Long-Term Exposure to Ambient Fine Particulate Matter and Mortality from Renal Failure: A Retrospective Cohort Study in Hong Kong

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Running head: air pollution and renal failure

ABSTRACT

Numerous studies have indicated the ambient particulate matter is closely associated with increased cardiovascular disease, yet the evidence for its association with the renal disease remains under-recognized. We aimed to estimate the association between long-term exposure to fine particulate matter ($PM_{2.5}$) and renal failure (RF) mortality among participants of the Elderly Health Service Cohort in Hong Kong from 1998 to 2010. $PM_{2.5}$ concentration at the residential address of each participant was estimated based on a satellite-based spatiotemporal model. We used Cox proportional hazards regression to estimate the risks of overall renal failure (RF) and cause-specific mortality associated with $PM_{2.5}$. After excluding 5,373 subjects without information on the residential address or relevant covariates, a total of 61,447 participants were included in data analyses. We totally identified 443 RF deaths during the 10 years of follow-up. For an interquartile-range increase in $PM_{2.5}$ concentrations (3.22 μg/m^3), hazard ratios of RF mortality were 1.23 (95% confidence interval (CI): 1.06 to 1.43) among all cohort participants and 1.42 (95% CI: 1.16 to 1.74) among patients with chronic kidney disease. Long-term exposure to atmospheric $PM_{2.5}$ might be an important risk factor of RF mortality in the elderly population, especially among participants with existing renal diseases.

Keywords: fine particulate matter, renal failure, chronic kidney disease, long-term residential exposure

Abbreviations: $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; RF, renal failure; CKD, chronic kidney disease; AKI, acute kidney injury; SEC, surface extinction coefficients; TPU, tertiary planning units; BMI, body mass index; IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

The links between ambient air pollution and increased risks of cardiometabolic diseases such as hypertension and diabetes have been well investigated (1–5). Although the biological mechanisms regarding the associations warrant further exploration, mounting evidence indicated those potential pathways of oxidative stress, systemic inflammation, and disturbance of vascular tone might be the contributors (6–9). It is also hypothesized that impaired renal functions may relate to cardiovascular impacts of air pollution because the kidney is also a sensitive organ to oxidative stress, microvascular dysfunction, and systemic inflammation (10,11). Although the role of air pollution on the incidence and development of hypertension and diabetes is well documented in previous epidemiological and clinical studies, and it is widely accepted that hypertension and diabetes are major risk factors for both acute kidney injury (AKI) and chronic kidney disease (CKD) (10,12), direct human epidemiological evidence regarding the relationship of air pollution with renal diseases is limited.

Fine particulate matter (aerodynamic diameter ≤ 2.5 microns, $PM_{2.5}$) is mainly a product of fossil fuel combustion from vehicles and power plants, etc. Some but not all epidemiological studies suggested that $PM_{2.5}$ may increase the onset risks of CKD and end-stage renal disease (13–19). A cross-sectional study conducted among stroke patients in the USA observed that residential proximity to major roadways was inversely related to estimated glomerular filtration rate (20). Subsequent longitudinal studies indicated that chronic exposure to high $PM_{2.5}$ density would contribute to a decline of age-related glomerular filtration rate in older men (14,15). Another population-based study conducted in Taiwanese adults observed that a reduced renal function was associated with PM_{10} but not $PM_{2.5}$ (18). Experimental studies suggested that exposure to traffic emissions might promote renal oxidative stress and DNA damages, disturb renal hemodynamics, and exacerbate acute kidney injuries, but the findings were still controversial (21,22). A recent study also observed glomerulosclerosis in rats exposed to ambient particles over sixteen weeks (23).

Renal failure (RF) denotes the progressive loss of kidney function, including sub-categories of AKI, CKD, and unspecified RF. In this study, we evaluated the health impacts of long-term $PM_{2.5}$ exposure on the RF-related mortality risk in a longitudinal Chinese elderly cohort in Hong Kong (24). We adopted satellite-based data to measure yearly average $PM_{2.5}$ exposures in each individual. The aims of our study were to explore the associations between chronic exposures to $PM_{2.5}$ and mortality from RF among all cohort participants and those patients with existing CKD.

METHODS

Study population

A total of 66,820 participants were enrolled in the Department of Health Elderly Health Service (EHS) program from 1998 to 2000, accounting for approximately 9% of the elderly population (≥ 65) in Hong Kong. The enrolment was based on a voluntary principle. Elderly Health Centre located in each district of Hong Kong provided regular health assessments via structured and standardized interviews, as well as comprehensive clinical examinations. Doctors and registered nurses collected subjects' information, including socio-demographics, lifestyles, health behaviours, and others. Self-reported hypertension, diabetes, heart disease, stroke, and COPD/asthma were also collected as individual covariates by questionnaire at the baseline period. Details were reported in an earlier paper (24). Health assessments were operated during both the baseline period (from 1998 to 2000) and the follow-up period (to 2010). Approximately 70% of participants were still enrolled within 3 years after baseline assessments, indicating high follow-up compliance. The morbidity and mortality information were extracted by record linkages to the local Hospital Authority and Census and Statistics Department, respectively. This research protocol has obtained approval from the Hospital Authority Hong Kong West Cluster and the Institutional Review Board of the University of Hong Kong.

Outcome ascertainment

The causes of morbidity and mortality were encoded according to the International Classification of Diseases 9th and 10th Revision ((ICD-9 & ICD-10). Morbidity records from 1998 to 2010 and mortality records from 1998 to 2001 were coded by ICD-9 (RF: 584.5-586; AKI: 584.5-854.9; CKD: 585.1-585.9; unspecified RF: 586). Mortality records after 2001 were coded by ICD-10 (RF: N17-N19; AKI: N17; CKD: N18; unspecified RF: N19). The primary diagnoses of death were used as death causes. Almost all death events in Hong Kong occurred in the hospitals with an accurate death cause ascertainment (Schooling et al., 2016). The subjects who died in the first follow-up year after baseline were excluded from the analysis.

Exposure estimation model

Exposure measurements of $PM_{2.5}$ were deduced from satellite remote sensing data which were calibrated with ground meteorological observations (1,25). In brief, Aerosol Optical Depth (AOD) data, obtained from two NASA Earth Observing Systems satellite sensors were treated as an indicator for the particulate matter level in ambient air. Atmospheric $PM_{2.5}$ was measured by calculating Surface extinction coefficients (SEC) parameter by AOD at 1 km ×1 km spatial resolution after accounting for rain humidity

(25,26). Surface observations of hourly $PM_{2.5}$ from 1998 to 2010 were provided from monitoring stations governed by the local Environmental Protection Department. The exposure model of $PM_{2.5}$ was further derived by averaging the ground-level air concentrations on a yearly basis and then regressing the values over the corresponding annual average satellite SEC data. Cross-validation tests were used to confirm the validity of the approach. In short, we used concentrations from three sites for building the regression model ($PM_{2.5}$ ~ SEC) and then used the model to predict the concentrations at the 4th site from 2000 to 2011. We found that the predicted annual $PM_{2.5}$ was different from the observed data from EPD by around 9-12% (1,25,26). Annual $PM_{2.5}$ assessments were estimated with the exposure models between 1998 and 2010 and then matched with individual participants by geo-coded residential locations as the explanatory variable. In this Elderly Chinese Cohort, approximate 13.3% of participants had residential addresses changes during the study period, which was taken into account when estimating annual exposure (26).

Individual, ecological, and environmental covariates

We included individual, ecological, and environmental covariates as potential confounders in the regression models of air pollution and health (16,18). Individual-level covariates covered age, gender, body mass index (BMI), alcohol consumption, cigarette smoking, education, monthly expenditure, and physical exercise. Self-reported hypertension, diabetes, heart disease, stroke, and COPD/asthma accidents were also collected as individual covariates by questionnaire at the baseline period. Healthcare access for participants is relatively equitable in Hong Kong because of the virtually free public healthcare acting as the safety net for the whole community (27). We did not adjust for population density as a potential confounder because it was not found to be a predictor of RF mortality based on district-level data (**Web Figure 1**). Ecological covariates were about neighbourhood characteristics based on 197 Tertiary Planning Units (TPU) of Hong Kong, including the percentage of old people (≥ 65 years old), the percentage of tertiary education, and the percentage of household wage per capita over US$ 1923 (28). To estimate the passive exposure to second-hand smoke at baseline years, the percentage of smokers in the district was included as an environmental covariate (28).

Statistical analysis

We utilized Cox Proportional Hazard regression models to fit the relationship between annual $PM_{2.5}$ exposure and RF mortality among all cohort participants and those patients with existing CKD. We also estimated the associations between particulate matter exposure and the development of incident renal diseases including AKI, CKD, and unspecified RF. The attained age was chosen as the underlying time scale as it

automatically controlled for age as a confounding factor (29). The yearly $PM_{2.5}$ concentrations on city level were included in the model as a time-varying exposure of interest. The Cox proportional hazard assumption was tested before regression analysis.

We estimate hazard ratios (HRs) per interquartile-range (IQR) increments in $PM_{2.5}$ levels in regression models with hierarchical strategies for covariate adjustment (1,26). With age adopted as underlying time-scale variable, we controlled for the calendar year of entry and gender in Model 1. Besides covariates in Model 1, we additionally controlled for more individual covariates in Model 2, including body mass index (BMI), alcohol consumption, cigarette smoking, education, physical activity level, medication taken, monthly expenditure, and self-reported comorbidities at baseline, such as hypertension, diabetes, heart disease, stroke, and COPD and asthma. We further controlled for ecological and environmental covariates in Model 3, including Tertiary Planning Units characteristics (% old people, % tertiary education obtained, and % household income per capita ≥ US$ 1923 per month) as well as smoking rates in the district.

Sensitivity analyses were performed by: (i) not excluding subjects who died in the first follow-up year after baseline; (ii) excluding the death cases with less than three years of follow-up since enrolment; (iii) repeating the analysis on association of interest among patients with existing renal failure and all renal diseases only. Several stratification analyses were performed to examine potential heterogeneity by gender, BMI, as well as self-reported hypertension, diabetes, and heart disease at the baseline period. We examined the statistical significance of differences across subgroups by the subsequent algorithm: $(\beta_1 - \beta_2) \pm 1.96\sqrt{SE_1^2 + SE_2^2}$, where β_1 and β_2 are estimates for each subgroup with SE_1 and SE_2 being corresponding standard errors, respectively (30). The data were analysed using the statistical software R, version 3.3.2, and the 'survival' package.

RESULTS

A total of 66,820 participants were initially enrolled in the program. We firstly ruled out 1,932 (2.9%) participants for missing residential addresses for geocoding, 3,420 (5.1%) participants for missing $PM_{2.5}$ exposure estimates or wrong geocoding, and 21 (0.003%) participants for missing covariate data (**Figure 1**). The spatial distribution of the remained 61,447 subjects with complete data was shown in **Figure 2.** The mean age of participants at entry was about 72.0, and the proportion of women was 65.9%. Approximately 7.1% were categorized as underweight while 40.2% of participants were classified as the overweight or obese. There were 28.9% former or current smokers, 13.8% formal or regular drinkers, and 15.3% with hardly any physical

exercises. The majority of the participants (82.9%) had primary or below primary education. Approximately half of the participants reported active diseases (45.6%) and took regular medication (53.1%). According to self-reported co-morbidities, there were 36.0% enrolled participants with hypertension, 12.3% with diabetes, 12.4% with heart disease, 3.0% with stroke, and 5.6% with COPD or asthma (**Table 1**). No participants reported any kidney diseases in the baseline questionnaire forms and the identification of an incident CKD was based on data linkage to hospital admission records in the cohort follow up period.

At the baseline period from 1998 to 2000, the median values for $PM_{2.5}$ was 35.78 μg/m^3 and the corresponding IQR value was 3.22 μg/m^3. The median value was chosen as the cut-off point to differentiate high and low exposure categories. **Table 1** shows the distribution of covariates across high and low particulate matter exposures. Individual exposure to $PM_{2.5}$ of the cohort participants followed normal distributions (**Figure S1**). The correlation between annual $PM_{2.5}$ concentrations from satellite-based SEC and from general monitoring stations at the baseline period was 0.687 (p-value < 0.001).

In all three models, elevated $PM_{2.5}$ exposures were associated with a higher risk of RF mortality among all cohort participants and those incident CKD patients in statistical significance. The HR for RF mortality per IQR increment in $PM_{2.5}$ (3.22 μg/m^3) among all cohort participants was 1.23 (95% confidence interval [CI]: 1.06 to 1.43) (**Table 2**). During 10 years of follow-up, we totally identified 1,204 incident CKD patients, and the HR of interest increased to 1.42 (95% CI: 1.16 to 1.74) among the subpopulation of the CKD patients (**Table 2**). In further subgroup analyses, an IQR increment in $PM_{2.5}$ led to elevated mortality risk of AKI (2.03; 95% CI: 1.34 to 3.08), but not CKD (1.14; 95% CI: 0.96 to 1.36) or unspecified RF (1.19; 95% CI: 0.80 to 1.78) (**Table 3**). On the relation of air pollution with the development of all incident renal diseases, the risk estimates for AKI and CKD per IQR increase in $PM_{2.5}$ levels were 1.20 (95% CI: 1.04 to 1.38) and 0.95 (95% CI: 0.87, 1.03), respectively (**Web Table 1**).

The overall associations between fine particulate matter and RF mortality risk among all participants and CKD patients were close to linear (**Figure 3**). There is some indication that dose-response curves level off when the concentrations of $PM_{2.5}$ exceed over 40 μg/m^3. In subgroup results, we did not find risk estimate differences across gender, BMI, self-reported hypertension, diabetes, or heart diseases (**Table 4**). Consistent results were generated in the series of sensitivity analyses by including participants who died in the first follow-up year after baseline, excluding those death cases with less than three years of follow-up and estimating association of $PM_{2.5}$ with RF-related mortality among patients with existing renal failure and all renal diseases (**Web Table 2 and Web Table 3**).

DISCUSSION

In the current elderly cohort study in Hong Kong, particulate matter air pollution was associated with elevated risks of RF mortality among all cohort subjects and especially those CKD patients. On a more detailed analysis of the entire natural history of kidney disease, we did not find an association of air pollution with the development of incident CKD. Therefore, it is likely the overall association of air pollution with RF mortality reflects mainly the progression of CKD exacerbated by air pollution. However, caution is needed for this interpretation because the identification of an incident CKD case was based on self-reports and record linkage to public hospital admission data. No participants reported any kidney diseases in the baseline questionnaire forms, but it was possible that a fraction of the cohort participants were already chronic kidney disease patients; on the other hand, those admitted to hospitals due to CKD might represent just the fraction of incident CKD cases whose symptoms were severe enough for hospitalization. In comparison with the identification of incident CKD cases, the renal disease mortality data should be more accurate because almost all deaths in Hong Kong occurred in hospitals with an accurate and consistent death ascertainment (24). Therefore, the current findings contribute to the evidence base on the relation of long-term air pollution exposure with RF mortality in the elderly population.

Our findings were generally consistent with previous studies on air pollution and renal diseases. While the estimated effect sizes varied among the populations of the United States, mainland China, Taiwan, Korea, and Hong Kong, air pollution was consistently associated with elevated risks of kidney diseases. We found relatively higher risks of RF mortality associated with $PM_{2.5}$, especially among CKD patients in Hong Kong elderly cohort, but the effect size of CKD incidence associated with $PM_{2.5}$ was higher in the United States population than that in the Asian population. Specifically, cross-sectional studies in the US observed an association of $PM_{2.5}$ with a drop of estimated glomerular filtration rate (eGFR) and CKD prevalence (13,16). Studies in the cohort of US veterans found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10} corresponded to 27% and 7% increases in CKD incidence, respectively (14,15). In Asians, a series of cross-sectional studies found that exposure to PM_{10} or $PM_{2.5}$ associated with increased risks of membranous nephropathy, eGFR decline, and CKD prevalence in the population of mainland China, Taiwan, and Korea (18,19,31). And in a cohort study in Taiwan, it was estimated that a 10 $\mu g/m^3$ increment in $PM_{2.5}$ corresponded to 6% increases in CKD incidence (17).

Fine particulate matter air pollution was associated with elevated AKI mortality in the current study. AKI is a syndrome characterized by the rapid loss of the kidney's excretory function and interconnected with CKD (32). The risk factors for AKI include diabetes, cardiovascular disease, cancer and complex surgery (12). The association between air pollution and AKI might relate to $PM_{2.5}$ inhalation derived systemic inflammation and the subsequent exacerbation of AKI symptoms (8,33). By stratification analysis, we found a weak difference across gender or BMI about the association between $PM_{2.5}$ and RF mortality. The findings in Hong Kong elderly population were consistent with the observations from the Taipei metropolis (18). We did not observe risk estimate difference between participants with and without hypertension, diabetes, or heart diseases self-reported in the baseline questionnaires. The potential heterogeneity in the relation between air pollution and renal diseases by co-morbidities should be examined more systematically in future studies.

The biological mechanisms underlying the impacts of air pollutants on the renal system remain largely uncertain. Mehta and colleagues hypothesized that the adverse association was mediated by an increase in the diastolic blood pressure (DBP) (16). Numerous studies indicated the association between $PM_{2.5}$ exposure and markers of endothelial/vascular dysfunction, particularly the serum creatinine-derived eGFR decline, CKD and end-stage renal disease, which might result in the worst outcome of renal diseases (34,35). However, few studies explored the mediation function of DBP on the pathway from ambient air pollution to the renal diseases in human epidemiological studies. A second hypothesis is on the oxidative stress and air pollution induced inflammatory mediators, including IL-6, TNF-α, and plasminogen activator inhibitor-1. These immunological molecules may exaggerate vasoconstrictor responses to serotonin and phenylephrine, and result in severe renal diseases (6–8,36). A third hypothesis suggested that ambient air pollution might result in metabolic disturbances, including decreased insulin sensitivity, glucose intolerance, weight gain, higher blood lipid concentrations, and diabetes mellitus, most of which are risk factors for AKI, CKD, and even end-stage renal disease (37,38). It is likely that more than one mechanistic pathway are involved in the association between particulate matter air pollution and various renal diseases.

A few limitations of the present study need to be noted. First, participants were enrolled on a voluntary basis and they might be more health-conscious than the general elderly population in Hong Kong. Indeed, there were fewer smokers and drinkers in the cohort than in the general population (**Table 1**). Moreover, there were more women participants (65.9%) in this cohort than the overall elderly population in Hong Kong. Caution is needed to interpret the generalizability of the current findings. Second, we used surface extinction coefficients (SEC) from AOD within 1 km × 1 km of ground level to predict air concentrations of particulate matters.

Exposure variability was relatively modest for $PM_{2.5}$ (IQR≈9% of mean) (25), which was a restraint on the statistical power in the current study. Third, we did not perform specific clinical checks on the participants' renal functions at the baseline, especially their GRF levels. There might be some enrolled participants with slight renal dysfunctions but without obvious clinical symptoms. Fourth, residual confounding was still possible. Social-economic status was only controlled for by education level, monthly expenditure, and some district-level covariates, and information on hypertensive or diabetic medications was not available for the current analysis.

In conclusion, long-term exposure to fine particulate matter air pollution might be an important risk factor of RF mortality in the elderly population, especially among the subjects with existing chronic kidney disease. These population-level findings contribute to the evidence base on the relation of air pollution with renal diseases which should be further complemented by experimental and clinical studies.

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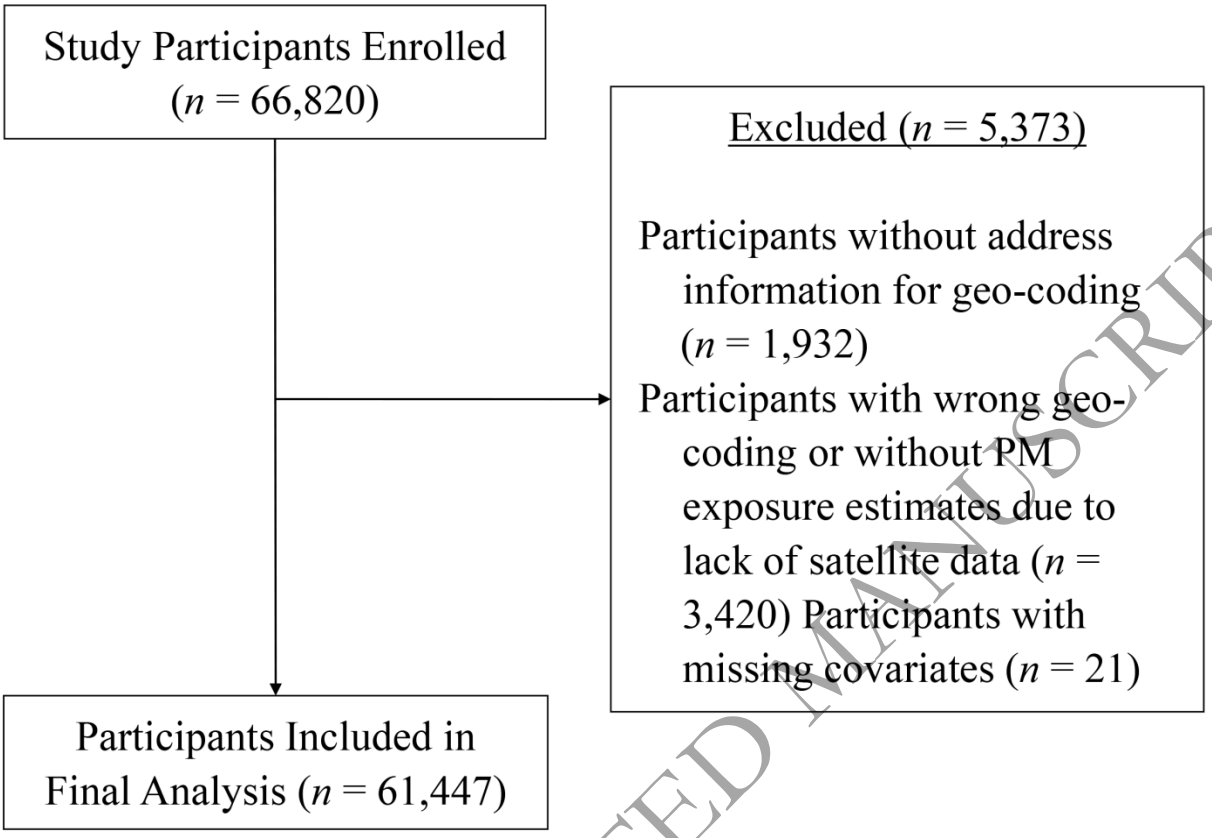
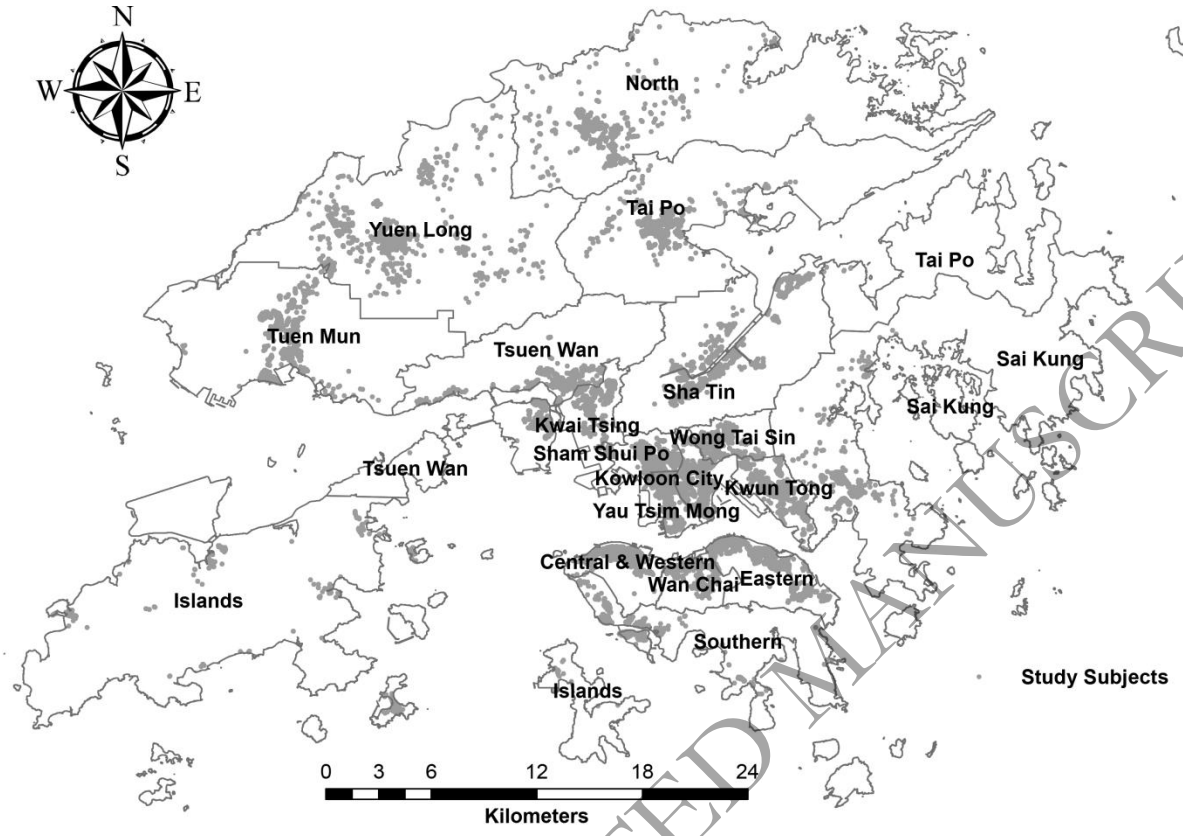
FIGURE TITLES AND LEGENDS

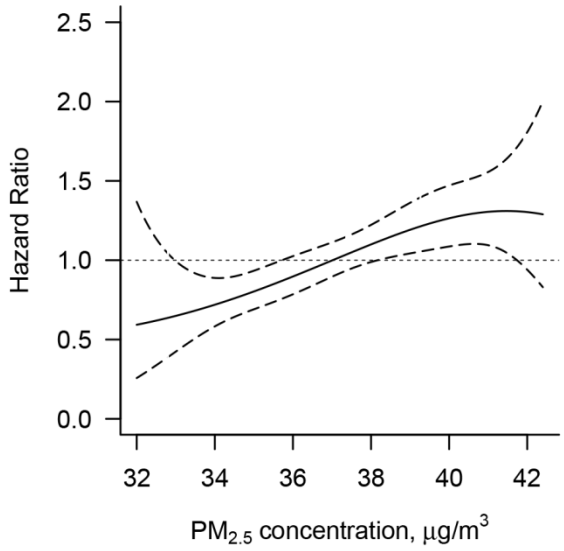
Figure 1. Description of the inclusion process for cohort participants in the analysis.

Figure 2. Spatial distribution of the cohort participants (n = 61,447) in Hong Kong at baseline (1998–2000).

Figure 3. Concentration-response relationships between fine particulate matter and the mortality from renal failure among all participants and CKD patients in the Elderly Health Service Cohort in Hong Kong from 1998 to 2010. Figure 3A shows the association with mortality from renal failure among all participants; Figure 3B shows the association among CKD patients.







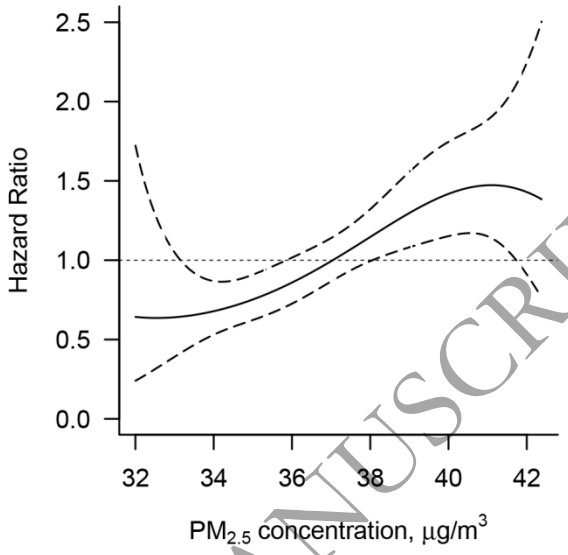


Table 1. Statistics of the Elderly Health Services cohort (n = 61447) by $PM_{2.5}$ exposure (μg/cm^3) in Hong Kong from 1998 to 2010.

Variables	All participants		Exposure to low level of $PM_{2.5}$		Exposure to high level of $PM_{2.5}$	
	No.	%	No.	%	No.	%
No. of participants	61447		30717		30730	
Age at entry [b]	72.0 (5.6)		72.0 (5.6)		72.1 (5.6)	
Gender						
Men	20933	34.1	10539	34.3	10394	33.8
Women	40514	65.9	20177	65.7	20337	66.2
BMI quartiles						
Underweight	4368	7.1	2106	6.9	2262	7.4
Normal weight	32370	52.7	15978	52.0	16392	53.3
Overweight	20921	34.0	10588	34.5	10333	33.6
Obese	3788	6.2	2044	6.7	1744	5.7
Cigarette smoking						
Never	43669	71.1	21947	71.5	21722	70.7
Former	11871	19.3	5881	19.1	5990	19.5
Current	5907	9.6	2888	9.4	3019	9.8
Alcohol consumption						
Never/social drinker	52986	86.2	26497	86.3	26489	86.2
Formal/regular drinker	8461	13.8	4219	13.7	4242	13.8
Physical activity in week						
Never [0]	9406	15.3	4314	14.0	5092	16.6
Medium [1-6]	7789	12.7	3839	12.5	3950	12.9
High [7]	44252	72.0	22563	73.5	21689	70.6
Education						
Below primary	28242	46.0	14415	46.9	13827	45.0
Primary	22656	36.9	10931	35.6	11725	38.2
Secondary or above	10549	17.2	5370	17.5	5179	16.9
Expenses/month						
Low (<128 USD)	10122	16.5	4323	14.1	5799	18.9
Medium (128-384 USD)	42152	68.6	21474	69.9	20678	67.3
High (≥385 USD)	9173	14.9	4919	16.0	4254	13.8
Medication taken						
Yes	32628	53.1	16262	53.9	16366	53.3
No	28819	46.9	14454	47.1	14365	46.7
Hypertension						
Yes	22123	36.0	10987	35.8	11136	36.2
No	39324	64.0	19729	64.2	19595	63.8
Diabetes						
Yes	7542	12.3	3742	12.2	3800	12.4
No	53905	87.7	26974	87.8	26931	87.6
Heart disease						
Yes	7618	12.4	3648	11.9	3970	12.9
No	53829	87.6	27068	88.1	26761	87.1
Stroke						
Yes	1817	3.0	831	2.7	986	3.2
No	59630	97.0	29885	97.3	29745	96.8
COPD						
Yes	3458	5.6	1702	5.5	1756	5.7
No	57989	94.4	29014	94.5	28975	94.3
TPU level covariates [b]						
Prevalence of age ≥ 65	12.11 (4.19)		11.39 (4.08)		12.83 (4.17)	
Prevalence of tertiary education	12.98 (7.96)		13.33 (8.24)		12.64 (7.66)	
Prevalence of income ≥ 1923 $/month	59.50 (11.60)		61.87 (10.95)		57.13 (11.75)	

Abbreviation: $PM_{2.5}$, fine particulate matter (aerodynamic diameter ≤ 2.5 μm); COPD, chronic obstructive pulmonary disease; TPU, tertiary planning units; BMI, body mass index.

[a] Low and high $PM_{2.5}$ exposure is defined by using the median (35.7756 μg/cm^3) as the cut-off point.

[b] Mean (SD) is shown for continuous variables, including Age at entry as well as three TPU level covariates.

Table 2. Hazard ratio (95% CI) per IQR increase in $PM_{2.5}$ associated with the morality from all renal failure using different models within the Elderly Health Services Cohort in Hong Kong from 1998 to 2010.

Models	All participants				CKD patients			
	No. deaths	HR	95%CI	P-value	No. deaths	HR	95%CI	P-value
Model 1 [a]	443	1.24	1.08, 1.43	0.002	253	1.56	1.30, 1.87	< 0.001
Model 2 [b]	443	1.27	1.11, 1.46	0.001	253	1.57	1.31, 1.90	< 0.001
Model 3 [c]	443	1.23	1.06, 1.43	0.007	253	1.42	1.16, 1.74	0.001

Abbreviation: $PM_{2.5}$, fine particulate matter (aerodynamic diameter ≤ 2.5 μm); IQR, interquartile range; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval.

[a] Calendar year of entry and gender were controlled in Model 1;

[b] Individual covariates at baseline were controlled in Model 2, gender, BMI, calendar year of entry, cigarette smoking, education, alcohol consumption, monthly expenses, physical activity level, medication taken, hypertension, diabetes mellitus, heart disease, stroke and COPD/asthma;

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

Table 3. Hazard ratio (95% CI) per IQR increase in $PM_{2.5}$ associated with the mortality from specific renal failure (AKI, CKD, and unspecified renal failure) using different models within the Elderly Health Services Cohort in Hong Kong from 1998 to 2010.

Models	AKI			CKD			Unspecified RF		
	No. deaths	HR	95%CI	No. deaths	HR	95%CI	No. deaths	HR	95%CI
Model 1 [a]	63	1.83	1.27, 2.65	319	1.16	0.99, 1.36	58	1.34	0.92, 1.97
Model 2 [b]	63	1.82	1.26, 2.65	319	1.18	1.01, 1.39	58	1.39	0.95, 2.05
Model 3 [c]	63	2.03	1.34, 3.08	319	1.14	0.96, 1.36	58	1.19	0.80, 1.78

Abbreviation: RF, renal failure; AKI, acute kidney injury; CKD, chronic kidney disease; IQR, interquartile range; $PM_{2.5}$, fine particulate matter (aerodynamic diameter ≤ 2.5 μm); HR, hazard ratio; CI, confidence interval.

[a] Calendar year of entry and gender were controlled in Model 1;

[b] Individual covariates at baseline were controlled in Model 2, gender, BMI, calendar year of entry, cigarette smoking, education, alcohol consumption, monthly expenses, physical activity level, medication taken, hypertension, diabetes mellitus, heart disease, stroke and COPD/asthma;

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

Table 4. Stratified analyses of the association between $PM_{2.5}$ and the mortality from total/specific renal failure in Model 3 within the Elderly Health Services Cohort in Hong Kong from 1998 to 2010 [a].

Stratified characteristic	RF			AKI			CKD			Unspecified RF		
	HR	95%CI	P [b]	HR	95%CI	P [b]	HR	95%CI	P [b]	HR	95%CI	P [b]
Gender												
Men	1.18	0.93, 1.49		3.58	1.56, 8.25		1.17	0.89, 1.52		0.75	0.42, 1.34	
Women	1.27	1.04, 1.54	0.638	1.75	1.08, 2.86	0.147	1.13	0.90, 1.43	0.865	1.90	1.07, 3.40	0.026
BMI												
Normal-weight	1.35	1.09, 1.67		2.22	1.21, 4.06		1.32	1.03, 1.70		1.08	0.63, 1.85	
Underweight	1.08	0.79, 1.47	0.242	1.71	0.82, 3.60	0.599	0.91	0.62, 1.32	0.099	1.51	0.65, 3.53	0.516
Overweight/Obese	1.16	0.86, 1.55	0.760	2.30	0.92, 5.75	0.627	1.05	0.75, 1.47	0.558	1.41	0.60, 3.29	0.910
Hypertension												
No	1.14	0.88, 1.48		2.01	1.09, 3.68		0.99	0.71, 1.37		1.21	0.67, 2.17	
Yes	1.28	1.07, 1.54	0.483	2.08	1.18, 3.68	0.928	1.22	0.99, 1.50	0.282	1.25	0.72, 2.17	0.932
Diabetes												
No	1.20	1.00, 1.44		2.05	1.29, 3.26		1.07	0.86, 1.33		1.33	0.83, 2.12	
Yes	1.30	1.00, 1.70	0.630	1.90	0.75, 4.84	0.890	1.29	0.96, 1.74	0.330	0.98	0.45, 2.10	0.501
Heart disease												
No	1.28	1.08, 1.52		2.13	1.35, 3.34		1.19	0.97, 1.45		1.26	0.79, 1.99	
Yes	1.05	0.76, 1.47	0.301	1.63	0.57, 4.70	0.652	1.02	0.69, 1.49	0.483	1.02	0.42, 2.51	0.689

Abbreviation: RF, renal failure; AKI, acute kidney injury; CKD, chronic kidney disease; $PM_{2.5}$, fine particulate matter (aerodynamic diameter ≤ 2.5 μm); BMI, body mass index; HR, hazard ratio; CI, confidence interval.

[a] All individual, ecological and environmental covariates were controlled in Model 3, including gender, BMI, calendar year of entry, cigarette smoking, education, alcohol consumption, monthly expenses, physical activity level, medication taken, hypertension, diabetes mellitus, heart disease, stroke and COPD/asthma, as well as the TPU level covariates (prevalence of age over 65, tertiary education, and income $\geq$ 1923/m USD), and smoking rate at district level.

[b] P standards for the result of Wald test between the stratified items, such as HR in men vs HR in women (in BMI, they are normal-weight vs underweight; normal-weight vs overweight/obese)