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Long-term exposure to ambient particulate matter and kidney function in older adults

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HIGHLIGHTS

- Exposure to PM_1, $PM_{2.5}$, and PM_{10} was associated with a reduction in the eGFR level.
- Exposure to PM_1, $PM_{2.5}$, and PM_{10} was associated with an increased odds of CKD and proteinuria.
- Long-term exposure to PM may adversely affect kidney function in older adults.
- Linear regression and logistic regression models were fit in this cross-sectional study.

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ABSTRACT

Background: Accumulating studies have linked ambient particulate matter (PM) pollution to impaired kidney function, but the results are still inconsistent and the effect of particulate matter with an aerodynamic diameter ≤1 μm (PM_1) on the kidney remains less clear.

Objective: This study aimed to investigate the association of long-term exposure to ambient PM_1, particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), and particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}) with kidney function in older adults.

Methods: In this cross-sectional study, we investigated 199,635 adults who were ≥65 years and underwent physical examinations in 695 community health service centers in Shenzhen, China from 2018 to 2019. An estimated glomerular filtration rate (eGFR) of each subject was derived by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Chronic kidney disease (CKD) was defined as eGFR <60 ml/min/1.73 m^2. Proteinuria was assessed by a urine dipstick test on freshly voided urine. A validated 10 km × 10 km grid dataset was used to assess long-term residential exposure to PM_1, $PM_{2.5}$, and PM_{10} for each subject. Linear regression models and logistic regression models were implemented to quantify the association of exposure to PM with eGFR level, CKD, and proteinuria.

Results: Each 10 μg/m^3 increase of exposure to PM_1, $PM_{2.5}$, and PM_{10} was associated with a 0.9%, 2.7%, and 1.0% decrease in eGFR level, an 18%, 36%, and 17% increase in odds of CKD, and a 15%, 11%, and 10% increase

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CO, carbon monoxide; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDRD, the Modification of Diet in Renal Disease; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; PM, particulate matter; PM_1, particulate matter with an aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; Scr, serum creatinine; SD, standard deviation; SO_2, sulfur dioxide; TC, total cholesterol; TG, triglyceride.

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in odds of proteinuria, respectively (all $p < 0.05$). The associations of exposure to PM with the eGFR level and CKD were stronger among women and subjects who were aged <75 years, never smoked, and never drank alcohol.

Conclusions: Long-term exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} was significantly associated with kidney function impairment in older adults.

1. Introduction

Ambient particulate matter (PM) pollution is a critical public health challenge worldwide, which poses a range of adverse effects on morbidity and mortality from various diseases and continues to be a leading contributor to the global disease burden (GBD 2019 Risk Factors Collaborators, 2020). Substantial studies have identified detrimental effects of ambient PM on cardiovascular diseases (CVDs) and suggested that macrovascular and microvascular damage and atherosclerosis are critical mechanisms (Ain and Qamar, 2021; Gill et al., 2011; Liang et al., 2020; Tian et al., 2019). As a highly vascularized organ, the kidney can be a vulnerable target organ for PM exposures because it is susceptible to the damage and dysfunction of vascular and atherosclerosis (Chade et al., 2005; Jourde-Chiche et al., 2019). In addition, previous *in vivo* studies have suggested that exposure to PM can directly lead to the activation of proinflammatory pathways in the kidney and induce renal oxidative injuries and endothelial dysfunction, which contributed to the development and progression of chronic kidney outcomes (Aztatzi-Aguilar et al., 2016; Tavera Busso et al., 2018). As growing evidence reveals the adverse effect of ambient PM pollution on kidney outcomes, including estimated glomerular filtration rate (eGFR) decline, chronic kidney disease (CKD), proteinuria, and end-stage renal disease, the potential harmful effect of ambient PM on kidney has drawn much attention globally.

To date, epidemiological studies regarding the effect of long-term exposure to ambient PM on eGFR decline are limited, and the findings remain inconsistent. Li et al. (2021b) and Mehta et al. (2016) reported that exposure to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) was associated with a reduction in eGFR level, while studies in America (Blum et al., 2020) and Taiwan, China (Chen et al., 2018; Yang et al., 2017) did not find significant associations. Some studies have explored the association between PM and CKD, including studies in America (Blum et al., 2020; Bowe et al., 2017, 2018; Bragg-Gresham et al., 2018), Korea (Hwang et al., 2021; Jeong et al., 2020; Kim et al., 2018), and China (Bo et al., 2021; Chan et al., 2018; Chen et al., 2018; Li et al., 2021a; Liang et al., 2021; Lin et al., 2020; Yang et al., 2017), and inconsistent results were provided. A meta-analysis study summarized studies before 2020 and reported that exposure to $PM_{2.5}$ and particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}) was significantly associated with an increased risk of CKD (Ye et al., 2021). In addition, two studies in mainland China in 2021 also found significant associations between exposure to $PM_{2.5}$ and CKD (Li et al., 2021a; Liang et al., 2021). Human evidence focusing on the effect of PM exposures on proteinuria is scarce. Overall, the association of exposure to ambient $PM_{2.5}$ and PM_{10} with kidney function remains inconclusive. Compared with $PM_{2.5}$ and PM_{10}, particulate matter with an aerodynamic diameter <1 μm (PM_1) had a larger surface area to mass ratio and infiltrability, and thus had more contact with the human body (Lin et al., 2016; Yang et al., 2019). Because PM_1 can permeate into the blood circulation and reach the kidney (Filep et al., 2016; Hassanvand et al., 2017), its exposure may exert remarkably detrimental effects on kidney function. However, the association between PM_1 exposure and kidney function remains less clear.

Therefore, we conducted a large cross-sectional study among 199,635 older adults in Shenzhen, China during 2018–2019 to investigate exposure-response associations of long-term exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} with the eGFR level, CKD, and proteinuria, and quantitatively explore its susceptible populations.

2. Methods

2.1. Study design and population

In this population-based cross-sectional study, subjects were enrolled from the Elder Health Management Program in Shenzhen, China. This program is one of the ongoing National Basic Public Health Service programs administrated by the Shenzhen Center for Chronic Disease Control since 2017. Individuals who were ≥65 years and had lived in Shenzhen for at least half a year were eligible for free health management services, including an annual physical examination provided by one of 695 community health service centers in Shenzhen. The physical examination consisted of anthropometric measurements, blood and urine tests, imaging analyses, and a standard questionnaire survey. Overall, 217,882 older adults participated in the physical examination from January 1, 2018, to December 31, 2019. After excluding adults with missing or extreme values on key variables and/or test data, 199,635 older adults were included as the subjects in the final analyses (Fig. 1). A detailed flow chart showing the selection process is shown in Fig. S1. This study was approved by the Ethics Committee of the Shenzhen Center for Chronic Disease Control with a waiver of informed consent.

2.2. Exposure assessment

We obtained daily grid data (spatial resolution: 10 km × 10 km) on 24-h average PM_1, $PM_{2.5}$, PM_{10}, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) concentrations, and maximum 8-h average ozone (O_3) concentrations during 2014–2019 in Shenzhen, China from our validated ChinaHighAirPollutants (CHAP) dataset. Using our proposed prediction model, the CHAP dataset was generated to provide high-resolution and high-quality ground-level air pollutants in China (Wei et al., 2019, 2021a, 2021b, 2022). The overall cross-validated coefficient of determination (R^2) for PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 0.82, 0.91, 0.88, 0.84, 0.84, 0.80, and 0.87, respectively. According to the geocoded residential address of each subject, the daily concentrations of each pollutant from the CHAP dataset were extracted to estimate the annual average concentration up to 4 years before the date of physical examination. As proposed by previous studies, the long-term exposure in our main analyses was defined as the mean of the 1 annual average concentration before the date of physical examination (Blum et al., 2020; Chen et al., 2018; Mehta et al., 2016; Yang et al., 2017).

2.3. Outcomes

The outcomes of interest included eGFR level, CKD, and proteinuria. As a common indicator to assess kidney function, eGFR has been widely used to diagnose, stage, and manage CKD (Inker and Titan, 2021). During the physical examination, a fasting venous blood sample of each subject was collected and analyzed immediately by an automatic biochemical analyzer in the qualified laboratory of the hospital which administrated the community health service center. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$eGFR = 141 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-1.210} \times 0.993^{Age} \times 0.993\ [\text{if female}] \times 1.05\ [\text{if Asian}]$$

where *Scr* is the concentration of serum creatinine (Scr) (mg/dl); κ is 0.7 for females and 0.9 for males; α is −0.328 for females and −0.412 for males; *min* indicates the minimum of Scr/κ or 1; *max* indicates the maximum of Scr/κ or 1 (Stevens et al., 2011). The CKD-EPI equations are the most accurate glomerular filtration rate estimating equations, which are applicable for general clinical use and have been validated in the Chinese population and older adults (Levey et al., 2014; Stevens et al., 2011). CKD was defined as eGFR <60 ml/min/1.73 m^2, which represents a ≥50% reduction in normal kidney function (Levey et al., 2003). Freshly voided urine samples were collected to estimate urine protein by urine dipstick tests. The urine dipstick test for protein offers a semi-quantitative measurement of urine protein concentration (−, +/−, 1 +, 2 +, 3 +, and 4 +), and a urine dipstick reading urine protein ≥1 + was defined as proteinuria (White et al., 2011). Internal and external quality control programs were routinely performed to ensure the accuracy and stability of the measurements.

2.4. Covariates

During the physical examination, information on sex, age, race, educational attainment, occupation, cigarette smoking, alcohol consumption, physical activity, medical histories, and medication use was collected by trained medical staff using a standardized questionnaire. The status of cigarette smoking was categorized into never (never smoked in the past life), former (habitually smoked in the past but quit for at least 1 month), or current (habitually smoked currently). Alcohol consumption was classified into never (almost never), non-habitual (6 times per week to once per month), or habitual (once per day or more). Physical activity was evaluated by the frequency of moderate-to vigorous-intensity physical activities (at least some sweating and shortness of breath) per week, which was categorized into never, less than once a week, once or more a week, and every day.

Barefoot height and weight were measured with subjects wearing light clothes. Body mass index (BMI) was calculated as the weight divided by the square of the height (kg/m^2) and categorized into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30 kg/m^2) (World Health Organization, 1995). The seated blood pressure was measured twice using a calibrated sphygmomanometer, and the mean value was applied for analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg (Bakris et al., 2019), or those reporting physician-diagnosed hypertension, having a history of hospital admissions for hypertension, or using anti-hypertensive medications. Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined by a fasting venous blood sample. Diabetes was defined as FBG ≥7.0 mmol/L (Cosentino et al., 2020) or those reporting physician-diagnosed diabetes, having a history of hospital admissions for diabetes, or using anti-diabetic medications. Dyslipidemia was defined as TC ≥ 6.20 mmol/L, TG > 2.25 mmol/L, HDL-C <1.03 mmol/L, LDL-C >4.13 mmol/L (Kopin and Lowenstein, 2017), or those using medications to treat dyslipidemia.

2.5. Statistical analysis

The eGFR level was log-transformed since its distribution was approximately log-normal. To investigate the association of exposure to PM with the eGFR level, we employed linear regression models to estimate the percent change (calculated as $[\exp(\beta) - 1] \times 100$) and its 95% confidence interval (CI) of eGFR. Logistic regression models were implemented to quantify the associations of exposure to PM with CKD and proteinuria. Odds ratio (OR) and its 95% CI were estimated per 10 μg/m^3 increase of pollutant exposure. In categorical analyses, exposure to each PM was divided into 4 groups based on its quartiles and using the concentrations of the first quartile as the reference level to calculate the estimates in concentrations of the second to the fourth quartile. We included the median of each quartile range as a continuous variable in the model to examine the linear trend of estimates across quartiles of exposure. All models were adjusted for sex, age, race, educational attainment, occupation, cigarette smoking, alcohol consumption, physical activity, BMI categories, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) medication use,

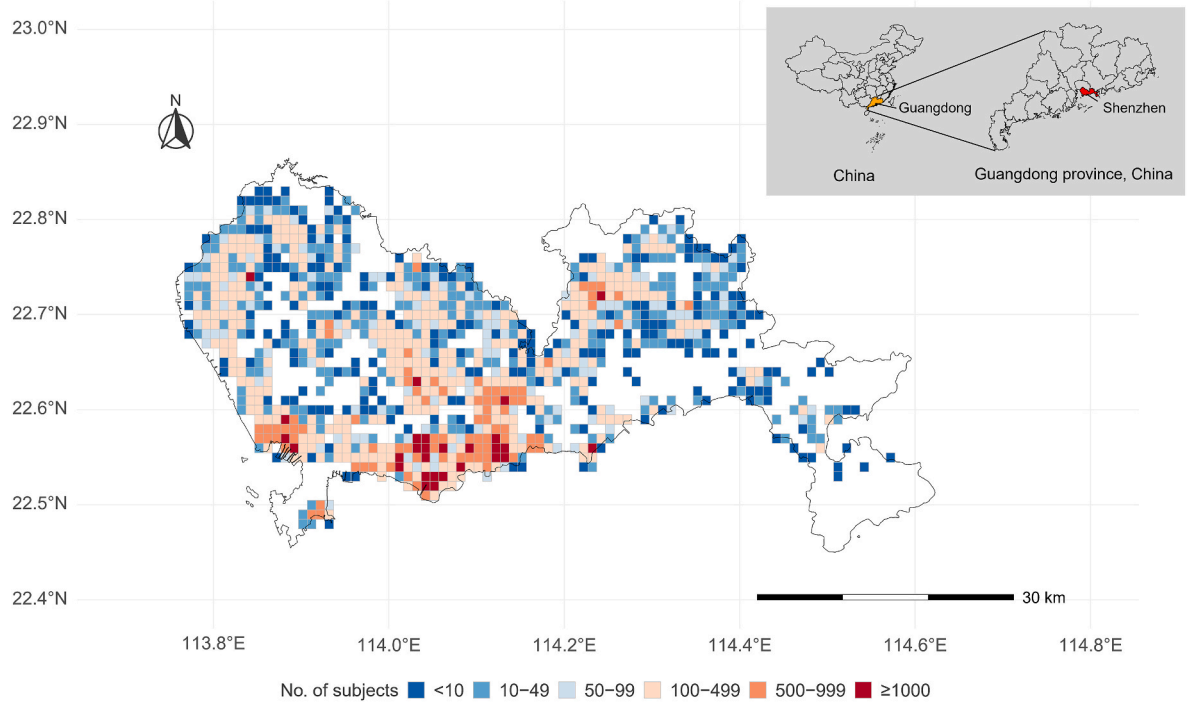

Fig. 1. Spatial distribution of 199,635 study subjects in Shenzhen, China, 2018–2019.
The grids with different colors indicate the number of study subjects at a 0.01° × 0.01° spatial resolution.

hypertension, diabetes, dyslipidemia, and season at the date of physical examination to account for potential confounding effects.

We conducted stratified analysis by sex (female, male), age (<75, ≥75 years), BMI (normal weight, overweight + obese), cigarette smoking (never, ever [former + current]), and alcohol consumption (never, ever [non-habitual + habitual]), and examined their potential effect modifications by likelihood ratio tests. The robustness of our results was evaluated by several sensitivity analyses, including 1) employing 2-pollutant models by further accounting for each exposure to SO_2, NO_2, CO, and O_3 in the same model and comparing the estimates using likelihood ratio tests; 2) using a 2-year, 3-year, or 4-year average annual concentration before the date of physical examination as the exposure metric; 3) estimating the eGFR level of each subject using the Modification of Diet in Renal Disease (MDRD) Study equation (Levey et al., 2006); 4) restricting analyses to subjects without hypertension, diabetes, or dyslipidemia; 5) adjusting for 1-year average ambient temperature and relative humidity in the models; 6) adjusting for ambient temperature and relative humidity on the date of physical examination in the models. All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the population

During the study period, we included 199,635 subjects with an average age of 70.9 years (standard deviation [SD]: 5.5 years), ranging from 65.0 to 109.2 years (Table 1). Most subjects never smoked (84.6%, n = 168,794) nor drank alcohol (84.4%, n = 168,433). Subjects with hypertension, diabetes, and dyslipidemia accounted for 61.0%, 27.9%, and 45.8% of all subjects, respectively. Mean eGFR of all subjects was 81.45 ml/min/1.73 m^2 (SD: 16.96 ml/min/1.73 m^2), and 11.1% (n = 22,231) and 8.9% (n = 17,792) of all subjects were classified as having CKD and proteinuria, respectively. The mean exposure to PM_1, $PM_{2.5}$, and PM_{10} were 17.54 μg/m^3 (SD: 3.62 μg/m^3), 28.21 μg/m^3 (SD: 3.89 μg/m^3), and 46.72 μg/m^3 (SD: 5.29 μg/m^3), respectively. PM_1, $PM_{2.5}$, PM_{10}, and SO_2 exposures were positively correlated with pairwise correlation coefficients higher than 0.60 (all $p < 0.05$) (Table S1).

Table 1
Characteristics of study subjects in Shenzhen, China, 2018–2019.

Characteristic	Value		
	Overall	Non-CKD	CKD
No. of subjects	199,635	177,404	22,231
Sex, male[a]	87,977 (44.1)	78,814 (44.4)	9163 (41.2)
Age, years[a]			
65-69	110,862 (55.5)	103,969 (58.6)	6893 (31.0)
70-74	47,632 (23.9)	42,419 (23.9)	5213 (23.4)
75-79	23,915 (12.0)	19,368 (10.9)	4547 (20.5)
≥80	17,226 (8.6)	11,648 (6.6)	5578 (25.1)
Race, Han[a]	198,650 (99.5)	176,505 (99.5)	22,145 (99.6)
Educational attainment[a]			
Lower than high school	144,357 (72.3)	128,960 (72.7)	15,397 (69.3)
High school or higher	52,745 (26.4)	46,206 (26.0)	6539 (29.4)
Unknown	2533 (1.3)	2238 (1.3)	295 (1.3)
Occupation, employed[a]	78,371 (39.3)	68,927 (38.9)	9444 (42.5)
Cigarette smoking[a]			
Non-smoker	168,794 (84.6)	149,361 (84.2)	19,433 (87.4)
Former smoker	12,961 (6.5)	11,676 (6.6)	1285 (5.8)
Current smoker	17,880 (9.0)	16,367 (9.2)	1513 (6.8)
Alcohol consumption[a]			
Non-drinker	168,433 (84.4)	148,851 (83.9)	19,582 (88.1)
Non-habitual drinker	21,719 (10.9)	19,803 (11.2)	1916 (8.6)
Habitual drinker	9483 (4.8)	8750 (4.9)	733 (3.3)
Physical activity[a]			
Never	31,881 (16.0)	27,894 (15.7)	3987 (17.9)
Lower than once a week	16,154 (8.1)	14,220 (8.0)	1934 (8.7)
Once or more a week	20,866 (10.5)	18,443 (10.4)	2423 (10.9)
Every day	130,734 (65.5)	116,847 (65.9)	13,887 (62.5)
BMI[a]			
Underweight	7477 (3.7)	6637 (3.7)	840 (3.8)
Normal weight	125,629 (62.9)	112,115 (63.2)	13,514 (60.8)
Overweight	59,827 (30.0)	52,841 (29.8)	6986 (31.4)
Obese	6702 (3.4)	5811 (3.3)	891 (4.0)
ACEI or ARB medication use[a]	32,305 (16.2)	26,710 (15.1)	5595 (25.2)
Hypertension[a]	121,681 (61.0)	105,258 (59.3)	16,423 (73.9)
Diabetes[a]	55,642 (27.9)	47,465 (26.8)	8177 (36.8)
Dyslipidemia[a]	91,517 (45.8)	79,858 (45.0)	11,659 (52.4)
Proteinuria[a]	17,792 (8.9)	13,430 (7.6)	4362 (19.6)
Season at physical examination[a]			
Spring	79,018 (39.6)	70,144 (39.5)	8874 (39.9)
Summer	62,647 (31.4)	54,999 (31.0)	7648 (34.4)
Autumn	44,951 (22.5)	40,442 (22.8)	4509 (20.3)
Winter	13,019 (6.5)	11,819 (6.7)	1200 (5.4)

Value as n or n (%).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease.
[a] The distribution was significantly different between non-CKD subjects and CKD subjects.

3.2. Associations of exposure to PM with the eGFR level, CKD, and proteinuria

As shown in Table 2, long-term exposure to PM_1, $PM_{2.5}$, and PM_{10} was consistently associated with a lower eGFR level. Each 10 μg/m^3 increase of exposure to PM_1, $PM_{2.5}$, and PM_{10} was significantly associated with a 0.9%, 2.7%, and 1.0% reduction in eGFR level, respectively (all $p < 0.05$). In the categorical analyses, we observed that the percent change of the eGFR level decreased across quartiles of exposure to all air pollutants (p for linear trend <0.05).

Long-term exposure to PM_1, $PM_{2.5}$, and PM_{10} was consistently associated with increased odds of CKD and proteinuria (Table 3). Each 10 μg/m^3 increase of exposure to PM_1, $PM_{2.5}$, and PM_{10} was significantly associated with an 18%, 36%, and 17% increase in odds of CKD and a 15%, 11%, and 10% increase in odds of proteinuria, respectively. The categorical analyses yielded increasing trends of the ORs across quartiles of exposure to all pollutants (all p for linear trend <0.05).

3.3. Stratified analysis and sensitivity analysis

In the stratified analysis, we observed significantly stronger associations of exposure to PM_1, $PM_{2.5}$, and PM_{10} with the eGFR level and CKD among women and subjects who were <75 years, never smoked, and never drank alcohol (p for effect modification <0.05) (Tables S2 and 4). We identified significantly stronger associations of exposure to PM_1, $PM_{2.5}$, and PM_{10} with proteinuria in women and exposure to PM_1 with proteinuria in subjects who never smoked (p for effect modification <0.05).

In the sensitivity analysis, the associations of exposure to $PM_{2.5}$ and PM_{10} with CKD remained significant when adjusting for NO_2, CO and O_3 (Table S3). We did not identify significant association between exposure to PM_1 and CKD when exposure to CO or O_3 was included. When adjusting for SO_2 exposure, no significant association between $PM_{2.5}$ exposure and CKD was found, and the associations of exposure to PM_1 and PM_{10} with CKD gave reverse results to the single-pollutant models. The associations of PM_1, $PM_{2.5}$, PM_{10} exposures with proteinuria remained significant with further adjustment for exposure to SO_2, NO_2, CO and O_3. Compared with the results of applying a 2- to 4-year mean annual concentration as the exposure metric, we identified the strongest estimates on the associations of 1-year exposure to PM_1, $PM_{2.5}$, and PM_{10} with CKD (Table S4). Exposure to all pollutants was significantly associated with increased odds of proteinuria when using a 1- to 4-year average annual concentration. Using the MDRD Study equation to estimate the eGFR level gave significant results and slightly lower reductions of eGFR compared with the main analyses (Table S5). We did not find a significant association between PM_1 exposure and eGFR when the MDRD Study equation was applied. Restricting subjects to those

Table 2
Estimated percent change (95% CI) of eGFR associated with long-term exposure to ambient particulate matter in Shenzhen, China, 2018–2019.

Pollutant	Per 10μg/m^3 increase	Quartile of exposure				
		Quartile 1 (Reference)	Quartile 2	Quartile 3	Quartile 4	*p* for linear trend
PM_1	−0.9 (−1.2, −0.6)	0	−1.5 (−1.8, −1.2)	−1.9 (−2.2, −1.6)	−1.2 (−1.5, −0.9)	<0.001
$PM_{2.5}$	−2.7 (−2.9, −2.4)	0	−0.5 (−0.8, −0.2)	−3.1 (−3.4, −2.8)	−1.1 (−1.4, −0.8)	<0.001
PM_{10}	−1.0 (−1.2, −0.8)	0	−3.1 (−3.4, −2.8)	−0.7 (−1.0, −0.4)	−1.3 (−1.6, −1.0)	<0.001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; PM_1, particulate matter with an aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm.

Table 3
Estimated odds ratio (95% CI) of CKD and proteinuria associated with long-term exposure to ambient particulate matter in Shenzhen, China, 2018–2019.

	Pollutant	Per 10 μg/m^3 increase	Quartile of exposure				
			Quartile 1 (Reference)	Quartile 2	Quartile 3	Quartile 4	*p* for linear trend
CKD	PM_1	1.18 (1.13, 1.23)	1	1.23 (1.18, 1.28)	1.22 (1.16, 1.27)	1.23 (1.17, 1.28)	<0.001
	$PM_{2.5}$	1.36 (1.31, 1.41)	1	1.11 (1.06, 1.16)	1.34 (1.29, 1.40)	1.21 (1.16, 1.27)	<0.001
	PM_{10}	1.17 (1.14, 1.20)	1	1.29 (1.23, 1.34)	1.15 (1.11, 1.20)	1.23 (1.18, 1.28)	<0.001
Proteinuria	PM_1	1.15 (1.10, 1.20)	1	1.09 (1.04, 1.14)	1.03 (0.98, 1.08)	1.18 (1.13, 1.23)	<0.001
	$PM_{2.5}$	1.11 (1.07, 1.16)	1	1.11 (1.06, 1.16)	0.99 (0.95, 1.04)	1.15 (1.10, 1.20)	<0.001
	PM_{10}	1.10 (1.07, 1.14)	1	1.02 (0.97, 1.06)	1.09 (1.05, 1.15)	1.13 (1.08, 1.18)	<0.001

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; PM_1, particulate matter with an aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm.

without hypertension, diabetes, or dyslipidemia yielded higher estimates compared with the results with all subjects included (Tables S6 and S7). Similar results were observed when further adjusting for ambient temperature and relative humidity (Tables S8–S11).

4. Discussion

In this large cross-sectional study on approximately 0.2 million older adults in Shenzhen, China, we quantitatively investigated the chronic effects of ambient PM_1, $PM_{2.5}$, and PM_{10} on eGFR, CKD, and proteinuria. We found that long-term exposure to PM_1, $PM_{2.5}$, and PM_{10} was significantly associated with a reduction in eGFR level and an increased odds of CKD and proteinuria, suggesting that exposure to ambient PM can adversely affect kidney function in older adults. These associations were generally stronger among women and those who were less than 75 years, never smoked, and never drank alcohol.

The association between PM and the eGFR level has been investigated in a few studies. A cross-sectional study including 2,546,047 young adults (aged 18–45 years) in China found that each 10 μg/m^3 increase in 1-year average exposure to ambient PM_1 and $PM_{2.5}$ was significantly associated with a 0.64% and 0.72% reduction of eGFR level, respectively (Li et al., 2021b) (mean exposure to PM_1 and $PM_{2.5}$ were 46.8 and 60.9 μg/m^3, respectively), which were close to our estimates. Similar findings were also reported in United States veterans (Mehta et al., 2016). In contrast, a study in America (mean age: 63 years) reported that no significant association was identified between exposure to $PM_{2.5}$ and eGFR, and the inconsistency may attribute to the low $PM_{2.5}$ exposures in this study (<20 μg/m^3) (Blum et al., 2020). Studies in Shanghai (Wang et al., 2020) and Taiwan (Chen et al., 2018; Yang et al., 2017), China also did not identify a significant association between exposure to $PM_{2.5}$ and eGFR. Exposure to PM_{10} was significantly associated with a reduced eGFR level in previous studies (Chen et al., 2018; Kim et al., 2018; Paoin et al., 2021; Wang et al., 2020; Yang et al., 2017), which was consistent with our findings. Previous studies on the associations of exposure to PM with CKD mainly focused on $PM_{2.5}$ and PM_{10}. Consistent with our study, Liang et al. (2021) and Li et al. (2021a) found that each 10 μg/m^3 increase in $PM_{2.5}$ exposure was significantly associated with a 24% and 28% increase in odds of CKD in China, although the estimates were lower than our result (38%). Subjects in these two studies were selected from 13 provinces in China with the age >18 years and the $PM_{2.5}$ exposure was obviously higher than us (median exposure to $PM_{2.5}$ were 44.63 μg/m^3 and 57.4 μg/m^3, respectively), which may in part contribute to the high heterogeneity in comparison with our study. Significant associations between exposure to $PM_{2.5}$ and incident CKD were found in several cohort studies (Blum et al., 2020; Bowe et al., 2018; Chan et al., 2018; Lin et al., 2020). However, the two studies in Taiwan, China did not identify a significant association between $PM_{2.5}$ and CKD in older adults (Chen et al., 2018; Yang et al., 2017). As for PM_{10}, consistent with our results, both the studies in Taiwan, China found that each 10 μg/m^3 increase in PM_{10} exposure was significantly associated with a 27% increase in odds of CKD (Chen et al., 2018; Yang et al., 2017); however, the study in Korea did not found a significant association between PM_{10} and CKD (Kim et al., 2018), which may be attributed to the differences in exposure assessment strategies (city-level exposures). Few studies explored the associations of exposure to PM with proteinuria. Li et al. (2021a) defined proteinuria by urinary albumin-creatinine ratio and found a significant association between exposure to $PM_{2.5}$ and proteinuria (OR = 1.40 per 10 μg/m^3 increase of $PM_{2.5}$ exposure), which was consistent with our study. However, Chen et al. (2018) did not identify a significant association of exposure to $PM_{2.5}$ and PM_{10} with proteinuria in older adults.

Although the exact biological mechanisms for the association between PM exposures and kidney function impairment remain less clear, nephrotoxicity attributed to PM may partially share the pathway of PM-related CVDs. Extensive evidence shows that exposure to PM can lead to oxidative stress, systemic inflammation, endothelial changes, and further accelerate atherosclerosis, which may contribute to kidney injuries (Aztatzi-Aguilar et al., 2016; Feng et al., 2016). A recent *in vivo* study reported that exposure to $PM_{2.5}$ induced early renal tubule cell injury, contributing to epithelial-mesenchymal transition change and interstitial fibrosis in the kidney, and further developing into chronic organic damage (Lin et al., 2021). In addition, some toxic components of PM can accumulate and concentrate on the kidney (Li et al., 2015), which may lead to kidney function impairment. For example, mercury, cadmium, and lead are common constituents of PM, which are well-recognized toxins to cause kidney injuries (Harari et al., 2018; Hodgson et al., 2007; Satarug et al., 2010). Moreover, we found PM with different particle size did not exert identical effect on the kidney function, which may ascribe to the heterogeneity in toxic constituents and emission sources of PM (Lin et al., 2016). The variety on mechanisms of particle deposition in human body also may be a reason to different hazardous effects caused by PM, which depended on the particle size,

Table 4
Estimated odds ratio (95% CI) of CKD and proteinuria associated with each 10 μg/m^3 increase of exposure to ambient particulate matter in stratified analyses in Shenzhen, China, 2018–2019.

Subgroups	CKD			Proteinuria		
	PM_1	$PM_{2.5}$	PM_{10}	PM_1	$PM_{2.5}$	PM_{10}
Sex						
Female	1.36 (1.28, 1.43)[a]	1.65 (1.57, 1.74)[a]	1.33 (1.28, 1.38)[a]	1.20 (1.13, 1.27)[a]	1.16 (1.09, 1.22)[a]	1.13 (1.08, 1.18)[a]
Male	0.96 (0.90, 1.03)[a]	1.03 (0.97, 1.09)[a]	0.97 (0.93, 1.02)[a]	1.09 (1.02, 1.16)[a]	1.07 (1.01, 1.14)[a]	1.07 (1.02, 1.12)[a]
Age						
<75 years	1.24 (1.18, 1.31)[a]	1.43 (1.36, 1.50)[a]	1.21 (1.17, 1.26)[a]	1.13 (1.08, 1.19)	1.11 (1.06, 1.16)	1.10 (1.06, 1.14)
≥75 years	1.07 (1.00, 1.14)[a]	1.24 (1.16, 1.31)[a]	1.10 (1.05, 1.15)[a]	1.19 (1.09, 1.30)	1.12 (1.03, 1.22)	1.10 (1.03, 1.17)
BMI						
Normal weight	1.16 (1.10, 1.23)	1.33 (1.27, 1.40)	1.15 (1.11, 1.19)	1.20 (1.13, 1.27)	1.15 (1.09, 1.22)	1.13 (1.08, 1.18)
Overweight + Obese	1.20 (0.97, 1.48)	1.36 (1.12, 1.65)	1.15 (1.00, 1.33)	1.15 (0.94, 1.40)	1.17 (0.98, 1.41)	1.14 (1.00, 1.31)
Cigarette smoking						
Never	1.21 (1.16, 1.27)[a]	1.43 (1.37, 1.49)[a]	1.21 (1.17, 1.24)[a]	1.17 (1.11, 1.23)[a]	1.13 (1.08, 1.18)	1.11 (1.07, 1.15)
Ever	0.97 (0.86, 1.09)[a]	1.01 (0.91, 1.12)[a]	0.96 (0.89, 1.04)[a]	1.03 (0.93, 1.15)[a]	1.04 (0.94, 1.15)	1.06 (0.98, 1.14)
Alcohol consumption						
Never	1.19 (1.14, 1.25)[a]	1.39 (1.33, 1.45)[a]	1.18 (1.15, 1.22)[a]	1.16 (1.10, 1.21)	1.12 (1.07, 1.17)	1.11 (1.07, 1.14)
Ever	1.07 (0.95, 1.21)[a]	1.17 (1.04, 1.30)[a]	1.06 (0.98, 1.16)[a]	1.08 (0.97, 1.21)	1.08 (0.97, 1.20)	1.08 (1.00, 1.17)

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; PM_1, particulate matter with an aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm.

[a] Significantly different associations by a given stratification variable ($p < 0.05$).

shape, density, airway geometry, and breathing pattern (Kodros et al., 2018). Further studies are needed to elucidate underlying biological mechanisms.

We found that women were more susceptible to PM exposures on the kidney function, which was also observed in the two studies in China (Li et al., 2021b; Yang et al., 2017). A comprehensive analysis reported that the prevalence of CKD among adults living in 32 high-income and low- and middle-income countries was higher in women than that in men (Mills et al., 2015), and therefore women may be more vulnerable to PM-induced kidney function impairment. Another reason proposed by previous studies for the susceptibility in women was that they had slightly greater airway reactivity and deposition of particles in lung than men (Li et al., 2021b; Zhang et al., 2018). Furthermore, the associations of exposure to PM_1, $PM_{2.5}$, and PM_{10} with the eGFR level and CKD appeared to be consistently stronger for younger subjects (<75 years old) than older subjects (≥75 years old). The exact mechanism underlying the effect modification was not fully understood. Younger individuals may sustain longer exposure to ambient PM due to more ambient physical activity time. Since PM exposures were estimated at fixed residential addresses, the activity patterns of subjects were not considered in our study. In addition, older individuals may have more comorbidities, which may dominate the major effect of kidney function impairment, thus the adverse effect of PM on the kidney was partly masked (Li et al., 2021a). As shown in the sensitivity analyses, restricting subjects to those without hypertension, diabetes, or dyslipidemia gave higher estimates.

Stronger associations were identified among subjects who never smoked and never consumed alcohol compared with their counterparts. Previous studies reported stronger associations between exposure to PM_{10} and CKD in subjects who never smoked (Yang et al., 2017) and stronger associations of exposure to PM_1 and $PM_{2.5}$ with eGFR decline in subjects who never smoked and never drank alcohol (Li et al., 2021b). The biological mechanism to the effect modification remained unclear. Cigarette smoking and alcohol consumption are acknowledged factors to induce systematic oxidative stress and inflammation (Burke and Fitzgerald, 2003; Wu and Cederbaum, 2003), which may share similar toxic pattern of PM exposures and play a dominant role in smokers or drinkers. Therefore, additional PM exposures might not further boost the adverse effect on kidney function through the same mechanisms (Li et al., 2021b; Zhang et al., 2018).

When using the MDRD Study equation to estimate eGFR, we found slightly lower reductions of eGFR compared with applying CKD-EPI equation, and we did not observe significant association between PM_1 and eGFR. CKD-EPI equation and MDRD Study equation are both common approaches to estimate eGFR level in clinical practice (Chan et al., 2018; Mehta et al., 2016; Wang et al., 2020). However, as previous studies proposed, the MDRD Study equation performed less accurate than CKD-EPI equation, especially at relatively higher levels of glomerular filtration rate and in populations without CKD (Stevens et al., 2011; Wang et al., 2020). In our study, eGFR values assessed by MDRD Study equation were obviously higher than that assessed by CKD-EPI equation in CKD subjects (mean: 89.05 vs 85.43 ml/min/1.73 m^2) and slightly higher in non-CKD subjects (mean: 50.34 vs 49.73 ml/min/1.73 m^2). Therefore, the application of MDRD Study equation made it more difficult to detect significant reductions in eGFR caused by PM exposures. In addition, we found that the associations of PM exposures with CKD were affected by adjustment for SO_2, which may largely ascribe to the high correlations between PM and SO_2 (correlation coefficients: 0.74–0.81), and thus the effects of PM and SO_2 were difficult to separate (Li et al., 2021c).

Our findings add to the current body of studies by providing further supportive evidence for the detrimental effect of ambient PM exposures on kidney function. In addition, we identified the significant association between exposure to PM_1 and kidney function impairment, which was rarely explored previously. Compared with the conventional risk factors to reduced kidney function, ambient PM pollution may be a factor that is relatively lacking awareness to associate with kidney function impairment, and therefore we hope our findings draw the public concern of the adverse effects of PM exposures on kidney function in older adults.

This study has several strengths. First, taking advantage of the large sample size (approximate 0.2 million), we can better characterize the association between ambient PM exposures and kidney function with sufficient statistical power and representative estimates. Second, we assessed PM exposures up to 4-year period at residential addresses with a validated grid air pollution dataset. This approach enabled us to conduct individual-level exposure assessment with relatively higher accuracy compared with previous studies that applied data from one single or several air quality monitoring stations in a city as a proxy for individual-level exposure. Third, to minimize confounding effects and yield accurate estimates, we took into consideration a wide range of factors that may confound the associations between PM exposures and the kidney function, including socioeconomic status, lifestyle factors, clinical conditions, and medication use.

Some limitations should be acknowledged in our study. First, the cross-sectional design of this study limits our ability to provide strong causal-inference evidence because only a single measurement was applied. However, as we assessed the PM exposures of subjects up to 4 years before the date of physical examination, the period of CKD or proteinuria subjects from health status to morbid status was very

probable to be included. Therefore, the temporality between PM exposures and disease occurrence was likely to established in most subjects. Even so, the results in our study still need to be interpreted with caution because of the cross-sectional nature. Second, given that our findings were based on a sample of individuals ≥65 years, the generalization of our results is limited to older adults only. Moreover, as the exposure range of PM was relatively narrow in our study, additional investigations are required to confirm whether our results can be extrapolated to other regions or countries. Third, we included individuals who lived in Shenzhen for at least half a year to determine if the individual was a permanent resident, which has been widely applied in studies in China. It is possible that some subjects in our study lived in Shenzhen less than 1 year, which may lead to exposure misclassification. However, the number of these subjects may be considerably small because all subjects were older adults aged ≥65 years who were unlikely to move frequently, which may not exert a remarkable effect on the associations. Fourth, a single value of eGFR <60 ml/min/1.73 m^2 was utilized to define CKD, which is commonly applied in large-scale epidemiological studies. However, this definition is different from the diagnosis of CKD in clinical practices (requiring 2 measurements of eGFR <60 ml/min/1.73 m^2 separated by at least 90 days), and therefore misclassification may exist. Additionally, Scr and urine protein was estimated based on a single measurement, which may be interfered with by various causes, including dietary habits, acute kidney injury, and nephrotoxic exposures.

5. Conclusions

We found that long-term exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} was significantly associated with a reduction in eGFR level and an increased odds of CKD and proteinuria, suggesting that exposure to PM can adversely affect kidney function in older adults. These findings add to the understanding of chronic adverse effects of exposure to ambient PM_1, $PM_{2.5}$, and PM_{10} on kidney function. Our study highlights the necessity to encourage public health efforts on reducing ambient PM exposures to prevent kidney function impairment among older adults. Further studies were warranted to confirm our findings in other populations and regions.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2022.119535.

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