Fine Particulate Matter and Cause-specific Mortality in the Hong Kong Elder Patients with Chronic Kidney Disease

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Abstract

Emerging epidemiologic studies suggested that particulate matter (PM) was a risk factor for the incidence of chronic kidney disease (CKD). However, few studies were conducted to examine whether PM was associated with cause-specific deaths in the CKD progression. This study aimed to estimate the association between fine particulate matter ($PM_{2.5}$) and a spectrum of deaths among CKD patients. We took leverage of the Elderly Health Service cohort (n=66,820), a large Hong Kong elderly cohort followed up till 2010. A total of 902 CKD incident patients in the cohort were identified during the follow-up period. We estimated yearly $PM_{2.5}$ at the residential address for each CKD patient based on a satellite-based spatiotemporal model. We used Cox proportional hazards models with attained age as the underlying timescale to assess the association between long-term exposure to $PM_{2.5}$ and cause-specific mortality among CKD patients. A total of 496 patients died during the follow-up, where 147 died from cardiovascular disease, 61 from respiratory disease and 154 from renal failure. The mortality hazard ratio (HR) per interquartile-range increase in $PM_{2.5}$ (4.0 $\mu g/m^3$) was 1.97 (95% confidence interval (CI): 1.34 to 2.91) for ischemic heart disease (IHD) among CKD patients, and was 1.42 (95%CI: 1.05 to 1.93) for CKD among those patients concomitantly with hypertension. Associations were not of statistical significance between $PM_{2.5}$ and mortality hazard ratios of all-cause, stroke, and pneumonia among CKD patients. Our findings suggest that long-term exposure to $PM_{2.5}$ may contribute to the CKD progression into ischemic heart diseases.

1. Introduction

Chronic kidney disease (CKD) represents a considerable global-health burden. The prevalence of CKD varies between 7% and 12% worldwide, and deaths from CKD were high and were elevated by 31.7% in the last decade (GBD, 2016; Mills et al., 2015; Romagnani et al., 2017). Along with the worldwide CKD prevalence, the CKD prevalence in China was about 10.8% based on a national survey taken from 2007 to 2010 (Zhang et al., 2016, 2010). Previous studies to estimate global and local burdens of CKD only considered deaths from the end-stage renal disease (ESRD), failed to capture other deaths related to CKD, which could substantially underestimate the health burden of CKD (Tonelli et al., 2006).

Emerging epidemiologic studies suggested that environmental pollutants were associated with increased risk of renal system diseases, especially for particulate matter (PM) air pollution (Gansevoort et al., 2013; Webster et al., 2017; Xu et al., 2018). For example, a positive association between PM and CKD incidence was found in the population of Taiwan, Korean, and the US (Bowe et al., 2018, 2017; Chan et al., 2018; Kim et al., 2018; Yang et al., 2017). The majority of previous studies only examined the association between PM and CKD incidence (among the healthy population) with few investigated the role of PM on CKD progression among patients with existing kidney damage (Bowe et al., 2018). The underlying biological mechanism linking PM with CKD incidence and progression including inflammatory reaction, atherosclerotic progress, endothelial dysfunction, and vascular wall degeneration (Blacher et al., 2003; Muntner et al., 2004; Sarnak, 2003; Shlipak et al., 2003; Vervloet and Cozzolino, 2017).

Accordingly, we aimed to assess the association of long-term chronic exposure to $PM_{2.5}$ with a spectrum of deaths (all-cause, cardiovascular, respiratory, and renal failure) among CKD patients, taking leverage of the Elderly Health Service Cohort, a large elderly cohort in Hong Kong.

2. Materials and methods

2.1 Study population

The Elderly Health Service cohort is a prospective cohort developed in Hong Kong to facilitate the understanding of aging in a global context. Based on the voluntary principle, 66,820 subjects aged 65 years older or above, about 9% of Hong Kong elders, were registered between 1998 and 2001 and then followed up till 2010. More details about the Elderly Health Service cohort have been described elsewhere(Schooling et al., 2014). Incident CKD cases were identified by the ninth version of International Classification of Diseases (ICD-9: 585) by record linkage to the Hospital

Authority, which is a statutory body running public hospitals for all of the Hong Kong population. A total of 902 CKD patients were recruited as a CKD cohort for the following analysis after excluding 302 patients who died in the first year (**Figure 1**). We started to follow up CKD patients when they were identified as CKD and were recruited to the CKD cohort. The spatial distribution of the CKD cohort was shown in **Figure 2**. Structured and standardized interview and physical examinations were carried out by registered nurses and doctors to collect participants' social demographical information and assess their health conditions, including body mass index (BMI), lifestyle, pre-existing chronic conditions, and others. Their mortality information has been obtained by record linkage to the Death Registry separately in Hong Kong. Ethics approval was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

2.2 Outcome ascertainment

The primary mortality diagnosis was coded based on ICD-9 from 1998 to 2001 and ICD-10 after 2001 (ICD-9 and ICD-10). Mortality records were coded as all-cause (ICD-9: 001-999 or ICD-10: A00-Z99), cardiovascular disease (CVD, ICD-9: 390-459 or ICD-10: I00-I99), ischemic heart disease (IHD, ICD-9: 410-414 or ICD-10: I20-I25), stroke (ICD-9: 430-438 or ICD-10: I60-I69), respiratory disease (ICD-9: 460-519 or ICD-10: J00-J99), pneumonia (ICD-9: 480-486 or ICD-10: J12-J18), renal failure (ICD-9: 584-586 or ICD-10: N17-N19), and ESRD (ICD-9: 585.6 or ICD-10: N18.6). The agreement between these two mortality ICD coding systems was over 90% in Hong Kong (Hong Kong Department of Health, 2005).

2.3 Exposure estimation model

Annual estimates of $PM_{2.5}$ exposures from 1998 to 2010 were deduced from satellite-based aerosol optical depth (AOD) recordings and ground-level monitoring data (Qiu et al., 2017; Wong et al., 2015). Briefly, two Earth Observing System satellites of National Aeronautics and Space Administration (NASA) captured the remote sensing imaging, from which AOD was retrieved and utilized as a common measure of tropospheric $PM_{2.5}$ levels. Accounting for rainy days and humidity, the variable-surface extinction coefficients (SEC) was further computed from AOD at a spatial resolution of 1 km^2. Missing SEC data because of cloud cover problem were filled by using multiple imputation procedure. Four general monitoring stations from the Environmental Protection Department (EPD) monitored $PM_{2.5}$ concentrations in Hong Kong. Annual mean ground-level concentrations were calculated and then regressed over the corresponding average SEC values to build up a comprehensive exposure model of $PM_{2.5}$. A cross-validation test was applied to confirm the validity of the approach (Qiu et al., 2018, 2017; Wong et al., 2015). We used concentrations from three sites for building the regression model ($PM_{2.5}$ ~ SEC) and then used the model to predict the $PM_{2.5}$

concentrations at the 4th site during the time period. We found the percentage absolute bias of the predicted annual $PM_{2.5}$ was around 9-12%. Each participant's residential address was geo-coded and then linked with the annual satellite SEC estimates. Approximately, 13.3% of participants changed their residential addresses during the study period, which was considered when estimating annual exposure.

2.4 Individual and environmental covariates

Individual and neighborhood covariates were controlled in our regression models. Specifically, we adjusted for individual-level covariates including age, sex, body mass index (BMI), physical exercise, smoking status, alcohol use, education background, monthly expenditure, and self-reported hypertension and diabetes. Neighborhood characteristics were controlled as environmental covariates, including the percentage of the aged (65 years or older), of tertiary education, and of household income ≥ 1923 USD/month based on 197 Hong Kong's Tertiary Planning Units (TPU), as well as the percentage of smokers in each district of Hong Kong to control for the exposure to environmental tobacco smoke.

2.5 Statistical analysis

Time-dependent Cox proportional hazards model was adopted to investigate the association between annual exposure to $PM_{2.5}$ and mortality from all cause and cause-specific diseases among CKD patients (Miller et al., 2007; Ostro et al., 2010; Sun et al., 2019b; Wong et al., 2015). Annual exposure to $PM_{2.5}$ for each individual in CKD cohort was included as the time-dependent predictor , and their attained age was selected as the underlying time scale to fully adjust for the confounding by age (Kim et al., 2017; Thiãbaut and Benichou, 2004). We estimated hazard ratios (HRs) of deaths per interquartile-range (IQR) increment in $PM_{2.5}$ concentrations in regression models with multistep covariate adjustments (Qiu et al., 2018, 2017): Model 1 only included sex and calendar year of entry; Model 2 further controlled for BMI, physical exercise, smoking consumption, alcohol drinking, education background, monthly expenses, self-reported hypertension and diabetes; Model 3 additionally accounted for TPU-level factors (%the aged, %tertiary education, and %household income 1923 USD/month) and district-level smoking rate. Then plots of the scaled Schoenfeld residuals and Martingale residuals were used to test proportional Hazards assumption and linear assumption, respectively. We applied Bonferroni method to limit potential Type I error due to multiple tests for the four broad causes of mortality and a P-value < 0.0125 (0.05/4) was considered as statistically significant (Bland and Altman, 1995; Sun et al., 2019a).

To examine potential effect modifications, we carried out stratification analyses by gender, BMI, hypertension and diabetes. We conducted three sensitivity analyses to confirm the robustness of our findings. First, we estimated the

mortality HRs from all cause and cause-specific diseases among patients with renal failure (ICD-9: 548.5-586); second, we included the subjects who died within the first year after enrollment; third, we excluded subjects who suffered from death within the first two years after entrance into the cohort. All statistical analyses were completed in the R software (version 3.3.2).

3. Results

During the follow-up for the CKD cohort by 2010, we found 496 CKD patients died from all-cause, 142 from CVD, 61 from respiratory disease, and 154 from renal failure excluding those who died in the first year after recruitment. The average age of the patients was about 73 and more than half were women (57.9%). Approximately 31.2% were categorized as overweight/obese and 15.2% performed no exercise. There were 36.7% current/former smokers and 3.1% regular/former drinkers. Based on self-reported co-morbidities, 34.9% CKD patients had hypertension and 67.0% had diabetes (**Table 1**). The concentration of $PM_{2.5}$ followed an approximately normal distribution and showed an increasing trend between 1998 and 2010 (**Figure S1**). The annual mean and median concentrations of $PM_{2.5}$ were about 37.8 $\mu g/m^3$ (IQR of 4.0 $\mu g/m^3$) at the baseline. The linearity assumption was not strictly met with the effects of $PM_{2.5}$ on CKD when concentration of $PM_{2.5}$ is over 40 $\mu g/m^3$, while Martingale residual plots of $PM_{2.5}$ on other cause-specific mortality were close to global linearity.

In all three models, the association of IHD mortality risk with $PM_{2.5}$ was in statistical significance (**Table 2 & Table S1**). Specifically, the HR per IQR increase (4.0 $\mu g/m^3$) of $PM_{2.5}$ levels for IHD mortality was 1.97 (95% confidence interval [CI]: 1.34 to 2.91) in Model 3 (**Table 2**). The HR for all-cause mortality was 1.16 (95%CI: 1.01 to 1.33) before adjusting any covariates and was 1.13 (95%CI: 0.98 to 1.30) from the fully adjusted model. The HRs for pneumonia and renal failure in association with an IQR increment in $PM_{2.5}$ were 1.34 (95%CI: 0.85 to 2.13) and 1.18 (95%CI: 0.91 to 1.52), respectively. In subgroup analyses, the association was in statistical significance (HR: 1.42; 95%CI: 1.05 to 1.93) between IQR-increase in $PM_{2.5}$ and mortality risk of renal failure for CKD patients with existing hypertension (**Table 3**). No other difference was shown across gender, BMI, and diabetes.

The natural spline model confirmed that the association between $PM_{2.5}$ and IHD mortality in Model 3 was close to linear (ρ value comparing the fit of the linear model to the spline model = 0.97), and the mortality risk might occur and gradually amplified when the $PM_{2.5}$ concentration elevated over about 38 $\mu g/m^3$ (**Figure 3**). Concentration-response relationships of all-cause, pneumonia, and renal failure mortality risks associated with $PM_{2.5}$ were shown in **Figure S2**. Three sensitivity analyses concluded similar results showing the robustness of the findings (**Table 4**).

4. Discussion

In the 902 confirmed CKD patients, we found a positive association between IHD mortality and ambient $PM_{2.5}$ concentration, which suggested that long-term exposure to $PM_{2.5}$ could be related to more IHD deaths among CKD patients. Additionally, CVD plays an indispensable role in the entire history of kidney diseases and the deaths from CVD are comparable to the deaths from renal failure along with the CKD exacerbation based on well-documented evidence (Angelantonio et al., 2010; Go et al., 2004; Sarnak, 2003; Wen et al., 2008). Therefore, it indicates that elevated $PM_{2.5}$ level might exacerbate IHD events in CKD progression. Consolidating previous results (Bowe et al., 2018; Chan et al., 2018), our findings suggest that $PM_{2.5}$ not only play a critical role in kidney exacerbation but also in circulatory damage along with CKD progression, especially IHD events.

Our finding of a positive association between $PM_{2.5}$ and IHD mortality for CKD patients is in concert with previous epidemiological studies on the relationships of air pollution with CKD incidence and progression to ESRD. Studies in the US male population found that PM air pollution could increase GFR decline, relate to the prevalence and incidence of CKD (Bowe et al., 2017, 2018; Bragg-gresham et al., 2018; Amar J Mehta et al., 2016), and studies in Taiwanese and Korean adults also observed that the higher PM air pollution levels were related to reduced renal function as well as an elevated risk of CKD development and incidence of nephrotic syndrome (Chan et al., 2018; Kim et al., 2018; Yang et al., 2017). Whether old or young people, Asian or Western population, the relationships between PM air pollutants and the CKD incidence is widely documented. However, the incidence is only a part of the whole natural history of CKD, existed but limited studies continued to find the association between PM air pollution and CKD progression: Dr. Bowe and colleagues suggested that $PM_{2·5}$ levels were linked to the higher risk of progress to ESRD (Bowe et al., 2018). Our present study further found the positive association between annual exposure to $PM_{2.5}$ and the IHD deaths among CKD patients, deducing that PM air pollution might exacerbate CKD progression to cardiovascular events. Certainly, more evidence in various regions and populations is warranted to complete the whole story in the PM-related renal health effects.

The plausible biological mechanisms underpinning the $PM_{2.5}$ impacts on the IHD events in CKD progression mainly contain indirect and direct pathways: $PM_{2.5}$ deposited in lung and alveoli provokes pulmonary and systemic inflammation (including IL-6, TNF-a, and plasminogen activator inhibitor-1), activates autonomic nervous system imbalance, promotes oxidative stress, then damages remote organs, such as kidney (Chin, 2015; Ostro et al., 2014; Sørensen et al., 2003). Ultrafine particles translocated into circulatory or lymphatic systems lead to dysfunction of

fibrinolysis and coagulation, increase atherosclerotic progression, exaggerate vasoconstrictor responses to phenylephrine and serotonin, decrease in flow-mediated dilatation, or lead to metabolic disturbances, including higher blood lipid concentrations and glucose intolerance, then impact on the distant renal system (Auchincloss et al., 2008; Chin, 2015; Fuks et al., 2011; Rhoden et al., 2005; Sun et al., 2005; Wilker et al., 2014). Notably, inhaled particles < 30 nm in diameter can be selectively accumulated in kidneys by filtration and excretion, then directly induce vascular inflammation and renal damage (Miller et al., 2017), but the experimental design about the direct impact of $PM_{2.5}$ on the renal system is still limited. Mounting evidence indicated that IHD events can be triggered by reduced renal function through anemia, abnormal apolipoprotein levels, increased arterial calcification, elevated plasma homocysteine, left ventricular hypertrophy, enhanced coagulability, and arterial stiffness (Blacher et al., 2003; Hsu et al., 2002; Levin et al., 1999; London et al., 2003; Muntner et al., 2004; Raggi et al., 2002; Shlipak et al., 2003), but few studies was designed to disentangle the co-associations in the confusing triangle system among $PM_{2.5}$, CKD, and IHD. More biological evidence is warranted to verify the association between $PM_{2.5}$ and CKD progression, or the complex synergistic effects between $PM_{2.5}$ and CKD on various cardiovascular events.

We also found that association was not in statistical significance between $PM_{2.5}$ and renal failure mortality for CKD patients with existing hypertension. It suggested the synergistic effect between hypertension and $PM_{2.5}$ might accelerate CKD progression to renal failure, which is in consistence with the progressive impact of hypertension on CKD development (Horowitz et al., 2015; Kearney et al., 2005). However, epidemiological studies in Taiwan and Beijing found a slightly stronger association of PM with CKD prevalence among participants who were non-hypertension versus hypertension (Huang et al., 2019; Yang et al., 2017). The discrepancy might result from the age distribution differences among studies: the average age of 73 in our study was higher than the studies in Taiwan and Beijing. We observed slightly higher impacts of hypertension here probably because age is also a critical risk factor for both hypertension and CKD development and progression (Horowitz et al., 2015; Webster et al., 2017). Additionally, adults with early comorbidities could be more health-conscious. The slightly stronger association between $PM_{2.5}$ and IHD deaths among CKD patients with existing diabetes, in the current study, was also interesting. Mehta et al. and Chen et al. however found that the association between $PM_{2.5}$ and CKD incidence was stronger in nondiabetic than diabetic participants (Chan et al., 2018; Amar J. Mehta et al., 2016). Hopefully future cohort studies with a larger number of CKD patients could help resolve these discrepancies which are likely due to small sample sizes in co-morbidity sub-groups. Previous studies indicated that the low-income population had a relevantly higher risk for CKD prevalence than the high-income population, suggesting the potential impact of social-economic status (SES) on CKD morbidity and mortality (Jha et al., 2013; Masson et al., 2015). However, ambient $PM_{2.5}$ concentrations were weakly associated with

the relevant SES index in our model (**Table S3),** including education level and monthly expenditure for individuals, as well as the percentage of tertiary education and the percentage of household income ≥ 1923 USD/month in each TPU. These weak associations suggested that $PM_{2.5}$ could not be a surrogate factor for SES, and the relationship of $PM_{2.5}$ with IHD events among CKD patients could not be a mirage generated by the SES differences of CKD patients.

This study has several limitations needing to be discussed. Firstly, the identification of incident CKD cases was based on record linkages to public hospital admission data and we did not perform clinical checks again on their renal functions when enrollment. The enrolled CKD patients could be at moderate-to-high stages because their symptoms were severe enough for hospitalization. Secondly, SEC from AOD within 1 km^2 of ground level was used to estimate the exposure to $PM_{2.5}$. Exposure variability of ambient $PM_{2.5}$ was relatively modest (IQR ≈ 11% of mean) possibly because of about 15.7% missing SEC date due to cloud over(Qiu et al., 2018, 2017; Wong et al., 2015). The statistical power was still restrained although these missing data were imputed with the predicted mean matching method in multiple imputation procedure. Third, participant enrollment was based on voluntariness and there were more female (57.9%) and health-conscious (73.6% with everyday exercise and 96.9% are never/social drinker) subjects than the general elderly population in Hong Kong. Caution is hence needed to interpret the generalizability of our findings. Fourth, the linearity assumption was not strictly met with the effects of $PM_{2.5}$ on CKD when concentration of $PM_{2.5}$ is over 40 $\mu g/m^3$, which warrants caution in interpreting the results and further studies to address this issue. Last, an increasing number of studies unveiled that long-term exposure to various constituents of $PM_{2.5}$ played different roles in adverse health effects(Chung et al., 2015; Ostro et al., 2010). Future studies are warranted to further excavate which constituents of $PM_{2.5}$ are more responsible for CKD progression.

5. Conclusion

In conclusion, long-term exposure to ambient $PM_{2.5}$ was associated with IHD mortality for CKD patients in statistical significance, suggesting that PM pollutants might exacerbate cardiovascular events in CKD progression. Efforts to control the air pollution might release the health-care burden of kidney diseases among the Hong Kong older population.

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Table 1. Descriptive statistics of the CKD cohort in the analysis.

Variable	All participants (n = 902)
Fine particulate matter ($PM_{2.5}$, μg/m^3)	
Median (IQR)	37.8 (4.0)
Mean (SD)	37.8 (2.9)
Individual-level covariates	
Age at entry, mean (±SD)	72.8 (6.0)
Gender, n (%)	
Male	380 (42.1%)
Female	255 (57.9%)
BMI, n (%)	
Under/normal-weight [< 25 kg/m^2]	621 (68.8%)
Overweight/obese [≥ 25 kg/m^2]	281 (31.2%)
Physical exercise, n (%)	
Never [0 day per week]	137 (15.2%)
Medium [1-6 days per week]	101 (11.2%)
High [7 days per week]	664 (73.6%)
Smoking status, n (%)	
Never/social smoker	571 (63.3%)
Former/current smoker	331 (36.7%)
Alcohol use, n (%)	
Never/social drinker	874 (96.9%)
Former/current smoker	28 (3.1%)
Education, n (%)	
Below primary	452 (50.1%)
Primary	328 (36.4%)
Secondary or above	122 (13.5%)
Monthly expenditure, n (%)	
Low [< 128 USD/month]	134 (14.9%)
Medium [128-384 USD/month]	631 (70.0%)
High [≥ 384 USD/month]	137 (15.2%)
Hypertension, n (%)	
Yes	315 (34.9%)
No	587 (65.1%)
Diabetes, n (%)	
Yes	604 (67.0%)
No	298 (33.0%)
Environmental covariates	
Prevalence of age ≥ 65, mean (±SD)	12.3% (4.3%)
Prevalence of tertiary education, mean (±SD)	12.5% (7.5%)
Prevalence of income ≥ 1923 USD/month, mean (±SD)	58.6% (11.3%)
Smoking rate, mean (±SD)	11.2% (0.7%)

Abbreviation: CKD, chronic kidney disease; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; IQR, interquartile range; BMI, body mass index.

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Table 2: Hazard ratio (95% CI) per IQR increase in $PM_{2.5}$ associated with the total and specific morality risks for CKD patients

	No. of deaths	Model 1 [a]	Model 2 [b]	Model 3 [c]
All-cause	496	1.16 (1.01 , 1.33)	1.17 (1.02 , 1.35)	1.13 (0.98 , 1.30)
Cardiovascular	142	1.18 (0.92 , 1.52)	1.24 (0.96 , 1.61)	1.19 (0.91 , 1.55)
IHD	70	1.90 (1.32 , 2.73)	2.04 (1.40 , 2.97)	1.97 (1.34 , 2.91)
Stroke	27	0.88 (0.49 , 1.57)	0.98 (0.54 , 1.78)	0.97 (0.53 , 1.79)
Respiratory	61	1.28 (0.87 , 1.88)	1.34 (0.89 , 1.99)	1.33 (0.88 , 2.02)
Pneumonia	51	1.31 (0.86 , 2.00)	1.35 (0.87 , 2.09)	1.34 (0.85 , 2.13)
Renal failure	154	1.25 (0.98 , 1.60)	1.24 (0.97 , 1.60)	1.18 (0.91 , 1.52)
CKD	144	1.24 (0.96 , 1.59)	1.23 (0.95 , 1.59)	1.17 (0.89 , 1.53)

Abbreviation: IQR, interquartile range; $PM_{2.5}$, fine particulate matter (aerodynamic diameter less than 2.5 μm); CI, confidence interval; IHD, ischemic heart disease; CKD, chronic kidney disease.

[a] Model 1: adjusted for gender and calendar year of entry;

[b] Model 2: adjusted for all individual-level covariates, including gender, year of entry, BMI, smoking status, alcohol use, education, monthly expenditure, physical exercise, hypertension and diabetes);

[c] Model 3: adjusted all covariates in Model 2 and environmental-level covariates (prevalence of age over 65, tertiary education, income ≥ 1923 USD/month in TPU level, and smoking rate at district level).

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Table 3. Stratified analyses of the associations between $PM_{2.5}$ and deaths from all-cause, IHD, pneumonia and renal failure among CKD patients in Model 3 [a].

	All cause		IHD		Pneumonia		Renal failure	
	HR(95%CI)	$P_{interaction}$ [b]	HR(95%CI)	$P_{interaction}$	HR(95%CI)	$P_{interaction}$	HR(95%CI)	$P_{interaction}$
Gender								
Men	1.17 (0.93, 1.46)	0.699	2.14 (1.17, 3.91)	0.726	1.52 (0.72, 3.19)	0.679	1.16 (0.78, 1.72)	0.924
Women	1.11 (0.93, 1.32)		1.88 (1.17, 3.02)		1.26 (0.73, 2.18)		1.19 (0.87, 1.62)	
BMI								
Under/normal weight	1.12 (0.96, 1.32)	0.927	2.15 (1.40, 3.31)	0.340	1.46 (0.89, 2.40)	0.369	1.13 (0.84, 1.51)	0.545
Overweight/Obese	1.14 (0.86, 1.51)		1.38 (0.60, 3.17)		0.88 (0.32, 2.44)		1.32 (0.83, 2.10)	
Hypertension								
No	0.95 (0.75, 1.21)	0.076	1.75 (0.93, 3.30)	0.639	1.03 (0.48, 2.19)	0.382	0.77 (0.50, 1.19)	0.017
Yes	1.22 (1.03, 1.45)		2.10 (1.31, 3.35)		1.53 (0.88, 2.65)		1.42 (1.05, 1.93)	
Diabetes								
No	1.10 (0.92, 1.30)	0.535	1.67 (1.05, 2.67)	0.217	1.44 (0.85, 2.43)	0.568	1.05 (0.77, 1.43)	0.185
Yes	1.20 (0.94, 1.52)		2.69 (1.43, 5.09)		1.10 (0.48, 2.52)		1.47 (0.97, 2.22)	

Abbreviation: IQR, interquartile range; $PM_{2.5}$, fine particulate matter (aerodynamic diameter less than 2.5 μm); CI, confidence interval; IHD, ischemic heart disease; CKD, chronic kidney disease.

[a] adjusted for all individual-level and environmental-level covariates: gender, year of entry, BMI, smoking status, alcohol use, education, monthly expenditure, physical exercise, self-reported active diseases, prevalence of age over 65, tertiary education, income ⩾ 1923 USD/month at TPU level and smoking rate at district level.

[b] Significance test on the difference between subgroups by P-value of interaction.

Table 4: Sensitivity analyses of the associations between an IQR increase in $PM_{2.5}$ and deaths from all-cause, IHD, pneumonia and renal failure.

	No. of deaths	Model 1 [a]	Model 2 [b]	Model 3 [c]
Association among patients with renal failure				
All-cause	664	1.15 (1.02 , 1.30)	1.18 (1.05 , 1.33)	1.14 (1.01 , 1.30)
IHD	87	1.97 (1.42 , 2.72)	2.14 (1.52 , 3.00)	2.08 (1.45 , 2.97)
Pneumonia	71	1.44 (1.00 , 2.06)	1.54 (1.06 , 2.23)	1.57 (1.06 , 2.35)
Renal failure	186	1.19 (0.95 , 1.48)	1.23 (0.98 , 1.55)	1.18 (0.93 , 1.50)
Including those died in the first year				
All-cause	798	0.98 (0.89 , 1.09)	1.00 (0.90 , 1.11)	0.99 (0.88 , 1.11)
IHD	102	1.41 (1.05 , 1.90)	1.42 (1.05 , 1.93)	1.42 (1.03 , 1.96)
Pneumonia	76	1.04 (0.73 , 1.46)	1.04 (0.73 , 1.48)	1.07 (0.74 , 1.57)
Renal failure	264	1.05 (0.88 , 1.27)	1.07 (0.89 , 1.29)	1.07 (0.87 , 1.30)
Excluding those died in the first two years				
All-cause	318	1.26 (1.07 , 1.49)	1.30 (1.09 , 1.54)	1.23 (1.02 , 1.48)
IHD	53	2.12 (1.40 , 3.22)	2.28 (1.47 , 3.52)	2.12 (1.34 , 3.36)
Pneumonia	36	1.63 (0.99 , 2.67)	1.73 (1.03 , 2.92)	1.86 (1.05 , 3.30)
Renal failure	96	1.20 (0.88 , 1.64)	1.19 (0.87 , 1.64)	1.10 (0.79 , 1.53)

Abbreviation: IQR, interquartile range; $PM_{2.5}$, fine particulate matter (aerodynamic diameter less than 2.5 μm); CI, confidence interval; IHD, ischemic heart disease; CKD, chronic kidney disease.

[a] Model 1: adjusted for gender and calendar year of entry;

[b] Model 2: adjusted for all individual-level covariates, including gender, year of entry, BMI, smoking status, alcohol use, education, monthly expenditure, physical exercise, hypertension and diabetes);

[c] Model 3: adjusted all covariates in Model 2 and environmental-level covariates (prevalence of age over 65, tertiary education, income ≥ 1923 USD/month in TPU level, and smoking rate at district level).

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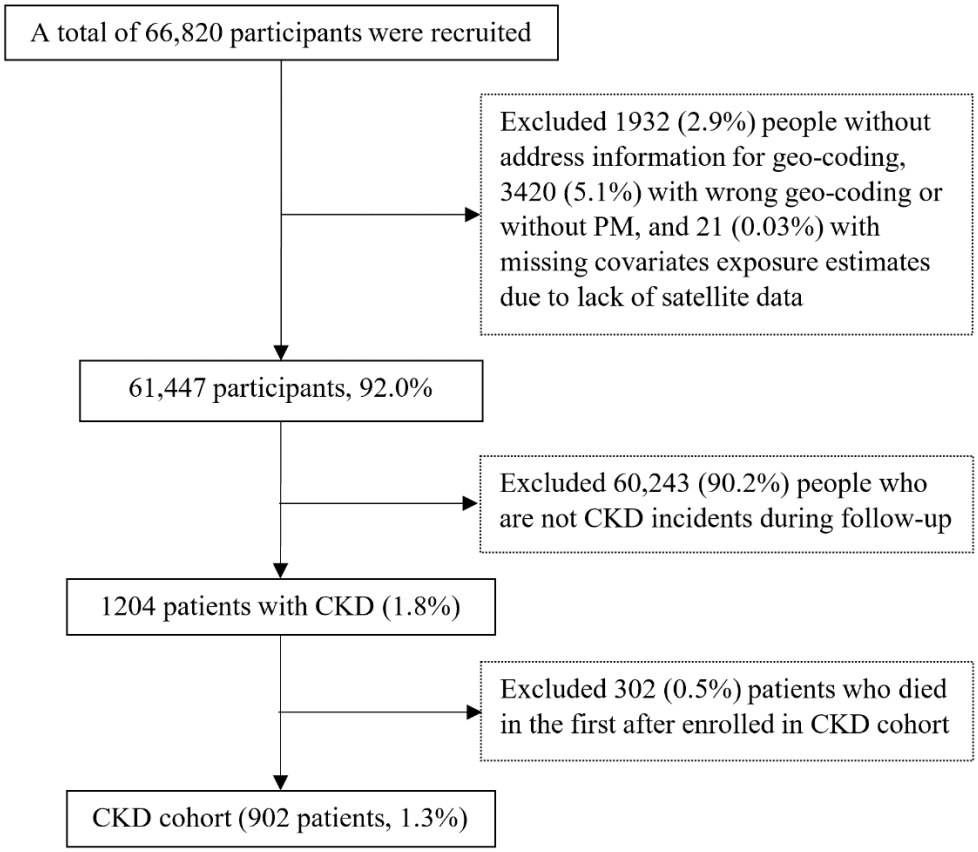
Figure titles and legends

Figure 1: Flowchart describing inclusion of participants in analysis.

Figure 2: Spatial distribution of air pollution exposure and CKD patients in Hong Kong. The left panel shows varying levels of surface extinction coefficients (SEC) indicating the concentrations of fine particulate matter ($PM_{2.5}$) at baseline. The right panel shows the spatial distribution of the CKD cohort (n = 902) with various exposure levels to ambient $PM_{2.5}$.

Figure 3: Concentration-response relationship between $PM_{2.5}$ and IHD mortality among CKD patients. Red line with shade area represents the hazard ratio of IHD mortality with corresponding confidence interval. Grey area at the bottom is the density distribution of fine particulate matter.



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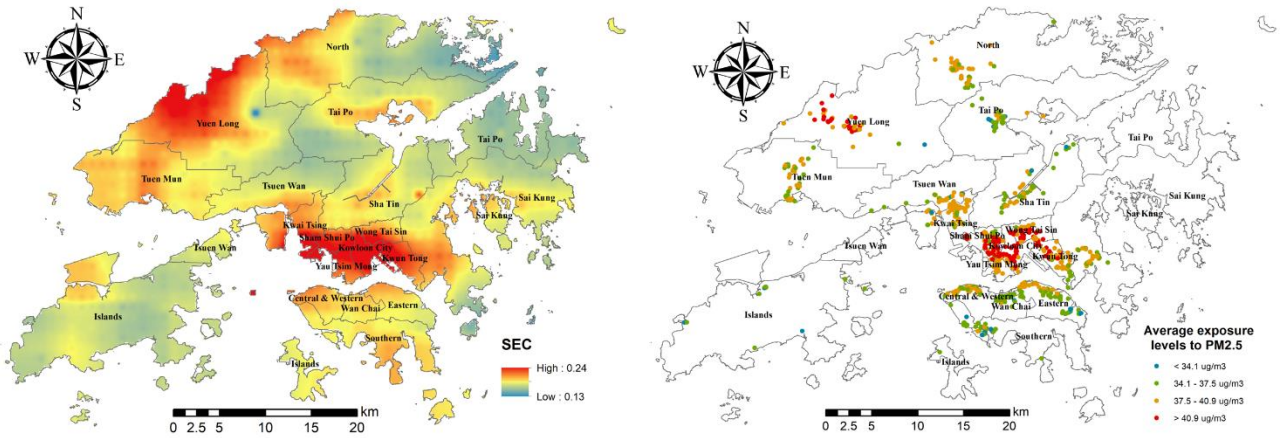

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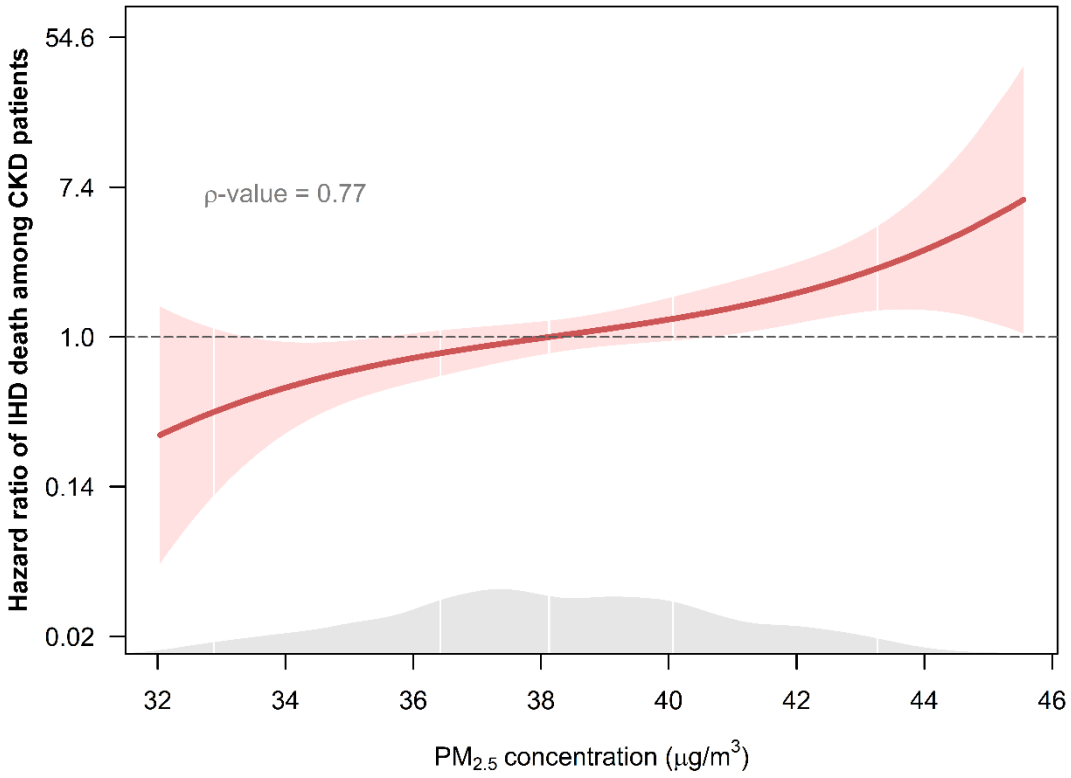

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