

Long-Term Exposure to Ambient Fine Particulate Matter and Chronic Kidney Disease: A Cohort Study

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BACKGROUND: Chronic kidney disease (CKD) is a serious global public health challenge, but there is limited information on the connection between air pollution and risk of CKD.

OBJECTIVE: The aim of this study was to investigate the association between long-term exposure to particulate matter (PM) with an aerodynamic diameter of less than 2.5 μm (PM_{2.5}) and the development of CKD in a large cohort.

METHODS: A total of 100,629 nonCKD Taiwanese residents age 20 y or above were included in this study between 2001 and 2014. Ambient PM_{2.5} concentration was estimated at each participant's address using a satellite-based spatiotemporal model. Incident CKD cases were identified by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m². We collected information on a wide range of potential confounders/modifiers during the medical examinations. Cox proportional hazard regression was applied to calculate hazard ratios (HRs).

RESULTS: During the follow-up, 4,046 incident CKD cases were identified, and the incidence rate was 6.24 per 1,000 person-years. In contrast with participants with the first quintile exposure of PM_{2.5}, participants with the fourth and fifth quintiles exposure of PM_{2.5} had increased risk of CKD development, adjusting for age, sex, educational level, smoking, drinking, body mass index, systolic blood pressure, fasting glucose, total cholesterol, and self-reported heart disease or stroke, with an HR [95% confidence interval (CI)] of 1.11 (1.02, 1.22) and 1.15 (1.05, 1.26), respectively. A significant concentration–response trend was observed ($p < 0.001$). Every 10 $\mu\text{g}/\text{m}^3$ increment in the PM_{2.5} concentration was associated with a 6% higher risk of developing CKD (HR: 1.06, 95% CI: 1.02, 1.10). Sensitivity and stratified analyses yielded similar results.

CONCLUSIONS: Long-term exposure to ambient PM_{2.5} was associated with an increased risk of CKD development. Our findings reinforce the urgency to develop global strategies of air pollution reduction to prevent CKD. <https://doi.org/10.1289/EHP3304>

Introduction

Chronic kidney disease (CKD) represents a serious global public health challenge and is increasingly prevalent in both developed and developing countries. The Global Burden of Disease Study 2015 estimated that deaths from CKD had increased by 31.7% from 0.9 million in 2005 to 1.2 million in 2015 and ranked as the 17th leading cause of death worldwide (GBD 2015; Mortality and Causes of Death Collaborators 2016). The most severe stage of CKD, end-stage renal disease, requires costly dialysis or transplant, seriously affects patients' quality of life, and results in an enormous economic burden. Besides itself posing a direct threat, CKD is also closely associated with other forms of morbidity, especially cardiovascular disease, the leading global cause of death

(Gansevoort et al. 2013). The cardiovascular mortality rate is about two to three times higher in patients with stage 3 or 4 CKD than in those with normal kidney function [Kidney Disease: Improving Global Outcomes (KDIGO) Work Group 2013; Chronic Kidney Disease Prognosis Consortium 2010].

The traditional cardiovascular risk factors, such as obesity, hypertension and diabetes, are also CKD risk factors. Air pollution has been regarded as a novel risk factor for cardiovascular diseases. Exposure to PM with an aerodynamic diameter of less than 2.5 μm (PM_{2.5}) is causally associated with an increased risk of cardiovascular diseases (Brook et al. 2010). However, there is limited information about CKD and air pollution. To our knowledge, published research on the association between air pollution and incident CKD is limited to analyses of data from a cohort of U.S. veterans (Bowe et al. 2017, 2018). We therefore conducted a large cohort study to investigate the association between long-term exposure to PM_{2.5} and the development of CKD in 100,629 adults in Taiwan.

Methods

Study Participants

The participants included in this study were drawn from a large cohort in Taiwan. The details of the cohort have been described in previous publications (Zhang et al. 2017; Wen et al. 2008; Zhang et al. 2018; Chang et al. 2016). Briefly, more than 0.5 million Taiwanese people participated in a standard medical examination program run by a private firm (MJ Health Management Institution, Taipei, Taiwan) from 1994 to 2014 (Chang et al. 2016). The participants received a series of

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medical examinations, including general physical examination, anthropometric measurements, and functional tests of blood and urine. They also took part in a standard self-administered questionnaire survey during each visit and were encouraged to visit the medical center annually. All procedures of the program were approved in accordance with ISO 9001 standards (Chang et al. 2016). Each participant gave written consent prior to participation to authorize the use of data generated from the medical examination program. Personal identification was removed, and the data remained anonymous when released for research purposes. Ethical approval for this study has been obtained from the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee.

The details of participant selection for the present study are shown in Figure 1. The cohort database accumulated 590,976 participants between 1996 and 2014 (the questionnaire data have been computerized since 1996). We selected 432,433 participants who joined the program between 2001 and 2014, when the 2-y average $PM_{2.5}$ exposure assessment was available. We computed their estimated glomerular filtration rate (eGFR) based on their serum creatinine level using the equation from the Modification of Diet in Renal Disease (MDRD) Study (National Kidney Foundation 2002). We excluded 3,375 participants with an $eGFR \geq 200$ mL/min/1.73 m² or < 2 mL/min/1.73 m² because the values suggested that the measurements were probably incorrect due to occasional technical errors (Levey et al. 2009). We further excluded participants

who had made only one medical visit. After these exclusions, 159,944 participants were selected. We then limited the cohort to participants without CKD at baseline by excluding those with an $eGFR \leq 60$ mL/min/1.73 m² [Kidney Disease: Improving Global Outcomes (KDIGO) Work Group 2013] or who reported physician-diagnosed kidney disease at their first visit. Because urinary protein is also an important syndrome for CKD, we also excluded those with urinary protein level ≥ 2.0 g/L at baseline, leaving 147,658 participants without prevalent CKD who were ≥ 20 years of age at baseline and had complete data for key variables, including demographics, socioeconomic status, lifestyle, blood tests, and $PM_{2.5}$ exposure. Finally, we excluded participants with < 3 years of follow-up, resulting in a final cohort of 100,629 participants enrolled between 2001 and 2011 for the present analysis. The follow-up duration of the 100,629 participants ranged from 3.0 to 13.0 y (mean, 6.5 y). The number of medical visits ranged from 2 to 18, with a mean of 4.2, totaling 424,455 medical observations. The mean \pm SD visit interval was 2.0 ± 1.5 y. The selection process did not bring in substantial differences among the participants in terms of the distribution of age, sex, and cardiovascular risk factors (Table S1).

Air Pollution Exposure Assessment

The details for estimation of $PM_{2.5}$ air pollution have been described elsewhere (Zhang et al. 2017). In brief, $PM_{2.5}$ exposure was estimated at each participant's address using a satellite-based spatio-temporal model with a high spatial resolution of 1 km \times 1 km based on the aerosol optical depth data, which were derived from the two Moderate Resolution Imaging Spectroradiometer (MODIS) instruments aboard Terra and Aqua satellites from the U.S. National Aeronautics and Space Administration (Li et al. 2005; Lin et al. 2015). We have validated this model with ground-measured data from more than 70 monitoring stations in Taiwan, and the results are presented elsewhere (Zhang et al. 2017). The correlation coefficients between the average satellite-retrieved and ground-level monitoring $PM_{2.5}$ concentrations ranged from 0.79 to 0.83 in different years, and the mean percentage errors were around 20%.

The participants' residential addresses were usually collected during each medical visit so the medical report could be mailed to them. Some participants provided a company address instead of a residential address. The address was geocoded into latitude and longitude data, and address-specific yearly average $PM_{2.5}$ concentrations were then calculated. For participants who provided their company address, $PM_{2.5}$ was estimated at their company address. We estimated the annual average $PM_{2.5}$ concentrations for the calendar year of each participant's medical examination and the annual average for the previous year. The mean of these two averages (2-y average) was then calculated as an indicator of long-term exposure to ambient $PM_{2.5}$ air pollution in this study. The baseline 2-y average $PM_{2.5}$ concentrations (hereafter called "baseline $PM_{2.5}$ exposure") thus referred to average of the enrollment year and the previous year. The follow-up 2-y average $PM_{2.5}$ concentrations (hereafter called "follow-up $PM_{2.5}$ exposure") referred to average of the follow-up medical examination year and the previous year.

Health Outcome and Covariates

An overnight fasting blood sample was taken in the morning, and the serum creatinine was analyzed using a HITACHI 7150 (before 2005) or a TOSHIBA C8000 (after 2005) analyzer with the uncompensated Jaffe method involving an alkaline picrate kinetic test (Myers et al. 2006). The eGFR level was calculated based on the following MDRD equation:

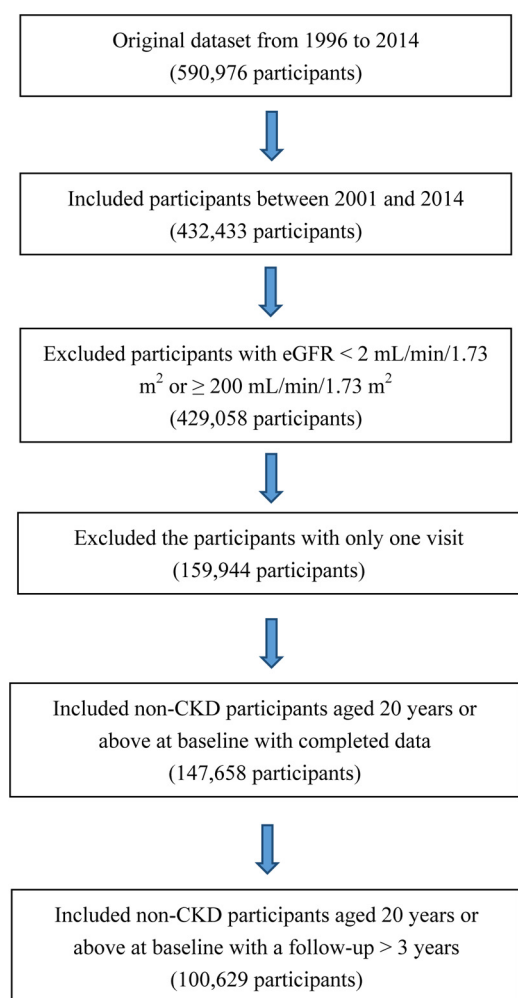


Figure 1. Flowchart of participant selection.

$$186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women})$$

where serum creatinine is in mg/dL.

Health outcome is incident CKD in the present study. After the baseline assessment at the first visit, all participants were followed up, and the incident CKD was identified by medical assessment (defined as eGFR less than 60 mL/min/1.73 m²) in subsequent visits [Kidney Disease: Improving Global Outcomes (KDIGO) Work Group 2013]. The end point was the first occurrence of CKD or the last visit if CKD did not occur.

In addition to serum creatinine measurement, the participants underwent a number of other medical examinations during their visits. The procedures of the medical examination program in this population have been described in previous publications (Zhang et al. 2017; Wen et al. 2008; Chang et al. 2016; Zhang et al. 2018). All examinations or tests were performed by trained medical professionals, and detailed information, including information on quality control, can be accessed in the technical reports released by the MJ Health Research Foundation (Chang et al. 2016).

A wide range of potential confounders or modifiers were considered. Weight (to the nearest 0.1 kg) and barefoot height (to the nearest 0.1 cm) were measured with participants wearing light clothes using an auto-anthropometer (KN-5000A, Nakamura). Seated blood pressure was measured using a computerized auto-mercury sphygmomanometer (CH-5000, Citizen). An overnight fasting blood sample was also taken to measure total cholesterol using an auto-analyzer (7150, Hitachi). Urinary protein was analyzed using a ROCHE Miditron/ROCHE Cobas U411 semiautomated computer-assisted urinalysis system. Urinary protein results were reported at six levels: negative (<0.1 g/L), trace (0.1 ~ 0.2 g/L), 1 plus (0.2 ~ 1.0 g/L), 2 plus (1.0 ~ 2.0 g/L), 3 plus (2.0 ~ 4.0 g/L), and 4 plus (>4.0 g/L).

A self-administered questionnaire was used to collect information on demographic characteristics, occupational exposure, lifestyle, and medical history.

The following covariates were included in the data analysis: age (years), sex (male and female), education level [lower than high school (<10 y), high school (10–12 y), college or university (13–16 y) and postgraduate (>16 y)], smoking (never, ever, and current), and drinking (<once/week, 1–3 times/wk, and >3 times/wk), body mass index [BMI, calculated as weight (kg) divided by the square of height (m)], systolic blood pressure (mmHg), fasting glucose (mg/dL), total cholesterol (mg/dL), self-reported heart disease or stroke (yes or no), and urinary protein (at four levels: negative, trace, 1 plus, and 2 plus; participants with a level of 3 plus or above were excluded, as mentioned above).

Statistical Analysis

We applied the Cox proportional hazard regression to investigate the association between PM_{2.5} and the incidence of CKD. The time scale used in the models was time-in-study (i.e., follow-up time). Five models were developed with the use of covariates from baseline visits: *a*) a crude model, with no adjustment; *b*) Model 1, adjusted for age, sex, education level, smoking, and drinking; *c*) Model 2, further adjusted for BMI, systolic blood pressure, fasting glucose, total cholesterol, and self-reported heart disease or stroke; *d*) Model 3, further adjusted for baseline eGFR level (a major determinant of kidney outcomes) (Tangri et al. 2011); and *d*) Model 4, further adjusted for the urinary protein level to observe its effects on the associations, because the urinary protein level is an important indicator for evaluation of renal function and the progress of CKD (Wen et al. 2008). We used the results from Model 2 as our main model, because both eGFR and urinary protein levels might

be precursors of CKD. The hazard ratio (HR) and 95% confidence interval (CI) were calculated to indicate the PM_{2.5} effects. The participants were categorized into five groups based on quintiles of baseline PM_{2.5} exposure and those with PM_{2.5} in the lowest quintile served as the reference group. A trend test was performed with the PM_{2.5} quintile treated as a numeric variable (an ordinal variable coded as 1–5) in the models. We also treated PM_{2.5} as a continuous variable and effect estimates were reported for each 10 µg/m³ increase in the PM_{2.5} concentration.

We also conducted stratified analysis by baseline age (<65 y vs ≥65 y), baseline sex (male versus female), baseline smoking (never smoker versus ever smoker), baseline BMI (<25 kg/m² versus ≥25 kg/m²), baseline hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-reported physician-diagnosed hypertension: yes versus no), baseline diabetes (defined as fasting glucose ≥126 mg/dL or self-reported physician-diagnosed diabetes: yes versus no), and baseline self-reported heart disease or stroke, because previous studies had suggested that these factors could amplify the adverse effects of PM air pollution (Brook et al. 2010). We introduced an interaction term [PM_{2.5} (continuous variable) × each factor (dichotomous variable)] in the Cox regression model to investigate the potential modifying effects. Each factor was examined separately. *P* values were calculated for the product terms.

A series of sensitivity analyses were performed by *a*) including only participants who used a residential address (16,574 participants with 226 cases were excluded because they provided a company address); *b*) including only participants whose eGFR was measured with a HITACHI 7150 before 2005 (36,634 participants with 805 cases were excluded, because their eGFR were measured with a TOSHIBA C8000 since 2005); *c*) including all 147,658 nonCKD participants 20 years of age or older at baseline (i.e., the 47,029 participants with a follow-up duration less than 3 y plus the 100,629 participants with a follow-up duration greater than 3 y); and *d*) using a time-varying Cox model with PM_{2.5} and covariates treated as time-varying variables; *e*) conducting a sensitivity analysis (for comparison) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Stevens et al. 2011) for eGFR calculation.

All statistical analyses were performed using R (version 3.2.3; R Core Team). A two-tailed *p*-value <0.05 was considered to indicate statistical significance.

Results

Table 1 summarizes the participants' general characteristics at baseline. The distribution of these characteristics was generally similar across the participants grouped by PM_{2.5} quintiles. Among the 100,629 participants, 4,046 incident CKD cases developed during the follow-up (the number of cases in the categories of eGFR of 45~60, 30~45, 15~30, and ~15 mL/min/1.73 m² were 3,944, 92, 8, and 2, respectively). The incidence rate was 6.24 per 1,000 person-years.

The locations of the participants are shown in Figure S1. The southwestern areas were generally the most heavily polluted and the middle-eastern areas were the least heavily polluted. The spatial pattern of exposure contrast throughout the island generally remained stable during the study period. Figure 2 shows the distribution of baseline PM_{2.5} exposure. The baseline PM_{2.5} exposure increased slightly from 2001 to 2004 (the mean baseline PM_{2.5} exposure was 25.0, 26.7, 29.1, and 29.9 µg/m³, respectively, for participants enrolled in year 2001, 2002, 2003, and 2004), and then declined and remained relatively stable from 2005 to 2011 (the mean baseline PM_{2.5} exposure was 27.5, 27.2, 27.4, 27.5, 28.1, 26.4, and 25.2 µg/m³, respectively for year

Table 1. Baseline characteristics of study participants stratified by PM_{2.5} quintiles between 2001 and 2011.

Characteristics	All (N = 100629)	1st quintile (N = 20119)	2nd quintile (N = 20130)	3rd quintile (N = 20122)	4th quintile (N = 20136)	5th quintile (N = 20122)
Mean 2-year PM _{2.5} µg/m ³ (range)	27.1 ± 8.0 (5.8–49.6)	19.1 ± 1.8 (5.8–21.1)	22.2 ± 0.6 (> 21.1–23.3)	24.2 ± 0.6 (> 23.3–25.5)	29.0 ± 3.4 (> 25.5–36.1)	41.1 ± 2.9 (> 36.1–49.6)
Age mean ± SD, (years)	38.9 ± 11.3	39.9 ± 11.6	38.8 ± 11.2	38.1 ± 11.0	38.6 ± 11.3	39.0 ± 11.3
Male	52,837 (52.5)	10,280 (51.1)	10,694 (53.1)	10,669 (53.0)	10,774 (53.5)	10,420 (51.8)
Education						
Lower than high school	13,354 (13.3)	3,074 (15.3)	2,472 (12.3)	2,271 (11.3)	2,722 (13.5)	2,815 (14.0)
High school	20,351 (20.2)	4,320 (21.5)	3,901 (19.4)	3,631 (18.0)	4,081 (20.3)	4,418 (22.0)
College	25,534 (25.4)	5,289 (26.3)	5,003 (24.9)	5,074 (25.2)	4,856 (24.1)	5,312 (26.4)
University	29,777 (29.6)	5,389 (26.8)	6,046 (30.0)	6,470 (32.2)	6,029 (29.9)	5,843 (29.0)
Postgraduate	11,613 (11.5)	2,047 (10.2)	2,708 (13.5)	2,676 (13.3)	2,448 (12.2)	1,734 (8.6)
Cigarette smoking						
Never	74,172 (74.2)	14,855 (73.8)	14,791 (73.5)	14,923 (74.2)	14,903 (74.0)	15,240 (75.7)
Former	5,441 (5.4)	1,136 (5.6)	1,098 (5.5)	1,049 (5.2)	1,123 (5.6)	1,035 (5.1)
Current	20,476 (20.3)	4,128 (20.5)	4,241 (21.1)	4,150 (20.6)	4,110 (20.4)	3,847 (19.1)
Alcohol drinking						
Never	84,024 (83.5)	16,758 (83.3)	16,904 (84.0)	16,849 (83.7)	16,787 (83.4)	16,726 (83.1)
Former	2,292 (2.3)	470 (2.3)	430 (2.1)	459 (2.3)	433 (2.2)	500 (2.5)
Current (≥ 1 time/week)	14,313 (14.2)	2,796 (14.4)	2,796 (13.9)	2,814 (14.0)	2,916 (14.5)	2,896 (14.4)
Body mass index mean ± SD, (kg/m ²)	22.9 ± 3.5	22.9 ± 3.4	22.9 ± 3.4	22.8 ± 3.5	23.0 ± 3.5	22.9 ± 3.5
Systolic blood pressure mean ± SD, (mmHg)	117.0 ± 16.4	116.9 ± 16.4	117.0 ± 16.3	116.9 ± 16.1	116.8 ± 16.6	117.2 ± 16.7
Fasting glucose mean ± SD, (mg/dL)	98.1 ± 17.7	98.2 ± 18.4	98.1 ± 17.3	98.2 ± 17.1	98.1 ± 18.0	97.8 ± 17.7
Total cholesterol mean ± SD, (mg/dL)	190.1 ± 34.6	189.9 ± 34.1	190.4 ± 34.7	190.5 ± 35.0	191.1 ± 34.9	188.7 ± 34.4
eGFR mean ± SD, (mL/min/1.73m ²)	87.0 ± 14.9	86.5 ± 14.5	87.5 ± 15.0	87.9 ± 15.1	86.5 ± 14.9	86.7 ± 14.8
Self-reported heart disease or stroke	2,122 (2.1)	481 (2.4)	390 (1.9)	440 (2.2)	406 (2.0)	405 (2.0)
Hypertension	12,603 (12.5)	2,684 (13.3)	2,534 (12.6)	2,393 (11.9)	2,432 (11.1)	2,560 (12.7)
Diabetes	3,242 (3.2)	682 (3.4)	626 (3.1)	584 (2.9)	670 (3.3)	680 (3.4)
Address						
Residential address	84,055 (83.5)	18,839 (93.6)	16,755 (83.2)	15,560 (77.3)	15,515 (77.1)	17,386 (86.4)
Company address	16,574 (16.5)	1,280 (6.4)	3,375 (15.8)	4,562 (22.7)	4,621 (22.9)	2,736 (13.6)

Note: Data are presented as mean ± SD for continuous variables and number (percentage) for categorical variables. Data are complete for all variables.

2005, 2006, 2007, 2008, 2009, 2010, and 2011). The overall mean ± SD was 27.1 ± 8.0 µg/m³ with an IQR of 10.4 µg/m³.

Table 2 shows the association between the PM_{2.5} and the incidence of CKD. A higher level of PM_{2.5} was associated with a higher risk of developing CKD. In the main model (Model 2), in contrast with the participants with the first quintile exposure, participants with the fourth or fifth quintiles were significantly associated, with an HR (95% CI) of 1.11 (1.01, 1.22) or 1.15 (1.05, 1.26) in CKD development, respectively. A significant concentration–response trend was observed (*p* < 0.001). Every 10 µg/m³ increment in the PM_{2.5} level was associated with a 6% increased

risk of developing CKD (HR: 1.06, 95% CI: 1.02, 1.10). An additional adjustment for baseline eGFR or urinary protein produced only marginal changes in the results.

Table 3 shows the results of the stratified analyses for potential modifiers. No significant effect modifications were observed when data analyses were stratified by age, sex, BMI, hypertension, diabetes, and cardiovascular disease history (all *p* values > 0.05).

The results of sensitivity analyses 1 to 4 are presented in Table 4. Overall, the associations were consistent by excluding participants using company address, using TOSHIBA C8000

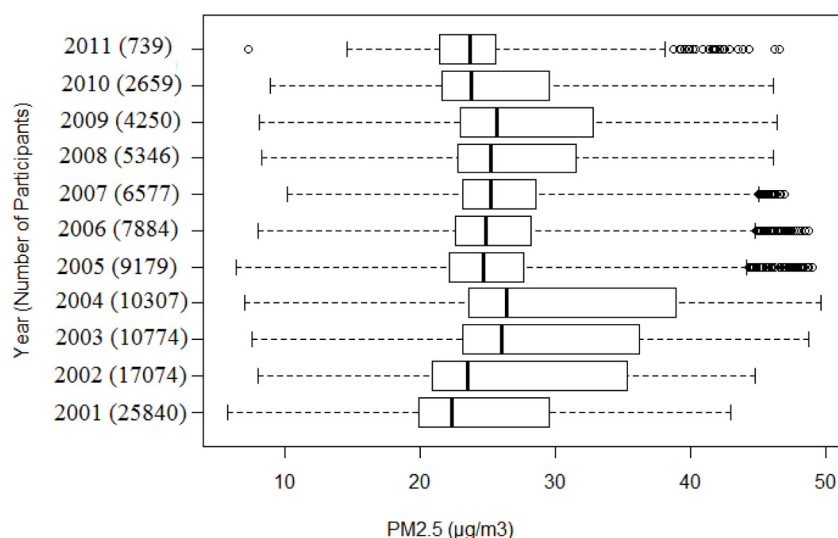


Figure 2. Distribution of baseline PM_{2.5} exposure of the participants by year. Boxes cover the 25–75th percentile (interquartile range: IQR) with a center line for the median concentration. Whiskers extend to the highest observation within 3 IQRs of the box, with more extreme observations shown as circles.

Table 2. Associations between incident CKD and long-term PM_{2.5} exposure in Taiwanese adults between 2001 and 2011 (N = 100,629).

Exposure	Crude Model ^a		Adjusted Model 1 ^b		Adjusted Model 2 ^c		Adjusted Model 3 ^d		Adjusted Model 4 ^e	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
1st Quintile (5.8–21.1 µg/m ³)	Ref	—	Ref	—	Ref	—	Ref	—	Ref	—
2nd Quintile (>21.1–23.3 µg/m ³)	0.97 (0.88,1.06)	0.50	1.06 (0.96,1.16)	0.24	1.05 (0.95,1.15)	0.36	1.09 (0.99,1.19)	0.09	1.09 (0.99,1.20)	0.07
3rd Quintile (>23.3–25.5 µg/m ³)	0.91 (0.83,1.01)	0.06	1.05 (0.95,1.16)	0.31	1.04 (0.94,1.15)	0.46	1.11 (1.01,1.23)	0.03	1.11 (1.01,1.23)	0.03
4th Quintile (>25.5–36.1 µg/m ³)	1.06 (0.96,1.17)	0.23	1.13 (1.03,1.25)	0.01	1.11 (1.01,1.22)	0.03	1.16 (1.05,1.28)	0.002	1.16 (1.05,1.28)	0.003
5th Quintile (>36.1–49.6 µg/m ³)	1.06 (0.97,1.16)	0.21	1.16 (1.06,1.27)	0.002	1.15 (1.05,1.26)	0.003	1.17 (1.07,1.29)	0.001	1.16 (1.06,1.27)	0.002
Trend Test	—	0.07	—	0.001	—	0.002	—	<0.001	—	0.001
10 µg/m ³ Increment	1.04 (1.00,1.08)	0.03	1.06 (1.02,1.10)	0.002	1.06 (1.02,1.10)	0.003	1.06 (1.02,1.10)	0.002	1.05 (1.01,1.09)	0.007

Note: CKD defined as eGFR <60 mL/min/1.73 m². Covariates introduced in the Cox regression models were from baseline visits. Participants in the first quintile of PM_{2.5} exposure served as a reference (Ref) group. Data are complete for all variables.

^aCrude model: PM_{2.5}.

^bModel 1: Crude model + age, sex, educational level, smoking, and drinking.

^cModel 2: Model 1 + BMI, systolic blood pressure, fasting glucose, total cholesterol, and self-reported heart disease or stroke.

^dModel 3: Model 2 + baseline eGFR.

^eModel 4: Model 3 + urine protein.

analyzer since January, 2005, or including participants with a follow-up duration of less than 3 y. Using time-varying Cox regression model also yielded similar results. The results of sensitivity analysis 5 using the CKD-EPI formula are presented in Table S2. We observed results very similar to those in Table 2.

Discussion

Our study shows that long-term exposure to ambient PM_{2.5} was associated with an increased risk of incident CKD (based on eGFR <60 mL/min/1.73 m² at a follow-up visit) among adult residents of Taiwan. Participants in this study with the fourth or the fifth quintiles of PM_{2.5} were significantly associated with increased risk of developing CKD, with an HR (95% CI) of 1.11 (1.01, 1.22) or 1.15 (1.05, 1.26), respectively, in comparison with the participants with the first quintile of PM_{2.5}. Every 10 µg/m³ increase in the 2-y average of PM_{2.5} was associated with a 6% increase in the risk of CKD (95% CI: 2%, 10%).

The association between PM_{2.5} exposure and CKD development remained robust after adjustment for a wide range of potential

confounders and modifiers. It is well documented that demographic and lifestyle factors are associated with the risk of CKD. We used time-in-study as time scale in this study, adjusting for age at baseline, which is the typical approach in a Cox model. Although some alternative time scales (such as attained age and calendar time) were proposed to reduce bias, there is no option that can be assumed with certainty to be “the best” (Griffin et al. 2012). We observed slightly stronger associations after adjusting for these factors. In addition to demographic factors and lifestyles, cardiovascular risk factors are also closely associated with CKD development. Emerging literature has also suggested that air pollution is associated with cardiovascular risk factors, such as hypertension and diabetes. However, adjustment for cardiovascular risk factors and diseases in this study did not significantly change the association, suggesting that they may not have significant intermediate effects in the association between PM exposure and CKD development. In addition, interaction tests did not show significant intermediate effects in subgroup analysis (Table 3). We also explored the potential effects of baseline eGFR and urinary protein. Our results showed that they had no significant influences on the association.

Current literature on PM_{2.5} and renal function is relatively sparse. A cross-sectional study was conducted in New Taipei City, Taiwan, with a sample size of 21,656 adults (Yang et al. 2017). Annual average PM₁₀ and PM_{course} concentrations at residential addresses were associated with lower eGFR and a higher prevalence of CKD, but PM_{2.5} was not significantly associated with either outcome. Another cross-sectional study was conducted in 1,103 patients with acute ischemic stroke in Boston, Massachusetts (Lue et al. 2013). This study found that living near a major roadway was associated with lower eGFR. Mehta et al. conducted a cohort study with 669 older men in the Boston metropolitan area (Mehta et al. 2016). Their results showed that an interquartile range (IQR) (2.1 µg/m³) increment in 1-y average PM_{2.5} was associated with a decrease of 1.87 (95% CI: 0.76, 2.99) mL/min/1.73m² in eGFR. Annual average exposures to PM_{2.5}, PM₁₀, nitrogen dioxide, and carbon monoxide were positively associated with incident CKD in a cohort of U.S. veterans (Bowe et al. 2017, 2018), which are in line with our findings. The HR of incident eGFR <60 mL/min/1.73 m² in the study by Bowe et al. was 1.21 per 10 µg/m³ PM_{2.5} increase (95% CI: 1.14, 1.29) (Bowe et al. 2018), a result slightly higher than that in our study (1.06 per 10 µg/m³ PM_{2.5} increase). Our results may not be directly comparable with this study because it was conducted in the United States, where air pollution levels are relatively lower, and their participants were elderly (veterans). More studies from different regions and populations are required.

Potential mechanisms for associations between PM_{2.5} and CKD are not clear. However, many cardiovascular risk factors, such as smoking, obesity, hypertension, and diabetes are also risk factors for CKD. Individuals with CKD should be viewed as one of the groups

Table 3. Associations between incident CKD and long-term PM_{2.5} exposure in Taiwanese adults in stratified analyses between 2001 and 2011.

Subgroups	Participants/Cases	HR (95%CI) ^a	P _{interaction}
Age			
<65 years	97698/3379	1.05 (1.00,1.09)	0.71
≥65 years	2931/667	1.06 (0.96,1.16)	
Sex			
Male	52837/1955	1.08 (1.03,1.14)	0.28
Female	47792/2091	1.04 (0.99,1.10)	
Smoking			
Never	74712/3105	1.05 (1.00,1.09)	0.21
Ever	25917/941	1.12 (1.03,1.21)	
BMI			
<25 kg/m ²	75693/2623	1.06 (1.01,1.11)	0.83
≥25 kg/m ²	24936/1423	1.07 (1.00,1.14)	
Hypertension			
No	88026/2701	1.07 (1.03,1.12)	0.38
Yes	12603/1345	1.03 (0.97,1.10)	
Diabetes			
No	97387/3621	1.07 (1.03,1.11)	0.28
Yes	3242/425	0.99 (0.88,1.11)	
Self-reported cardiovascular disease			
No	98507/3803	1.07 (1.03,1.11)	0.09
Yes	2122/243	0.90 (0.76,1.06)	

Note: Results (HR) are reported for each 10 µg/m³ increase in PM_{2.5}. Data are complete for all variables.

^aAdjusted for age (not in age-stratified analysis), sex (not in sex-stratified analysis), educational level, smoking (not in smoking-stratified analysis), drinking, BMI (not in BMI-stratified analysis), systolic blood pressure (not in hypertension-stratified analysis), fasting glucose (not in diabetes-stratified analysis), total cholesterol, and self-reported heart disease or stroke (not in cardiovascular disease-stratified analysis). All covariates were from baseline visits.

Table 4. Associations between incident CKD and long-term PM_{2.5} exposure in Taiwanese adults in sensitivity analyses.

Exposure	Sensitivity Analysis 1 ^a		Sensitivity Analysis 2 ^b		Sensitivity Analysis 3 ^c		Sensitivity Analysis 4 ^d	
	HR ^e (95% CI)	P	HR ^e (95% CI)	P	HR ^e (95% CI)	P	HR ^e (95% CI)	P
1st Quintile	Ref	—	Ref	—	Ref	—	—	—
2nd Quintile	1.05 (0.95,1.16)	0.34	0.98 (0.88,1.10)	0.76	0.98 (0.90,1.06)	0.55	1.06 (0.90,1.17)	0.25
3rd Quintile	1.04 (0.94,1.15)	0.49	1.02 (0.92,1.14)	0.69	0.94 (0.86,1.02)	0.12	0.93 (0.84,1.03)	0.14
4th Quintile	1.15 (1.04,1.27)	0.005	1.16 (1.04,1.29)	0.006	1.05 (0.97,1.13)	0.24	1.03 (0.93,1.14)	0.58
5th Quintile	1.15 (1.05,1.27)	0.004	1.17 (1.05,1.30)	0.005	1.08 (1.01,1.17)	0.04	1.15 (1.04,1.27)	0.006
Trend Test	—	0.001	—	<0.001	—	0.01	—	0.03
10 µg/m ³ Increment	1.06 (1.02,1.10)	0.003	1.08 (1.03,1.12)	<0.001	1.05 (1.02,1.09)	0.002	1.07 (1.02,1.11)	0.007

Note: CKD defined as eGFR <60 mL/min/1.73 m². Participants in the first quintile of PM_{2.5} exposure served as a reference (Ref) group. Data are complete for all variables. The cutoff points of the quintiles were based on the distribution of participants' baseline PM_{2.5} exposure unless otherwise indicated.

^aLimited to 84,055 participants who provided a residential address (3,820 cases), 16,574 participants who provided company address only were excluded. Mean baseline PM_{2.5} exposure = 27.0 ± 8.1 µg/m³.

^bLimited to 63,995 participants whose serum creatinine was measured by HITACHI 7150 before 2005 (3,241 cases). Mean baseline PM_{2.5} exposure = 26.9 ± 8.3 µg/m³.

^c147,685 participants, including 100,629 with ≥3 years of follow-up (included in main analysis) and 47,029 with <3 years of follow-up. Mean baseline PM_{2.5} exposure = 27.0 ± 7.8 µg/m³.

^dTime-varying Cox regression model with PM_{2.5} and covariates treated as time-varying variables (100,629 participants, 4,046 cases). Quintile cutoff points were based on the distribution over all observations, including the baseline PM_{2.5} exposure and follow-up PM_{2.5} exposure. Mean 2-year PM_{2.5} of all observations = 27.2 ± 7.7 µg/m³.

^eHR adjusted for age, sex, educational level, smoking, drinking, body mass index, systolic blood pressure, fasting glucose, total cholesterol, and self-reported heart disease or stroke. Covariates introduced in the Cox regression models were from baseline visits (except Sensitivity Analysis 4).

with the highest risk for cardiovascular disease (Gansevoort et al. 2013). We therefore speculate that part of the mechanism of PM-related CKD may be similar to the pathway of PM-related cardiovascular diseases. Mounting evidence shows that exposure to PM_{2.5} may lead to systemic inflammation, oxidative stress, and atherosclerosis, which can induce endothelial damage, resulting in glomerulosclerosis, tubular atrophy, and interstitial fibrosis (Webster et al. 2017). In addition, air pollutants, including particles, might traverse the alveolar space and penetrate the circulatory system, where they can produce adverse effects on remote organs (Chin 2015). Yan et al. reported that exposure to PM may advance glomerulosclerosis and tubular damage in an animal model (Yan et al. 2014). Another potential mechanism is the toxicity of chemical compounds contained in PM, such as various heavy metals and polycyclic aromatic hydrocarbons. Studies have shown that environmental and occupational exposure to various chemicals may damage renal function (Lunyer et al. 2016; Kataria et al. 2015). Further studies to clarify the mechanism of PM-induced CKD are warranted.

This study has several important strengths. First, a longitudinal cohort study design was used to investigate long-term exposure to PM_{2.5} and incident CKD. Second, the large sample size increased our statistical power to better characterize the association between PM_{2.5} exposure and CKD development. The associations remain robust after adjusting for the confounders/modifiers. Third, we used the satellite-based spatiotemporal model with a high spatial resolution to estimate the long-term exposure level to PM_{2.5}. This novel technology enables us to obtain the individual level of exposure to PM_{2.5} and overcome the spatial coverage and interpolation problems that occur when using only data from monitoring stations. Furthermore, using the satellite data allowed us to trace the change of PM_{2.5} exposure over time and consider the impact of change on the development of CKD.

This study also has certain limitations. One limitation is that a single measurement of eGFR <60 mL/min/1.73 m² was used to define CKD, as is common in large-scale epidemiological studies. In a clinical setting, diagnosis of CKD requires two measurements of eGFRs <60 mL/min/1.73 m² separated by at least 90 d. A single measurement of eGFR <60 mL/min/1.73 m² might be due to acute kidney disease or other diseases; thus, some participants may have been misclassified as having CKD based on this criterion. The study by Bowe et al. investigated the associations between PM_{2.5} and both incident eGFR <60 mL/min/1.73 m² diagnosed by a single measurement and incident CKD diagnosed based on two measurements from medical records. A lower HR was found for the

incident eGFR <60 mL/min/1.73 m² in comparison with the incident CKD [HR per 10 µg/m³ PM_{2.5} increase: 1.21 (95% CI: 1.14, 1.29) versus 1.27 (95% CI: 1.17, 1.38)] (Bowe et al. 2018). Another limitation of our study is that information on exposure to indoor PM_{2.5} is not available, although we have accounted for smoking, which is one of the most important sources of indoor air pollution in a developed economy. In addition, the ambient PM_{2.5} was estimated at fixed addresses and the participants' activity patterns were not considered. Meanwhile, a portion (16.5%) of the participants reported their company address rather than their residential address. However, our sensitivity analysis showed similar results when those participants who provided a company address were excluded. Third, the 100,629 participants included in this study were selected from a large cohort. Selection bias might be a concern. However, the excluded participants and included participants were comparable in terms of the distribution of age, sex, and cardiovascular risk factors. In addition, we investigated the association rather than prevalence estimate in this study. Thus, the exclusion should not affect our study conclusion. Moreover, a series of subgroup analyses and sensitivity analyses yielded similar results, demonstrating the robustness of the association. Fourth, we evaluated only the effects of particles because of the lack of information on gaseous air pollutants, such as nitrogen dioxide. This evaluation of only the effects of particles should not affect our conclusion, however, because these of pollutants are generally correlated. The collinear issue between pollutants remains to be solved. Finally, the main results of this study were based on the 2-y average PM_{2.5} exposure at baseline. The baseline PM_{2.5} exposure changed slightly over time during the study period (increased from 25.0 µg/m³ in 2001 to 29.9 µg/m³ in 2004, and declined from 27.5 µg/m³ in 2005 to 25.2 µg/m³ in 2011). However, the spatial pattern of exposure contrast throughout the island generally remained stable during the study period, and the Sensitivity Analysis 4, which took into account temporal variations of PM_{2.5} and other covariates, yielded similar results.

Conclusions

We found in this large-cohort study that long-term exposure to PM_{2.5} was associated with an increased risk of CKD. Although the estimated increase in risk was small at the individual level, the relevant public significance could be tremendous, given that exposure to air pollution is ubiquitous. CKD not only contributes to total mortality, but also seriously affects the patients' quality of life. Our findings support the global strategies of air pollution reduction to prevent CKD development.

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