$. Across the studied cities, we found a significantly decreasing trend of 4.95 (95% confidence intervals [CI]: 0.79~9.11) $\mu g/m^3$/year from 2013 to 2016 in the monthly concentrations of ambient $PM_{2.5}$ after the intervention (Figure S1). In contrast, before the intervention, there was no significant trend in $PM_{2.5}$ (0.29 $\mu g/m^3$/year; 95% CI: -3.66~4.25 $\mu g/m^3$/year) from 2009 to 2012. Spatial distributions of the $PM_{2.5}$ trends are documented in our previous publication (*17*). Detailed summaries of the studied population are presented in Table 1.

3.2. Associations. To illustrate the design of a difference-in-difference study, we first conducted a preliminary analysis (Figure S2). The actual changes in $PM_{2.5}$ exposure ($\Delta PM_{2.5}$ equals the concentration of $PM_{2.5}$ in 2015 minus the concentration in 2013) varied in different cities. Subjects were divided into two groups, namely, those who lived in the areas with a $\Delta PM_{2.5}$ below its upper quartile ($\Delta PM_{2.5} < -5.12\ \mu g/m^3$) as the treatment group, referring to a more efficient effect of the clean air actions and the rest as the control (Figure S2, upper panel). Because different magnitudes of $PM_{2.5}$ reduction were mostly driven by emission-control policies, the between-group difference in the temporal change in a biomarker (ΔBiomarker) could be utilized to reveal the policy's effect. The lower panel of Figure S2 suggests the intervention was associated to a positive change in GFR_{scr} (0.22 mL/min/1.73m^2) and GFR_{cys} (0.88 mL/min/1.73m^2) but a negative change in BUN (-0.14 mg/dL) or UA (-0.16 mg/dL). Because the reduction in GFR_{scr} or GFR_{cys}, and the increment of BUN or UA suggests a kidney impairment, the results consistently revealed the benefit of $PM_{2.5}$ reduction on kidney function.

Downloaded from https://spj.science.org on March 20, 2024

Table 1: Statistics of the population characteristics.

	Categorical variable	Group	Person (n, prevalence %)		
Constant variables	Total		5115 (100%)		
	Residence	Rural	3387 (66.2%)		
		Urban	1728 (33.8%)		
	Region	Midwest	1771 (34.6%)		
		North	1439 (28.1%)		
		Southeast	1905 (37.2%)		
	Sex	Female	2830 (55.3%)		
		Male	2284 (44.7%)		
		Unknown	1 (0.02%)		
	Education	Elementary and below	3619 (70.8%)		
		High and above	477 (9.33%)		
		Middle	1017 (19.9%)		
		Unknown	2 (0.04%)		
	Continuous variable		Mean (SD, IQR, person n)		
	Average body mass index (BMI, kg/m^2)		23.9 (3.8, 21.4 ~ 26.1, 5115)		
	Age at 2011 (year)		58.8 (8.9, 52.0 ~ 65.0, 5114)		
			Person-visit (N, prevalence %)		
	Categorical variable	Group	Total	Wave before intervention	Wave after intervention
Inconstant variables	Marriage	No	1709 (16.7%)	763 (14.9%)	946 (18.5%)
		Yes	8520 (83.3%)	4352 (85.0%)	4168 (81.5%)
		Unknown	1 (0.01%)	0 (0%)	1 (0.02%)
	Smoking	No	7246 (70.8%)	3645 (71.3%)	3601 (70.4%)
		Yes	2981 (29.1%)	1467 (28.7%)	1514 (29.6%)
		Unknown	3 (0.03%)	3 (0.06%)	0 (0%)
	Drinking	Frequent	2505 (24.5%)	1244 (24.3%)	1261 (24.7%)
		Never	6886 (67.3%)	3455 (67.6%)	3431 (67.1%)
		Rare	831 (8.1%)	413 (8.1%)	418 (8.2%)
		Unknown	8 (0.1%)	3 (0.06%)	5 (0.10%)
	Indoor temperature maintenance	Very hot	111 (1.1%)	88 (1.7%)	23 (0.5%)
		Hot	970 (9.5%)	561 (11.0%)	409 (8.0%)
		Bearable	8688 (84.9%)	4308 (84.2%)	4380 (85.6%)
		Cold	277 (2.7%)	122 (2.4%)	155 (3.0%)
		Very cold	18 (0.2%)	16 (0.3%)	2 (0.04%)
		Unknown	166 (1.6%)	20 (0.4%)	146 (2.9%)
	Cooking energy type	Clean	4701 (46.0%)	2043 (39.9%)	2658 (52.0%)
		Unclean	5440 (53.2%)	3040 (59.4%)	2400 (46.9%)
		Unknown	89 (0.9%)	32 (0.6%)	57 (1.1%)
	Continuous variable			Mean (SD, median, IQR)	
	GFR_{scr} (mL/min/1.73 m^2)		87.7 (10.1, 89.5, 83.0 ~ 94.6)	89.1 (9.7, 90.8, 84.3 ~ 95.8)	86.3 (10.3, 88.2, 81.8 ~ 93.2)
	GFR_{cys} (mL/min/1.73 m^2)		87.8 (19.9, 85.2, 75.7 ~ 98.7)	82.7 (19.0, 81.0, 71.1 ~ 92.0)	93.0 (19.5, 92.0, 80.2 ~ 105.1)
	Serum creatinine (SCR, mg/dL)		0.8 (0.2, 0.7, 0.6 ~ 0.9)	0.8 (0.2, 0.7, 0.6 ~ 0.9)	0.8 (0.2, 0.8, 0.7 ~ 0.9)
	Cystatin C (CYS, mg/L)		0.9 (0.3, 0.9, 0.8 ~ 1.0)	1.0 (0.3, 1.0, 0.9 ~ 1.1)	0.9 (0.2, 0.9, 0.7 ~ 1.0)
	Blood urea nitrogen (BUN, mg/dL)		15.6 (4.5, 15.0, 12.5 ~ 18.2)	15.6 (4.4, 15.0, 12.5 ~ 18.0)	15.7 (4.6, 14.8, 12.3 ~ 18.2)
	Uric acid (UA, mg/dL)		4.6 (1.3, 4.5, 3.7 ~ 5.4)	4.4 (1.2, 4.2, 3.5 ~ 5.1)	4.9 (1.4, 4.8, 3.9 ~ 5.7)

Downloaded from https://spj.science.org on March 20, 2024

Table 1: Continued.

Body weight (kg)	59.4 (11.7, 58.4, 51.5 ~ 66.3)	59.3 (11.4, 58.3, 51.4 ~ 66.2)	59.5 (11.9, 58.5, 51.5 ~ 66.5)
$PM_{2.5}$ ($\mu g/m^3$)	58.9 (18.5, 59.1, 44.1 ~ 73.9)	63.1 (18.9, 64.8, 49.2 ~ 78.8)	54.7 (17.0, 55.9, 40.7 ~ 69.7)

Table 2: The association between $PM_{2.5}$ and kidney function biomarkers, estimated directly from the fully adjusted regression or after a further correction using the bootstrap method.

		Biomarker change* for 10 $\mu g/m^3$ increment in $PM_{2.5}$ with 95% percentile intervals	
Method		Regression estimation (no correction for exposure measurement error)	Bootstrap estimation (after correction for exposure measurement error)
Biomarker change	GFR_{scr} (mL/min/1.73m^2)	**-0.421 (-0.784, -0.058)**#	**-0.396 (-0.766, -0.014)**
	GFR_{cys} (mL/min/1.73m^2)	0.018 (-1.161, 1.197)	-0.002 (-1.232, 1.149)
	BUN (mg/dL)	**0.379 (0.118, 0.640)**	**0.358 (0.098, 0.620)**
	UA (mg/dL)	**0.060 (0.003, 0.116)**	**0.057 (0.002, 0.115)**

#The estimated associations, which are statistically significant ($p < 0.05$), are highlighted by bolded numbers. *The positive/negative change means increase/decrease in a biomarker. For GFR_{scr} or GFR_{cys}, a negative association indicates for the toxic effect of $PM_{2.5}$; For BUN or UA, a positive association indicates for the toxic effect of $PM_{2.5}$.

Considering the $PM_{2.5}$ reduction as continuous, the between-group comparison of ΔBiomarker could be converted into a regression analysis (i.e., the difference-in-difference model), which enable a quantitative examination on the association between ΔBiomarker and $\Delta PM_{2.5}$, as shown in Figure S3. According to the fully adjusted models (Table 2), an increment of 10 $\mu g/m^3$ in $PM_{2.5}$ was associated to a change of -0.42 (95% CI: -0.78, -0.06) mL/min/1.73m^2, 0.02 (-1.16, 1.20) mL/min/1.73m^2, 0.38 (0.12, 0.64) mg/dL, and 0.06 (0.00, 0.12) mg/dL for GFR_{scr}, GFR_{cys}, BUN, and UA, respectively. The estimated effects of $PM_{2.5}$ were not sensitive to different model settings. The findings based on GFR_{scr}, BUN, and UA consistently suggested a significantly adverse effect of $PM_{2.5}$ exposure on kidney function. The large uncertainties in the estimated effect on GFR_{cys} might be due to its relatively small sample size (Table 1).

3.3. Sensitivity Analyses. Figure 1 presents the results from subgroup analyses. We found that the estimated effects were not significantly varied within the most of subpopulation indicators, except for the variables related to the socioeconomic status and age. Compared to the urban residents, rural people were more susceptible to the effect of $PM_{2.5}$ on GFR_{scr} ($p = 0.06$), GFR_{cys} ($p = 0.01$), and BUN ($p = 0.04$). The association between $PM_{2.5}$ and GFR_{scr} was also varied with education level at marginal significance ($p = 0.05$), with enhanced susceptibility in the lowest educated subpopulation. We also observed a trend that aging could enhance the associations between $PM_{2.5}$ and GFR_{scr} ($p = 0.11$) and GFR_{cys} ($p = 0.05$). Additionally, directions of the estimated associations reported by the nonlinear models were in consistent with the results from the main (linear) models (Figure S4). Furthermore, the baseline-varying effect models suggested that the adults with normal kidney function (e.g., $GFR_{scr} > \sim 80$ mL/min/1.73m^2 or BUN $< \sim$ 20 mg/dL), who might be exposed to less competing risk factors (e.g., alcohol usage), could be more susceptible to the toxic effect of $PM_{2.5}$, compared to those with poor kidney function (Figure S5). Finally, after normalizing the biomarkers, we still observed significant effect of $PM_{2.5}$ on GFR_{scr}, BUN, and UA (Figure S6).

We utilized a bootstrap method to evaluate how the exposure errors influenced the association estimates. The bootstrapped results were presented in Table 2. Generally speaking, the bootstrapped results were statistically comparable with the estimates before correcting the measurement errors. We also reevaluated the associations by urban-or-rural-specific exposures, and the reestimated results were statistically comparable with those from the main models for all biomarkers, except for UA (Figures S3-4). After incorporating the type of residential community into the exposure assessment, the association between $PM_{2.5}$ and UA was no longer statistically significant (Figure S3b). Given that, the effect estimations from our major outcomes, i.e., GFR_{scr} and BUN, were not significantly changed by the limitation of using city-level $PM_{2.5}$ data. Additionally, the bootstrapped method tends to report weaker associations between $PM_{2.5}$ and kidney function biomarkers, which suggests that the measurement errors in exposure may lead to underestimated uncertainties embedded in the associations. Finally, we also found for exposure in a longer term, the effects for per-unit change in $PM_{2.5}$ tend to show larger point estimates but with wider uncertainty ranges (Figure S7). Using a longer time-window for exposure might be more representative for the chronic effect of $PM_{2.5}$ on kidney function, but less representative to show the improved air quality.

Downloaded from https://spj.science.org on March 20, 2024

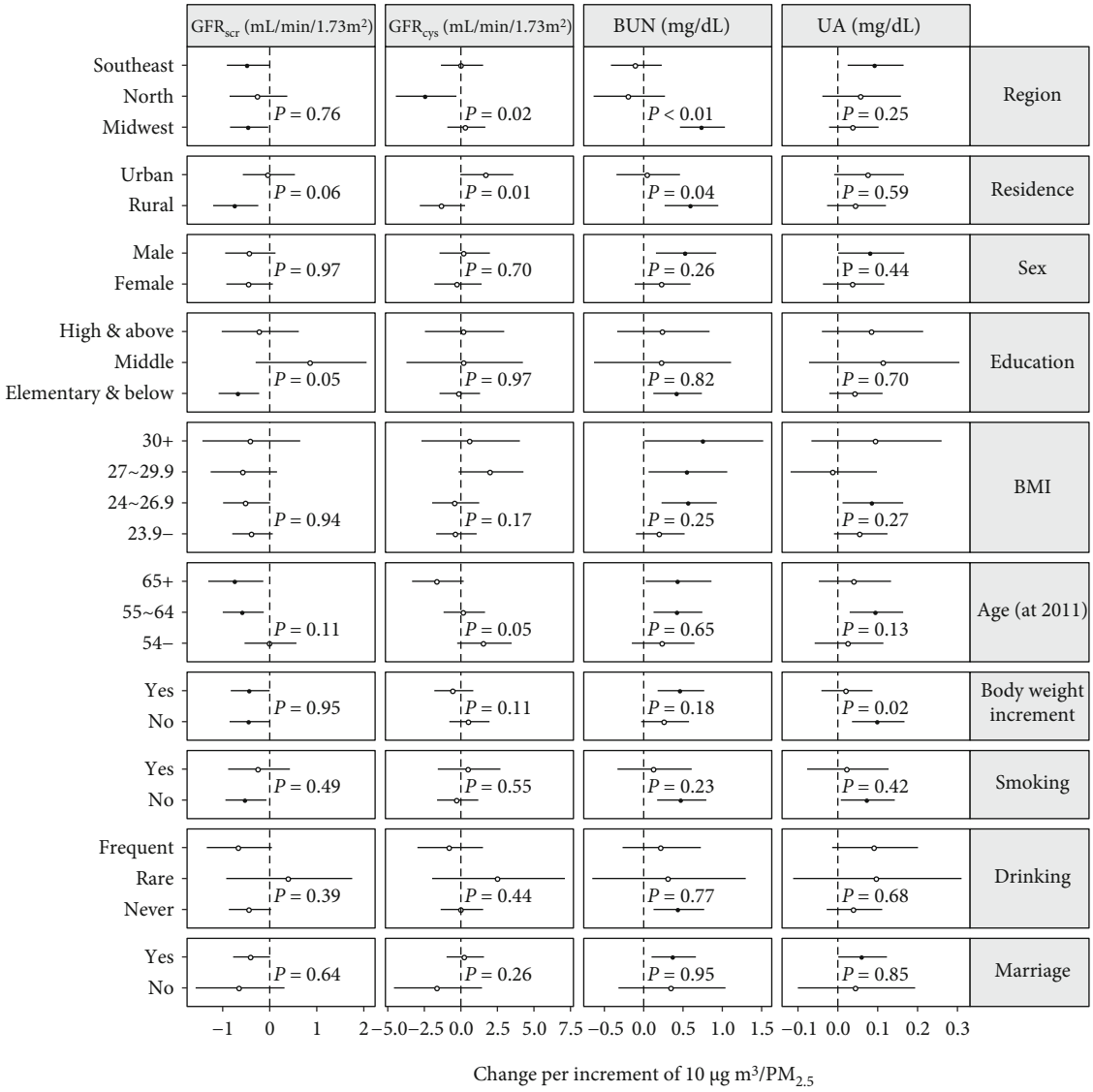


FIGURE 1: The subpopulation-specific effects of $PM_{2.5}$ on the biomarkers of kidney function. The fully adjusted model incorporated both the baseline covariates and the longitudinal covariates. The dots denote significant associations, and the circles denote nonsignificant ones. Longitudinal covariates denoted temporal changes in the inconstant variables (i.e., body weight, marriage, drinking, smoking, cooking energy type, and indoor temperature maintenance); the baseline covariates denoted values of the longitudinal variables in the baseline wave and the constant variables (i.e., residence, sex, education, age at 2011, and average BMI). Along *x*-axis, the positive/negative change means increase/decrease in a biomarker. For GFR_{scr} or GFR_{cys}, a negative association indicates for the toxic effect of $PM_{2.5}$; for BUN or UA, a positive association indicates for the toxic effect of $PM_{2.5}$.

4. Discussion

4.1. Summary of Previous Findings. Current evidence regarding the adverse effect of $PM_{2.5}$ on kidney remains scares and inconsistent. A recent meta-analysis reviewed literatures on this topic from archive inception to October 2019 indicated that, per 10 $\mu g/m^3$ increase in the long-term exposure to $PM_{2.5}$, the pooled effect on the eGFR decline was insignificant, estimated to be −4.11 (95% CI: −12.64, 4.42) (*30*). However, this review acknowledged that the analysis was based on only two available studies which may lead to large uncertainties. Specifically, a cohort study based on 669 US male veterans observed that a 2.1 $\mu g/m^3$ IQR higher 1-year $PM_{2.5}$ was significantly associated with decreased change in eGFR of -1.87 (–2.99, –0.76) mL/min/1.73 m^2, (*12*) while another cross-sectional study based on 21,656 Taiwanese concluded an insignificant association (*7*). To be noted, three other studies have also investigated the similar hypothesis but were not included in the meta-analysis (*8*, *10*, *11*). Two cross-sectional studies in African Americans and Taipei city residents reported insignificant associations (*8*, *11*), while another nationwide cohort study among 2,482,737 US veterans found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration was associated with significant increased risk of

Downloaded from https://spj.science.org on March 20, 2024

eGFR < 60 mL/min/1.73 m^2 (hazard ratio (HR) equals 1.21 (1.14 to 1.29)) and eGFR decline ≥ 30% (HR equals 1.28 (1.18, 1.39)) (*10*). The result from our study further confirmed the potential kidney toxicity of $PM_{2.5}$; although, the estimated effect [-0.42 (-0.78, -0.06) mL/min/1.73m^2 change in GFR_{src} per an increment of 10 $\mu g/m^3$ in $PM_{2.5}$] was smaller compared to the findings from previous study (*12*).

Apart from the decline in eGFR, evidence using other outcomes was also supportive for an adverse effect of $PM_{2.5}$ on kidney function. Significant associations between chronic exposure to $PM_{2.5}$ with the prevalence and incident of CKD and progression of ESRD were suggested from several nationwide cross-sectional and cohort studies (*7–10*), in which the definition of CKD and ESRD was largely based on the value of eGFR by SCR. Additionally, a unique study based on an 11-year collection of 71,151 native kidney biopsies from 938 hospitals across 282 cities in China observed that long-term exposure to $PM_{2.5}$ was associated with an increased risk of membranous nephropathy, the second leading type of glomerulopathy that contributed to 23.4% of all cases (*31*). Besides, the observational studies, a few biological evidences also indicate an association between $PM_{2.5}$ exposure and impaired kidney function (Supplmental S1.8).

4.2. Implications. Long-term exposure to ambient $PM_{2.5}$ has been known to cause premature deaths by increasing the risks of cardiorespiratory diseases. GBD study in 2016 estimated the global deaths and DALY attributed to $PM_{2.5}$ was about 4.1 million and 105.7 million, respectively (*32*). However, these numbers could underestimate the health impacts from air pollutants, because a recent study on the association between all-cause mortality and $PM_{2.5}$ showed that cardiorespiratory effects might not be the only explanation behind the mortality burden attributable to $PM_{2.5}$ (*33*). One recent study estimated that the annual global toll of CKD attributable to ambient $PM_{2.5}$ exposure is significant with 6.9 million incident cases of CKD and 11.4 million DALYs (*3*). representing about 10% of burden of disease reported from GBD 2016. In accordance with other evidence (*7–10*), our findings further reveal a causal linkage between $PM_{2.5}$ exposure and kidney impairment and suggest that kidney disease could be a nonnegligible outcome of the poor air quality. Future evaluations should incorporate the effects of $PM_{2.5}$ on kidney function and diseases, to accurately quantify the risks from nonoptimal air quality.

4.3. Limits. First, this study is based on all-available observations from a series of preestablished surveys with many general aims, which were not focused on kidney function specifically. Its representativeness depends on the missing patterns in the dataset. However, from the publicly available version of CHARLS, information on the missingness is limited, which can introduce potential bias into (e.g., survival bias), or lower the representativeness of our findings. Second, we reasoned the estimated effect might be biased due to exposure misclassification by the usage of monthly and city-level averages of $PM_{2.5}$ concentrations; although, this is the best dataset available for analysis because the CHARLS did not release the population data with a higher spatiotemporal resolution, in order to protect personal privacy. Finally, although the difference-in-difference analysis controls for some unchanged risk factors on kidney function (e.g., generic defects) by the study design itself, our findings could be undermined by the unmeasured longitudinal confounders. Such confounders can be environmental factors (i.e., lead) that shared the common emission sources of the ambient $PM_{2.5}$. The study design also controlled for the longitudinal factors that were progressed with time in the same pattern. Age is an example of such factor, if we assume it affects kidney function linearly. However, the design cannot fully control for nonlinear risk factors. For instance, the effect of 4-year's aging could be varied between individuals of different generations. Compared to conventional cross-sectional analyses, our difference-in-difference design is more capable to reveal a causal effect of $PM_{2.5}$, but the causality of our findings is not conclusive and should be reexamined in future.

5. Conclusion

Based on a quasiexperiment design, this study provides a strong evidence for the linkage between chronic exposure to ambient $PM_{2.5}$ and kidney impairment. The findings suggest clean air actions applied in China brings rapid improvement in air pollution and can lead to beneficial health effect by reducing the impact of kidney diseases.

Data Availability

All the analyses in this study are based on publicly-available datasets. Health outcomes can be freely obtained from http://opendata.pku.edu.cn/; and exposure data can be freely obtained from http://tapdata.org.cn/.

Ethical Approval

Ethics approval for the CHARLS project was obtained from the Ethics Review Committee of Peking University (IRB00001052–11015).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

TX and TZ designed the study. YH and TX participated in the data analysis and drafted the manuscript. TX, YZ, YY, and JiaL prepared the annual $PM_{2.5}$ exposure in China at the city-level basis. JiwL and CF analyzed its uncertainty. FK and TZ revised second version of the manuscript; all authors read and approved the final version of the manuscript and ensure this is the case. Yiqun Han and Tao Xue contributed equally to this work.

Acknowledgments

Appreciations to the China Center for Economic Research, National School of Development, Peking University for

Downloaded from https://spj.science.org on March 20, 2024

providing the CHARLS data. This work was supported by the National Natural Science Foundation of China (4217050142), PKU-Baidu Fund (2020BD031), Energy Foundation (G-2107-33169 and R-2109-33379), the Fundamental Research Funds for the Central Universities (BMU2021YJ042), and CAMS Innovation Fund for Medical Sciences (2017-I2M-1-004).

Supplementary Materials

Supplemental Methods Table S1: the assay methods for the kidney function measurements. Table S2: equations for GFR estimation. Figure S1: two waves of health surveys before and after intervention (black bars) with the time series of monthly ambient $PM_{2.5}$ averages (red lines) across the study period. Figure S2: illustration of the study design: a preliminary difference-in-difference analysis by treatment and control groups. Figure S3: estimated effects of $PM_{2.5}$ on the biomarkers of kidney function by different model runs. Figure S4: estimated nonlinear effects of $PM_{2.5}$ on the biomarkers of kidney function. Figure S5: estimated baseline-varying effects of $PM_{2.5}$ on the biomarkers of kidney function. Figure S6: estimated effects of $PM_{2.5}$ on the normalized biomarkers of kidney function by different model runs. Figure S7: estimated effects of $PM_{2.5}$ on the normalized biomarkers of kidney function by different time windows (i.e., periods of 1-4 years before biomarker measurement) for exposure. *(Supplementary Materials)*

References

[1] P. Romagnani, G. Remuzzi, R. Glassock et al., "Chronic kidney disease," *Nature Reviews Disease Primers*, vol. 3, no. 1, pp. 1–24, 2017.

[2] B. Bikbov, C. A. Purcell, A. S. Levey et al., "Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017," *The Lancet*, vol. 395, no. 10225, pp. 709–733, 2020.

[3] B. Bowe, Y. Xie, T. Li, Y. Yan, H. Xian, and Z. al-Aly, "Estimates of the 2016 global burden of kidney disease attributable to ambient fine particulate matter air pollution," *BMJ Open*, vol. 9, no. 5, article e022450, 2019.

[4] B. Bowe, E. Artimovich, Y. Xie, Y. Yan, M. Cai, and Z. al-Aly, "The global and national burden of chronic kidney disease attributable to ambient fine particulate matter air pollution: a modelling study," *BMJ Global Health*, vol. 5, no. 3, article e002063, 2020.

[5] R. D. Brook, S. Rajagopalan, C. A. Pope III et al., "Particulate matter air pollution and cardiovascular Disease," *Circulation*, vol. 121, no. 21, pp. 2331–2378, 2010.

[6] E. A. Kim, "Particulate matter (fine particle) and urologic diseases," *International Neurourology Journal*, vol. 21, no. 3, pp. 155–162, 2017.

[7] Y.-R. Yang, Y.-M. Chen, S.-Y. Chen, and C. C. Chan, "Associations between long-term particulate matter exposure and adult renal function in the Taipei metropolis," *Environmental Health Perspectives*, vol. 125, no. 4, pp. 602–607, 2017.

[8] S.-Y. Chen, D.-C. Chu, J.-H. Lee, Y.-R. Yang, and C. C. Chan, "Traffic-related air pollution associated with chronic kidney disease among elderly residents in Taipei City," *Environmental Pollution*, vol. 234, pp. 838–845, 2018.

[9] J. Bragg-Gresham, H. Morgenstern, W. McClellan et al., "County-level air quality and the prevalence of diagnosed chronic kidney disease in the US Medicare population," *PLoS One*, vol. 13, no. 7, article e0200612, 2018.

[10] B. Bowe, Y. Xie, T. Li, Y. Yan, H. Xian, and Z. al-Aly, "Particulate matter air pollution and the risk of incident CKD and progression to ESRD," *Journal of the American Society of Nephrology*, vol. 29, no. 1, pp. 218–230, 2018.

[11] A. M. Weaver, Y. Wang, G. A. Wellenius et al., "Long-term exposure to ambient air pollution and renal function in African Americans: the Jackson heart study," *Journal of Exposure Science Environmental Epidemiology*, vol. 29, no. 4, pp. 548–556, 2019.

[12] A. J. Mehta, A. Zanobetti, M. A. C. Bind et al., "Long-term exposure to ambient fine particulate matter and renal function in older men: the veterans administration normative aging study," *Environmental Health Perspectives*, vol. 124, no. 9, pp. 1353–1360, 2016.

[13] G. Li, J. Huang, J. Wang et al., "Long-term exposure to ambient $PM_{2.5}$ and increased risk of CKD prevalence in China," *Journal of the American Society of Nephrology*, vol. 32, no. 2, pp. 448–458, 2021.

[14] H.-J. Kim, J. Y. Min, Y. S. Seo, and K. B. Min, "Association between exposure to ambient air pollution and renal function in Korean adults. Annals of occupational environmental medicine," *Annals of Occupational and Environmental Medicine*, vol. 30, pp. 1–7, 2018.

[15] T. Xue, J. Liu, Q. Zhang et al., "Rapid improvement of $PM_{2.5}$ pollution and associated health benefits in China during 2013–2017," *Science China Earth Sciences*, vol. 62, no. 12, pp. 1847–1856, 2019.

[16] Q. Zhang, Y. Zheng, D. Tong et al., "Drivers of improved PM2.5air quality in China from 2013 to 2017," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 116, no. 49, pp. 24463–24469, 2019.

[17] J. Li, Y. Yao, W. Xie et al., "Association of long-term exposure to $PM_{2.5}$ with blood lipids in the Chinese population: Findings from a longitudinal quasi- experiment," *Environment International*, vol. 151, article 106454, 2021.

[18] T. Xue, T. Guan, Y. Zheng et al., "Long-term $PM_{2.5}$ exposure and depressive symptoms in China: a quasi-experimental study," *The Lancet Regional Health-Western Pacific*, vol. 6, article 100079, 2021.

[19] T. Xue, Y. Han, Y. Fan et al., "Association between a rapid reduction in air particle pollution and improved lung function in adults," *Annals of the American Thoracic Society*, vol. 18, no. 2, pp. 247–256, 2021.

[20] Y. Zhao, Y. Hu, J. P. Smith, J. Strauss, and G. Yang, "Cohort profile: the China health and retirement longitudinal study (CHARLS)," *International Journal of Epidemiology*, vol. 43, no. 1, pp. 61–68, 2014.

[21] Y. Zhao, J. Strauss, G. Yang et al., *China Health and Retirement Longitudinal Study–2011–2012 National Baseline Users' Guide*, National School of Development, Peking University, 2013.

[22] X. Pei, W. Yang, S. Wang et al., "Using mathematical algorithms to modify glomerular filtration rate estimation equations," *PLoS One*, vol. 8, no. 3, article e57852, 2013.

[23] L. A. Inker, C. H. Schmid, H. Tighiouart et al., "Estimating glomerular filtration rate from serum creatinine and cystatin C,"

Downloaded from https://spj.science.org on March 20, 2024

The New England Journal of Medicine, vol. 367, no. 1, pp. 20–29, 2012.

[24] C. Giordano, O. Karasik, K. King-Morris, and A. Asmar, "Uric acid as a marker of kidney disease: review of the current literature," *Disease Markers*, vol. 2015, 6 pages, 2015.

[25] S. Lopez-Giacoman and M. Madero, "Biomarkers in chronic kidney disease, from kidney function to kidney damage," *World Journal Of Nephrology*, vol. 4, no. 1, pp. 57–73, 2015.

[26] T. Xue, Y. Zheng, D. Tong et al., "Spatiotemporal continuous estimates of $PM_{2.5}$ concentrations in China, 2000-2016: A machine learning method with inputs from satellites, chemical transport model, and ground observations," *Environment international*, vol. 123, pp. 345–357, 2019.

[27] T. Xue, T. Zhu, Y. Zheng, and Q. Zhang, "Declines in mental health associated with air pollution and temperature variability in China," *Nature Communications*, vol. 10, no. 1, pp. 1–8, 2019.

[28] J. Li, T. Guan, Q. Guo et al., "Exposure to landscape fire smoke reduced birthweight in low- and middle-income countries: findings from a siblings-matched case-control study," *eLife*, vol. 10, article e69298, 2021.

[29] A. A. Szpiro, L. Sheppard, and T. Lumley, "Efficient measurement error correction with spatially misaligned data," *Biostatistics*, vol. 12, no. 4, pp. 610–623, 2011.

[30] M.-Y. Wu, W.-C. Lo, C.-T. Chao, M.-S. Wu, and C.-K. Chiang, "Association between air pollutants and development of chronic kidney disease: a systematic review and meta-analysis," *Science of the Total Environment*, vol. 706, article 135522, 2020.

[31] X. Xu, G. Wang, N. Chen et al., "Long-term exposure to air pollution and increased risk of membranous nephropathy in China," *Journal of the American Society of Nephrology*, vol. 27, no. 12, pp. 3739–3746, 2016.

[32] GBDRF Collaborators, "Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the global burden of disease study 2016," *The Lancet*, vol. 390, no. 10100, pp. 1345–1422, 2017.

[33] R. Burnett, H. Chen, M. Szyszkowicz et al., "Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 115, no. 38, pp. 9592–9597, 2018.

Downloaded from https://spj.science.org on March 20, 2024