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Long Term Exposure to Air Pollution and Mortality in an elderly cohort in Hong Kong

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Abstract

Background: Several studies have reported associations between long term exposure to air pollutants and cause-specific mortality. However, since the concentrations of air pollutants in Asia are much higher compared to those reported in North American and European cohort studies, cohort studies on long term effects of air pollutants in Asia are needed for disease burden assessment and to inform policy.

Objectives: To assess the effects of long-term exposure to particulate matter with aerodynamic diameter < 2.5μm ($PM_{2.5}$), black carbon (BC) and nitrogen dioxide (NO_2) on cause-specific mortality in an elderly cohort in Hong Kong.

Methods: In a cohort of 66,820 participants who were older than or equal to 65 years old in Hong Kong from 1998-2011, air pollutant concentrations were estimated by land use regression and assigned to the residential addresses of all participants at baseline and for each year during a 11 year follow up period. Hazard ratios (HRs) of cause-specific mortality (including all natural cause, cardiovascular and respiratory mortality) associated with air pollutants were estimated with Cox models, including a number of personal and area-level socioeconomic, demographic, and lifestyle factors.

Results: The median concentration of $PM_{2.5}$ during the baseline period was 42.2 $\mu g/m^3$ with an IQR of 5.5 $\mu g/m^3$, 12.1 (9.6) $\mu g/m^3$ for BC and 104 (25.6) $\mu g/m^3$ for NO_2. For $PM_{2.5}$, adjusted HR per IQR increase and per 10 $\mu g/m^3$ for natural cause mortality was 1.03 (95%CI: 1.01, 1.06) and 1.06 (95%CI: 1.02,1.11) respectively. The corresponding HR were 1.06 (95%CI: 1.02, 1.10) and 1.01 (95%CI: 0.96, 1.06) for cardiovascular disease and respiratory disease mortality, respectively. For BC, the HR of an interquartile range increase for all natural cause mortality was 1.03 (95%CI: 1.00, 1.05). The corresponding HR was 1.07 (95%CI: 1.03, 1.11) and 0.99 (95%CI: 0.94, 1.04) for cardiovascular disease and respiratory disease mortality. For NO_2, almost all HRs were approximately 1.0, except for IHD (ischemic heart disease) mortality.

Conclusion: Long-term exposure to ambient $PM_{2.5}$ and BC was associated with an elevated risk of cardiovascular mortality. Despite far higher air pollution exposure concentrations, HRs per unit increase in $PM_{2.5}$ were similar to those from recent comparable studies in North America.

Key words: Hong Kong, Air pollution, Mortality, Cohort study

Highlights

- Cohort studies on long term effects of exposure to high level air pollutants in Asia are needed
- Long-term exposure to $PM_{2.5}$ and BC, but not $NO_{2,}$ was associated with cardiovascular mortality in a cohort of elderly adults.
- Hazard ratios for $PM_{2.5}$ were similar to those in recent comparable studies in North America, despite far higher exposure levels.

1. Introduction

Multiple studies have reported associations between long term exposure to air pollutants and adverse health effects (Beelen et al. 2008; Beverland et al. 2012; Gan et al. 2011; Ostro et al. 2015; Ostro et al. 2010; von Klot et al. 2009). Hong Kong is one of the many high-density, high-rise cities in Asia with a significant air pollution issue. In common with many Asian cities, concentrations of air pollutants in Hong Kong are relatively high compared to most European and North American cities, with different composition and exposure patterns. Annual mean $PM_{2.5}$ in Hong Kong was reported by Lee et al. (2006) as 42.2 $\mu g/m^3$, in contrast to the range of $PM_{2.5}$ concentrations typically reported in Western cohort studies of 4.1 to 31 $\mu g/m^3$ (Cohen et al. 2017). Regional secondary particulate smog, which is transported from mainland China, and local street level air pollution serve as the two most important causes for the air pollution problem in Hong Kong (Lee et al. 2006). Regional smog in Hong Kong is formed by a mixture of emissions from traffic, industry and vegetative burning (Lee et al. 2006).

A previous analysis of an elderly cohort in Hong Kong observed that long term exposure to $PM_{2.5}$ was linked with natural cause and cardiovascular mortality (Wong et al. 2015). Wong used satellite-based estimates of $PM_{2.5}$ at a scale of 1 km x 1 km and did not assess other pollutants. This study used exposure estimates that may not have captured spatial variability in pollution levels in Hong Kong and may also have been subject to bias due to cloud cover, which may have been more common during period of higher or lower air pollution. Further, the monitoring data that was used in combination with the satellite-based estimates were from a limited number of Government network stations. Recently, land use regression models were developed for Hong Kong, allowing for improved characterization of spatial variability and assessment of additional pollutants (Lee et al. 2017)., In this study, we applied these higher resolution models to the same cohort in order to extend the prior analysis and strengthen the evidence base for epidemiological studies of effects of long term exposure at levels typical of Asian cities.

2. Methods

2.1 Study population

66,820 subjects, accounting for 9% of people who were older than or equal to 65 years old in Hong Kong, were enrolled from July 1998 to December 2001 by the Department of Health Elderly Health Service of the Hong Kong Government. The purpose of the cohort was to promote understanding of aging in Hong Kong where

the patterns of common chronic diseases and their determinants may differ from those in the West. The cohort, and it's study population, is described in detail by (Schooling et al. (2016). Briefly, Elderly Health Centers (EHC) located in each of the 18 districts in Hong Kong provided health assessments, using standardized and structured interviews, and comprehensive clinical examinations. Information on socio-demographics, lifestyle, and disease history was collected by doctors and registered nurses (Schooling et al. 2016). The health assessment was conducted at the baseline period as well as the follow-up period. There were no specific time points for the follow up health assessment; the participants voluntarily re-enrolled in the Elderly Health Center at least 1 year after their last health assessment. Follow-up compliance was high; nearly 70% of the participants re-enrolled within 3 years of their baseline assessment. Record linkage to the death registry (via Hong Kong Identification Number) was used to examine mortality up to December 31, 2011. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

2.2 Mortality outcomes

Deaths were coded according to the *International classification of Diseases, 10th Revision* (ICD-10; WHO 2010) including natural cause mortality (A00–R99), overall cardiovascular disease (I00–I99) and overall respiratory disease (J00–J47 and J80–J99). Subcategories included Ischemic heart disease (IHD) (I20–I25), cerebrovascular disease (I60–I69), Pneumonia (J12–J18) and chronic obstructive pulmonary disease (COPD) (J40–I44 and I47). Participants were excluded if they died within the first year of enrollment. The majority of deaths in Hong Kong occur in hospital, facilitating the consistent and accurate ascertainment of death (Schooling et al. 2016).

2.3 Exposure assessment

The LUR models were derived from street level measurements collected during two sampling campaigns conducted in 2014 and 2015. The model outcomes, including concentration maps, discussion of model performance and interpretation of results are described in detail by Lee et al. (2017).

In brief, two sampling campaigns, corresponding to warm (April 24, 2014 to May 30, 2014) and cool seasons (November 18, 2014 to January 06, 2015), were conducted at 84 sites in Hong Kong for $PM_{2.5}$ and BC. Measurements of NO_2 were collected with passive samplers at ~100 locations. Candidate spatial metrics were selected based on those used in other LUR models (Abernethy et al. 2013; Allen et

al. 2012). These predictors included an array of marine (port and shipping), air and road traffic, urban build-up and land use measures as well as information on locations of point and area air pollution sources. The $PM_{2.5}$ LUR (R^2 = 0.59, RMSE = 4 $\mu g/m^3$) model included length of expressways, distance to Shenzhen (mainland China), car park density, government and industrial land use as predictors. The BC model (R^2=0.50, RMSE = 4 $\mu g/m^3$) length of expressways, longitude, car park density, commercial, mixed, residential area, undeveloped land use as predictors. The NO_2 Model (R^2 = 0.46, RMSE = 28 $\mu g/m^3$) included length of elevated roads, building volume density, industrial land use and population density as predictors. The differing predictive variables between pollutants, and resulting differing spatial patterns (Lee et al, 2107), highlighted the need for separate assessments for the three pollutants. The concentrations of air pollutants estimated by the LUR models were assigned to all participants according to their geocoded residential addresses at baseline periods. For the entire follow up period, there were only 9.3% participants who changed address. Change in address was accounted for in the exposure estimate assignment.

It should be noted that population density and land use in Hong Kong is very unevenly distributed, with high density around coastal areas and very low density on higher ground, most of which is reserved parkland. The sampling campaign used to develop the LUR model was focused on developed land and roadside locations, which made it more suitable for predicting concentrations in populated areas.

2.4 Back-extrapolation of exposure estimates

Since the LUR model was developed in 2014, prior measured concentrations from 1998 to 2011 were used to extrapolate the LUR model estimates back in time. This back-extrapolation method was based on the assumption that there were no large geographical changes during the study period in Hong Kong. Multiple published analyses have demonstrated stability in spatial variation in air pollution over many years in Western cities (European study of cohorts for Air Pollution Effects 2012; Gulliver et al. 2013; Wang et al. 2013). While this assumption may not be valid in rapidly developing cities in mainland China, Hong Kong is a relatively geographically stable and well-developed city, therefore we considered this a robust assumption.

First, we calculated the moving average of pollutants concentrations from routine monitoring stations one year before and one year after the recruitment date on a

monthly basis for each participant. Second, in line with the ESCAPE methodology, the ratio (for BC, NO_2) or difference (for $PM_{2.5}$) was calculated between the moving average and annual average which covered the measurement period (2014) from routine monitoring stations for each participant. Third, we calculated the baseline back-extrapolated concentrations by multiplying the ratio or the difference and the modelled annual average covering the measurement period (2014). A similar method was also applied when estimating the yearly exposure. We used the concentration of elemental carbon from monitoring stations instead of BC, which was not available for the whole study period.

2.5 Statistical analysis

We fitted Cox proportional hazards models to estimate the associations between air pollutants and the health endpoints. The selected underlying time scale was time to event, with the duration being from date of enrolment to the date of death for the diseases studied or censored by the end of 2011. The estimated annual air pollutant concentrations at each participant's baseline year served as a time independent variable to estimate long term air pollutants exposure in the main analysis (Wong et al. 2015). We also checked the Cox proportional hazard (PH) assumptions by using the *cox.zph* function in the survival package in R. *Cox.zph* creates interactions with time for testing the PH assumption. Natural cubic splines with 3 degrees of freedom (df) were applied to plot the exposure-response relation of air pollutants with all natural cause and cardiorespiratory mortality. Three df models were selected following the application of Bayesian Information Criterion to evaluate the relative goodness of fit for Cox models with one, two, three and four df. Linearity was tested by comparing the fit of the spline and linear model using the likelihood ratio x^2 test (Abrahamowicz et al. 2003). Potential confounders included personal covariates demographic, socioeconomic, and lifestyle factors, Tertiary Planning Units (TPU) level covariates, sociodemographic variables and district level covariates smoking rate variables were also included in the models. There are 289 TPUs in Hong Kong, each with a population between 2000 and 110,000. These are aggregated into 18 districts with between 137,000 and 608,000 population. For the personal covariates (assessed at baseline), age at enrolment, gender, individual smoking status, body mass index (BMI), level of physical activity, education level and monthly expenses were included in the model. Moreover, for TPU-level covariates, percentage of participants who were equal to or older than 65 years old, percentage of participants whose educational level was higher than secondary school and average income per month within each TPU.

Finally, percentage of smokers were also adjusted at district level (Wong et al. 2015) as an indicator for secondhand smoke exposure. We applied 3 different models in our analysis. Model 1 only included the single pollutant. Model 2 adjusted age at entry, gender, individual smoking status, body mass index (BMI), physical activity, education level and monthly expenses. Model 3 adjusted percentage of participants who were equal to or older than 65 years old, percentage of participants whose educational level was higher than secondary school, average income per month and percentage of smokers. While duration of smoking, diet and alcohol consumption were not included quantitatively, the use of qualitative personal information, plus district and TPU-level quantitative socio-economic factors minimized the impact of these confounders.

Of the 66,820 participants who were included in the initial cohort, we excluded 3,602 due to an inability to geocode their residential address; 1,221 who were missing covariates (of whom 1999 were missing TPU-level covariates and 22 were missing individual-level covariates); 611 who lived in area outside of the domain of the LUR model, resulting in 61,386 participants in the final analysis.

Several sensitivity analyses were carried out to examine the robustness of the results in the main analysis; (i) using a co-pollutant model, (ii) annual concentrations as time-varying exposure, (iii) including the participants who died within one year after the enrolment, and (iv) excluding participants who died within the first 3 years. To evaluate potential effect modification, separate analyses were stratified by age at entry (<71 or ≥ 71 according to the median age 70), sex (male and female) and BMI (low <21.6 kg/m^2, middle 21.6-26.3 kg/m^2, high >26.3 kg/m^2). The *p* value for interaction term was assessed by evaluating the interaction between $PM_{2.5}$ and BC and the potential effect modifier.

R 3.3.2 was utilized to perform statistical analyses (R Development Core Team, 2016).

3. Results

Among the 61,386 participants who met the inclusion criteria, 33% were male and 67% were female; the average (SD) age was 70.2 (5.5) years (Table 1). The median follow-up time was 11 years. Residential locations of all participants are presented in Figure 1.

Annual concentrations of BC decreased gradually throughout the whole study period, in comparison to the concentrations of NO_2 and $PM_{2.5}$, which were more stable (Supplementary Information, Figure S1). The modelled distribution of $PM_{2.5}$ and NO_2 exposures at individual residential locations approximated a normal distribution during the baseline period, while the distribution of BC was right-skewed (Figure 2). The median concentration of $PM_{2.5}$ during the baseline period was 42.2 $\mu g/m^3$ with an IQR of 5.5 $\mu g/m^3$, 12.1 (9.6) $\mu g/m^3$ for BC and 104 (25.6) $\mu g/m^3$ for NO_2. Linear exposure-response relationships were observed between $PM_{2.5}$ and cardiovascular mortality (*p* value =0.77 comparing the fit of the spline model to a linear model), BC (*p* value =0.85), and NO_2 (*p* value =0.44). Overall, the three air pollutants were not strongly correlated; R^2: 0.00 (NO_2 vs $PM_{2.5}$), 0. 12 (NO_2 vs BC) and 0.32 (BC vs $PM_{2.5}$).

Hazard Ratios per IQR for the three models and three pollutants are shown in Table 2. For $PM_{2.5}$, the HR of an IQR (5.5 $\mu g/m^3$) increase for natural cause mortality, including all covariates, was 1.03 (95%CI: 1.01, 1.06). The corresponding HR for cardiovascular disease mortality was 1.06 (95%CI: 1.02, 1.10HRs for the associations between $PM_{2.5}$ and overall respiratory mortality was 1.01 (95%CI: 0.96, 1.06), but increased to 1.06 (95%CI: 0.97, 1.15) in the COPD subtype (Table 3). HRs per 10 $\mu g/m^3$ increase of $PM_{2.5}$ were higher, reflecting the IQR of 5.5 $\mu g/m^{-3}$ (Supplementary Information, Table S2). For example, HR of a 10 $\mu g/m^3$ increase for natural cause mortality was 1.06 (95%CI: 1.02, 1.11). The corresponding HR for cardiovascular disease mortality was 1.11 (95%CI: 1.03, 1.19.

For BC, the HR in a fully-adjusted model for an IQR (9.6 $\mu g/m^3$) elevation of BC for natural cause mortality was 1.03 (95%CI: 1.00, 1.05). The HR for cardiovascular disease mortality was 1.07 (95%CI: 1.03, 1.11). For the associations between BC and overall respiratory mortality the HR was 0.99 (95%CI: 0.94, 1.04), with similar results for each respiratory subtype.

For NO_2, the HRs for natural cause, cardiovascular and respiratory mortality were approximately equal to 1.0, except for IHD mortality 1.09 (95%CI: 1.00, 1.18). Including covariates in the models decreased HRs for $PM_{2.5}$ and BC, but increased HRs for NO_2.

In multi-pollutant models, the effects of BC on different outcomes were insensitive to inclusion of additional pollutants (Table 3). For $PM_{2.5}$ (Table 4) and NO_2 (Table 5), effect estimates remained also robust in multipollutant models.

Stratification analysis showed that HRs for IHD mortality associated with an IQR elevation in $PM_{2.5}$ and BC concentration was higher for people who were younger than 71 years old in comparison to people who were older than 71. The corresponding association for overall cardiovascular diseases was higher for men than for women for both $PM_{2.5}$ and BC. As for BMI, participants whose BMI >=26.3kg/m^2 had higher risks for natural cause and cardiovascular mortality, compared to those with lower BMI (Figure 3).

In the sensitivity analyses (Table S1-Table S3), the estimates remained similar across different inclusion and exclusion criteria, except for $PM_{2.5,}$ where the effects estimates diminished and became non-significant when yearly average concentration was utilized as exposure.

4. Discussion

This cohort study demonstrated that long-term exposure to $PM_{2.5}$ and BC, was associated with natural cause and cardiovascular mortality, but not respiratory mortality, among an elderly population in Hong Kong - a high-density and high-rise city in Asia. For NO_2, there was no evidence of positive associations for either cardiovascular or respiratory mortality. Effect estimates remained similar for various time exposure windows.

Associations between $PM_{2.5}$ and cardiovascular diseases have been reported in a large number of epidemiologic studies (Atkinson et al. 2014; Beelen et al. 2014). A recent Medicare cohort (Di et al. 2017), which covered 60,925,443 persons aged 65 years old or older from 2002 to 2012, reported that an elevation of 10 μg/m^3 for $PM_{2.5}$ was associated with a 7.3% (95%CI: 7.1, 7.5%) increase of natural cause mortality in low $PM_{2.5}$ concentrations. The results in our study are similar: an elevation of 10 μg/m^3 for $PM_{2.5}$ was associated with (6%, 95%CI: 2%, 11%) increase in all natural cause mortality, despite the much higher levels of exposure in the Hong Kong cohort (median 42.2 μg/m^3) than the Medicare cohort (mean 11.5 μg/m^3) and the differences in pollutant mixture.

Several studies have also reported long term associations between BC and cardiovascular mortality. For example, a study in Vancouver reported an IQR increase of BC estimated by LUR was associated with a 6% (95%CI: 3, 9%) increase of coronary heart disease mortality (Gan et al. 2011). While the Vancouver study suggested that BC might be partly responsible for the association between traffic related air pollution and cardiovascular outcomes. In our current study, we found both $PM_{2.5}$ and BC served as important indicators for the

association between air pollution and cardiovascular mortality. This may be due to different pollutant concentration levels and sources in Hong Kong (regional sources of $PM_{2.5}$ and relatively unregulated marine sources of BC) compared to Vancouver. A review of 22 European cohort studies, reported that a $10^{-5}m^{-1}$ increment for $PM_{2.5}$ absorbance, which has been used as a measure of BC in most European epidemiological studies (Janssen et al. 2012), was associated with a 9% (95%CI: -5, 22%) increase of overall cardiovascular mortality, a 7% (95%CI: -15, 28%) increase of ischemic heart disease death and a 21% (95%CI: -9, 0.51) increase of cerebrovascular disease death (Beelen, 2014). A suggestive association with cerebrovascular diseases was also reported, whereas we did not observe any such association. Differences in sample size, geographical coverage between our elderly cohort and studies of general population may be possible explanations for this difference.

In contrast, little evidence has been accumulated in regards to respiratory mortality. In our study we did not observe associations with respiratory mortality. In contrast, the Vancouver study reported that an IQR increase of BC was associated with a 7% (95%CI: 0, 13%) elevation in COPD mortality (Gan et al. 2013). A study in the Netherlands reported that an IQR increase of black smoke was associated with a 18% (95%CI: -1, 37%) elevation for respiratory disease (Beelen et al. 2008). In both Vancouver and the Netherlands, road traffic was regarded as an important source of BC, whereas in Hong Kong, besides road traffic, marine sources (defined as emissions from ports, ferry movements and shipping lanes) also played an important role on the spatial variability of BC concentration.

In our study, HRs for the associations between NO_2 and mortality were approximately 1.0, except for NO_2 and IHD mortality. Our findings were partly consistent with a retrospective cohort in Canada which reported that a 5 parts per billion increase in NO_2 was associated with 12% (95%CI: 7, 17%) and 15% (95%CI: 8, 21%) elevation in overall Cardiovascular and IHD mortality, respectively (Chen et al. 2013). Similarly, a study in Vancouver reported that per 8.4 $\mu g/m^3$ increase of NO_2 was associated with a 3% (95%CI: -1, 7%) elevation of IHD mortality (Gan et al. 2011). It is possible that the 'U-shaped' dose-response curve derived for NO_2 may have impacted HR calculations. The sampling campaign used to develop the LUR model was focused on developed land and roadside locations, which made it more suitable for predicting concentrations in populated areas. It is likely that this geographical sampling strategy led to a poor exposure model performance in low-level NO_2 areas.

In the stratification analysis, subjects who were younger than 71 years old had a higher risk of cardiovascular mortality than those who were older, which was consistent with a polled analysis by Singh et al. (2013). This may be due to healthy survivor effect. While there is some evidence reporting that those with higher BMI were more likely to suffer from cardiovascular diseases (Lavie et al. 2009), our study reported no significant difference in outcomes.

There are several strengths to our study. First, our exposure assessment methodology utilizing a custom LUR model allowed a greater spatial resolution in assigning individual exposure levels than previous satellite or monitoring network methods. For example, the satellite-based exposure assessment method previously used by Wong et al (2015) was limited to $PM_{2.5}$, had a greater spatial scale (1 km x 1 km) and a lower explanatory power than our LUR (0.39 vs 0.59),. Second, we were able to incorporate temporal variability into the spatial frame of individual exposure from by utilizing measurements made at general monitoring stations between baseline period and follow-up. Third, for each air pollutant, we also included the co-pollutant model to test the robustness of effect estimates. Fourth, there were only 9.3% participants who were not living in the same addresses during the follow-up period; the results were still robust after excluding these subjects (Supplementary Information, Table S4).

Our study also had several limitations. First, this study was restricted to an elderly population. These subjects pro-actively volunteered for enrolment to the study. As such, it is possible that they were more health-conscious and perhaps less prone than the general elderly population to the effects of air pollution, thus the results might not be generalizable to the whole population. Second, in the current study, traffic noise was not included in our analysis, although it may exert an influence on the association between air pollutants and cardiovascular mortality (Janssen et al. 2012). Several studies have estimated the joint effect of air pollutants and traffic noise with cardiovascular outcomes. After adjusting for traffic noise, the effect of air pollutants with cardiovascular outcomes remained constant or slightly reduced (Beelen et al. 2009; Fuks et al. 2016; Gan et al. 2012). In addition, a systematic review indicated that the confounding effect of air pollutants or noise on cardiovascular outcomes is low, i.e. causing changes of less than 10% (Tétreault et al. 2013). Based on these findings, lack of measurements of traffic noise seems less likely to influence the association between ambient air pollutants and cardiovascular mortality. Third, a lack of highly spatially resolved historical measurement data is clearly a weakness for our exposure assessment. We back

extrapolated the concentration to baseline period as well as the follow up period based on monitoring stations concentrations by assuming that there were no large geographical changes across the study period. Hong Kong is a relatively geographically stable and well-developed city, therefore we considered this a robust assumption, in line with many European studies using similar approaches.

Despite the use of targeted seasonal measurement campaigns, the predictive ability of the LUR models used in this study were low in comparison with some European and North American models but were similar to the majority of previous comparable studies in Asia (Lee et al. 2017). Exposure measurement error was present in the exposure estimates, as is the case in all studies applying such models in epidemiologic analyses. Given our efforts to develop models that described annual average exposure for the population of interest, we expect this measurement error to be primarily non-differential classical error and to therefore lead to epidemiologic effect estimates that may underestimate true associations.

5. Conclusions

This cohort study demonstrated that long-term exposure to ambient air pollutants (indicated by $PM_{2.5}$ and BC) was associated with an elevated risk of cardiovascular mortality. In Asia, where the air pollution concentrations are relatively high, our results shed new light on mortality from long term LUR modelled $PM_{2.5}$ and BC.

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Table 1. Descriptive statistics for health and covariate variables in the analysis.

Variables	**Percent or mean ± SD n=60,548**
Pollutant concentrations: Median (IQR)	
$PM_{2.5}$ ($\mu g/m^3$)	42.2 (5.5)
BC ($\mu g/m^3$)	12.1 (9.6)
NO_2 ($\mu g/m^3$)	104 (25.6)
Individual Level	
Age at entry	70.2 ± 5.5
Gender: Male (%)	19 739 (32.6)
Female (%)	40 809 (67.4)
BMI quartiles:	
1^{st} [<21.6] (%)	31 001 (51.2)
2^{nd} – 3^{rd} [21.6-26.3] (%)	13 260 (21.9)
4^{th} [>26.3] (%)	16 227 (26.8)
Smoking status	
Never (%)	44 079 (72.8)
Former (%)	11 020 (18.2)
Current (%)	5 389 (8.9)
Exercise in days per week	
Never [0] (%)	9 082 (15.0)
Medium [1-6](%)	7 811 (12.9)
High [7](%)	43 655 (72.1)
Education	
Below primary (%)	27 792 (45.9)
Primary (%)	22 342 (36.9)
Secondary or above (%)	10 475 (17.3)
Expenses/month in US$	
Low [<128] (%)	10 051 (16.6)
Medium [128-384] (%)	41 536 (68.6)
High [≥385] (%)	8 961 (14.8)
TPU[#] level	
age≥65	12.1 ± 4.2
> secondary education	13.1 ± 8.0
income≥US$1,923/month	60.0 ± 11.6
District level	
Smoking rate	11.0 ± 0.9

[#]TPU, Tertiary Planning Units

Table 2. Hazard ratio (95%CI) per IQR increase in each pollutant in main analysis using different models

Cause of death	Model 1 Unadjusted Single Pollutant	Model 2 Pollutant + Individual level covariates	Model3 Pollutant + Individual level covariates + area level covariates
$PM_{2.5}$			
All natural cause	1.07 (1.05, 1.09)*	1.06 (1.04, 1.08)*	1.03 (1.01, 1.06)*
Cardiovascular	1.10 (1.06, 1.14)*	1.09 (1.05, 1.12)*	1.06 (1.02, 1.10)*
Respiratory	1.05 (1.01, 1.10)*	1.05 (1.01, 1.10)*	1.01 (0.96, 1.06)
BC			
All natural cause	1.05 (1.03, 1.07)*	1.03 (1.01, 1.06)*	1.03 (1.00, 1.05)*
Cardiovascular	1.10 (1.05, 1.14)*	1.07 (1.03, 1.12)*	1.07 (1.02, 1.11)*
Respiratory	1.02 (0.97, 1.07)	1.01 (0.96, 1.06)	0.99 (0.94, 1.04)
NO_2			
All natural cause	0.94 (0.92, 0.97)	0.96 (0.94, 0.98)	1.00 (0.97, 1.03)
Cardiovascular	0.94 (0.9, 0.97)	0.95 (0.91, 0.99)	1.00 (0.95, 1.06)
Respiratory	0.91 (0.87, 0.96)	0.94 (0.89, 0.99)	0.99 (0.93, 1.06)

*P<0.05

Model 1 only included single pollutant. Model 2 adjusted age at entry, gender, body mass index (BMI), smoking status, physical activity, education level and monthly expenses. Model 3 adjusted percentage of participants who are equal to or older than 65 years old, percentages of subjects whose educational level are higher than secondary school and average income per month within each TPU and percentage of smokers were also adjusted on district level.

Table 3 Hazard ratio (95%CI) per IQR increase of $PM_{2.5}$ in multi-pollutant models using the baseline exposure in fully adjusted model including individual level covariates and area level covariates.

Cause of death	$PM_{2.5}$	$PM_{2.5}$ adjusted for BC	$PM_{2.5}$ adjusted for NO_2	$PM_{2.5}$ adjusted for BC and NO_2
All natural cause	1.03 (1.01, 1.06)*	1.03 (1.01, 1.05)*	1.03 (1.01, 1.06)*	1.03 (1.01, 1.05)*
Cardiovascular	1.06 (1.02, 1.10)*	1.04 (1.00, 1.08)*	1.06 (1.02, 1.1)*	1.04 (1.00, 1.09)
IHD	1.03 (0.97, 1.10)	1.02 (0.95, 1.08)	1.03 (0.96, 1.09)	1.01 (0.95, 1.08)
Cerebrovascular	1.06 (0.99, 1.13)	1.05 (0.98, 1.12)	1.06 (0.99, 1.13)	1.05 (0.98, 1.12)
Respiratory	1.01 (0.96, 1.06)	1.01 (0.97, 1.06)	1.01 (0.97, 1.06)	1.01 (0.97, 1.07)
Pneumonia	0.99 (0.94, 1.05)	1.00 (0.94, 1.06)	0.99 (0.94, 1.05)	1.00 (0.94, 1.06)
COPD	1.06 (0.97, 1.15)	1.07 (0.97, 1.16)	1.05 (0.97, 1.15)	1.06 (0.97, 1.16)

*P<0.05

Table 4 Hazard ratio (95%CI) per IQR increase of BC in main analysis in multi-pollutant models using the baseline exposure in fully adjusted model including individual level covariates and area level covariates.

Cause of death	BC	BC adjusted for $PM_{2.5}$	BC adjusted for NO_2	BC adjusted for $PM_{2.5}$ and NO_2
All natural cause	1.03 (1.00, 1.05)*	1.02 (0.99, 1.04)	1.03 (1.01, 1.05)*	1.02 (0.99, 1.04)
Cardiovascular	1.07 (1.03, 1.11)*	1.05 (1.01, 1.10)*	1.07 (1.03, 1.12)*	1.05 (1.00, 1.10)*
IHD	1.08 (1.01, 1.15)*	1.07 (1.00, 1.15)*	1.07 (1.00, 1.15)*	1.06 (0.99, 1.14)
Cerebrovascular	1.05 (0.98, 1.13)	1.03 (0.96, 1.11)	1.06 (0.98, 1.13)	1.02 (0.94, 1.10)
Respiratory	0.99 (0.94, 1.04)	0.99 (0.94, 1.04)	0.99 (0.94, 1.04)	1.00 (0.94, 1.05)
Pneumonia	0.99 (0.93, 1.05)	0.99 (0.93, 1.05)	0.99 (0.93, 1.05)	0.99 (0.93, 1.06)
COPD	0.98 (0.9, 1.08)	0.96 (0.88, 1.06)	0.98 (0.89, 1.07)	0.98 (0.88, 1.08)

*P<0.05

Table 5 Hazard ratio (95%CI) per IQR increase of NO_2 in main analysis in multi-pollutant models using the baseline exposure in fully adjusted model including individual level covariates and area level covariates.

Cause of death	NO_2	NO_2 adjusted for $PM_{2.5}$	NO_2 adjusted for BC	NO_2 adjusted for BC and $PM_{2.5}$
All natural cause	1.00 (0.97, 1.03)	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)
Cardiovascular	1.00 (0.95, 1.06)	0.99 (0.94, 1.05)	0.99 (0.93, 1.04)	0.98 (0.93, 1.03)
IHD	1.09 (1.00, 1.18)	1.08 (0.99, 1.18)	1.07 (0.98, 1.17)	1.07 (0.98, 1.16)
Cerebrovascular	1.00 (0.91, 1.09)	0.99 (0.90, 1.08)	0.99 (0.90, 1.08)	0.98 (0.89, 1.07)
Respiratory	0.99 (0.93, 1.06)	0.99 (0.92, 1.06)	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)
Pneumonia	0.98 (0.90, 1.06)	0.98 (0.90, 1.07)	0.98 (0.91, 1.07)	0.98 (0.91, 1.07)
COPD	1.02 (0.90, 1.16)	1.01 (0.89, 1.15)	1.03 (0.91, 1.17)	1.02 (0.90, 1.16)

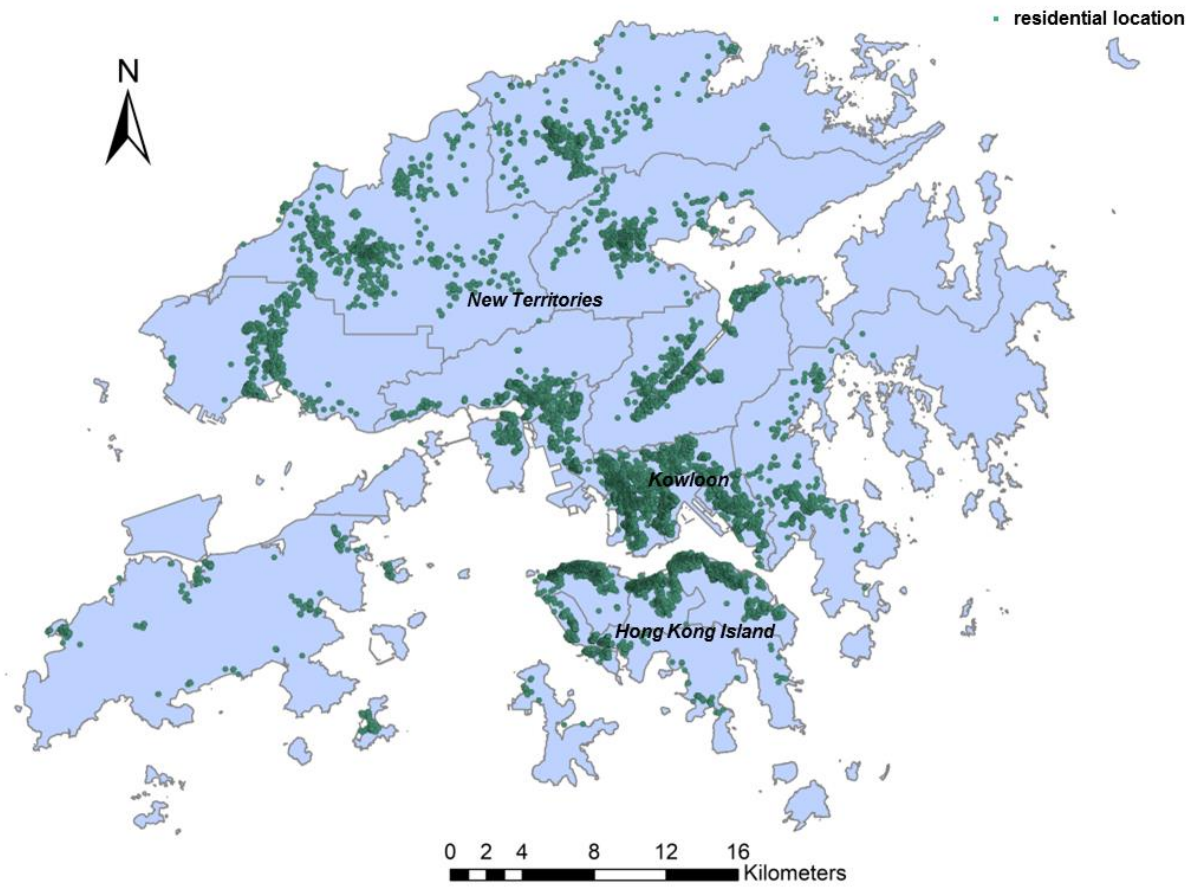


Figure 1. Spatial distribution of patients in the elderly cohort in Hong Kong (n= 61,386) at baseline (1998-2000).

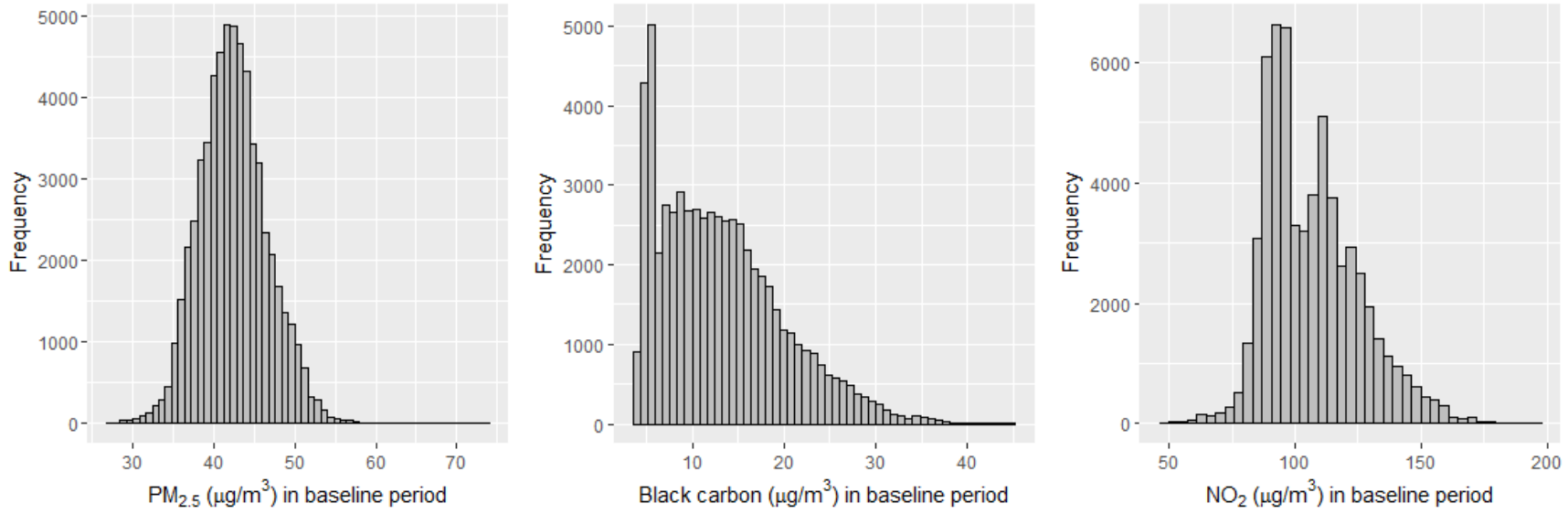


Figure 2. Distribution of $PM_{2.5}$, black carbon and NO_2 estimated at each participants' addresses during baseline period. X-axis represents the concentrations of black carbon and y-axis represents the frequency of addresses.

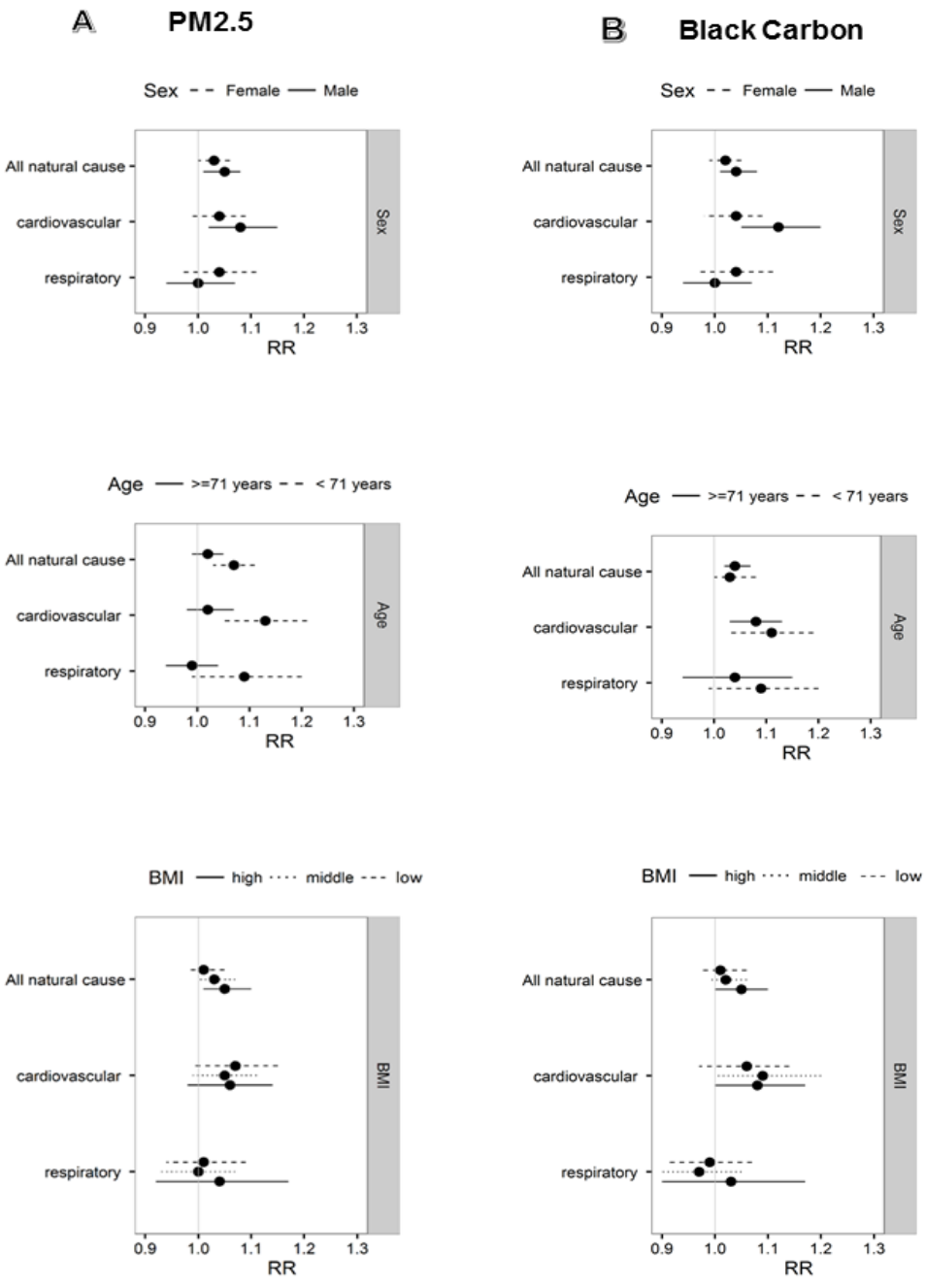


Figure 3. HRs and 95%CI with an IQR increase in $PM_{2.5}$ (A) and BC (B) concentration, stratified by sex, age and BMI (low <21.6kg/m^2, middle 21.6-26.3 kg/m^2, high >26.3 kg/m^2) adjusted for all other covariates.

Supplementary Material

Table S1. HRs (95%CI) for per IQR elevation of $PM_{2.5}$ in main analysis for average exposure at the baseline period and sensitivity analyses for exposure to average $PM_{2.5}$ yearly and for different inclusion and exclusion criteria.

Cause of Death	Main analysis - baseline exposure	Yearly Exposure	Including deaths within 1 year - baseline exposure	Excluding deaths within 3 years - baseline exposure
All natural cause	1.03 (1.01, 1.06)*	1.00 (0.98, 1.03)	1.03 (1.01, 1.05)*	1.04 (1.02, 1.07)*
Cardiovascular	1.06 (1.02, 1.10)*	1.02 (0.98, 1.06)	1.06 (1.02, 1.10)*	1.07 (1.03, 1.11)*
IHD	1.03 (0.97, 1.10)	0.98 (0.92, 1.05)	1.04 (0.98, 1.10)	1.03 (0.97, 1.10)
Cerebrovascular	1.06 (0.99, 1.13)	1.02 (0.95, 1.09)	1.05 (0.99, 1.12)	1.08 (1.01, 1.16)*
Respiratory	1.02 (0.97, 1.06)	0.99 (0.94, 1.04)	1.02 (0.97, 1.06)	1.02 (0.97, 1.07)
Pneumonia	1.00 (0.94, 1.06)	0.98 (0.92, 1.04)	1.00 (0.94, 1.06)	1.00 (0.95, 1.06)
COPD	1.06 (0.97, 1.15)	1.02 (0.93, 1.11)	1.06 (0.97, 1.15)	1.06 (0.97, 1.16)

*P<0.05

Table S2. HRs (95%CI) per **10 μg/m^3** increase of **$PM_{2.5}$** in main analysis for average exposure at the baseline period and sensitivity analyses for exposure to average $PM_{2.5}$ yearly and for different inclusion and exclusion criteria.

Cause of Death	Main analysis - baseline exposure[a]	Yearly Exposure	Including deaths within 1 year - baseline exposure	Excluding deaths within 3 years - baseline exposure
All natural cause	1.06 (1.02, 1.11)*	1.01 (0.97, 1.05)	1.06 (1.02, 1.1)*	1.08 (1.04, 1.12)*
Cardiovascular	1.11 (1.03, 1.19)*	1.03 (0.96, 1.11)	1.1 (1.03, 1.18)*	1.13 (1.05, 1.22)*
IHD	1.06 (0.95, 1.19)	0.97 (0.86, 1.09)	1.07 (0.96, 1.19)	1.06 (0.94, 1.19)
Cerebrovascular	1.11 (0.98, 1.25)	1.03 (0.91, 1.17)	1.09 (0.97, 1.23)	1.16 (1.02, 1.32)*
Respiratory	1.03 (0.94, 1.12)	0.98 (0.90, 1.07)	1.03 (0.95, 1.12)	1.03 (0.94, 1.13)
Pneumonia	1.00 (0.90, 1.11)	0.96 (0.86, 1.07)	1.00 (0.90, 1.11)	1.00 (0.90, 1.12)
COPD	1.10 (0.95, 1.29)	1.04 (0.88, 1.22)	1.11 (0.95, 1.29)	1.11 (0.94, 1.30)

*P<0.05

Table S3. HRs (95%CI) for per IQR elevation of BC in main analysis as well as sensitivity analyses for exposure to yearly exposure of BC and different inclusion and exclusion criteria.

Cause of death	Main analysis - baseline exposure	Yearly Exposure	Including deaths within 1 year - baseline exposure	Excluding deaths within 3 years - baseline exposure
All natural cause	1.03 (1.00, 1.05)*	1.02 (0.99, 1.06)	1.03 (1.00, 1.05)	1.03 (1.00, 1.05)
Cardiovascular	1.07 (1.03, 1.11)*	1.09 (1.02, 1.16)*	1.07 (1.03, 1.12)*	1.06 (1.02, 1.11)*
IHD	1.08 (1.01, 1.15)*	1.07 (0.96, 1.19)	1.08 (1.01, 1.15)*	1.08 (1.01, 1.15)*
Cerebrovascular	1.05 (0.98, 1.13)	1.07 (0.96, 1.20)	1.06 (0.99, 1.13)	1.04 (0.97, 1.12)
Respiratory	0.99 (0.94, 1.04)	0.96 (0.88, 1.04)	0.99 (0.94, 1.04)	1.00 (0.95, 1.05)
Pneumonia	0.99 (0.93, 1.05)	0.95 (0.86, 1.06)	0.99 (0.93, 1.05)	0.99 (0.93, 1.06)
COPD	0.98 (0.90, 1.08)	0.94 (0.81, 1.09)	0.98 (0.89, 1.07)	1.00 (0.90, 1.10)

*P<0.05

Table S4. HRs (95%CI) for per IQR elevation of NO_2 in main analysis as well as sensitivity analyses for exposure to yearly exposure of NO_2 and different inclusion and exclusion criteria.

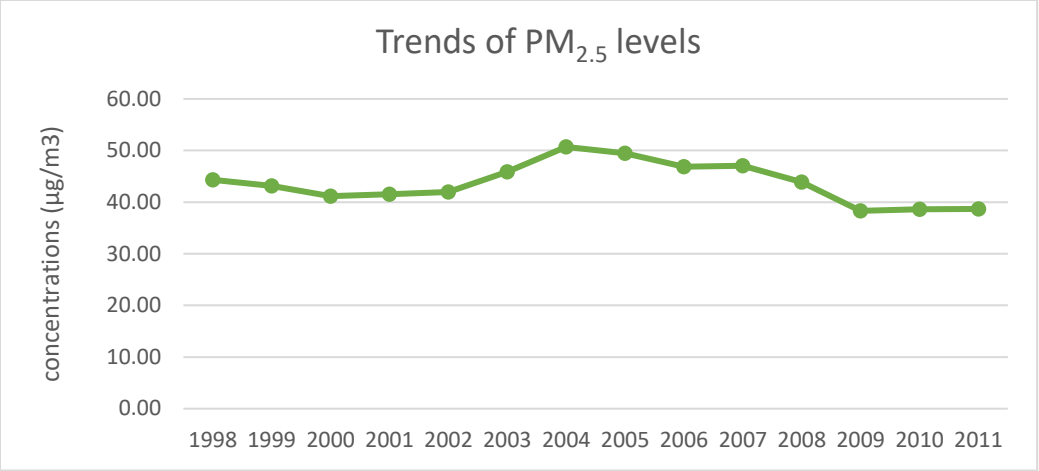
Cause of death	Main analysis - baseline exposure	Yearly Exposure	Including deaths within 1 year - baseline exposure	Excluding deaths within 3 years - baseline exposure
All natural cause	1.00 (0.97, 1.03)	0.99 (0.96, 1.02)	0.99 (0.97, 1.02)	1.00 (0.97, 1.03)
Cardiovascular	1.00 (0.95, 1.05)	0.99 (0.94, 1.05)	0.99 (0.94, 1.05)	1.00 (0.95, 1.06)
IHD	1.09 (1.00, 1.18)*	1.08 (0.99, 1.18)	1.08 (0.99, 1.17)	1.10 (1.01, 1.20)*
Cerebrovascular	1.00 (0.91, 1.09)	0.99 (0.9, 1.08)	0.99 (0.91, 1.08)	0.98 (0.89, 1.08)
Respiratory	0.99 (0.93, 1.06)	0.99 (0.92, 1.06)	0.99 (0.93, 1.05)	0.99 (0.92, 1.06)
Pneumonia	0.98 (0.9, 1.06)	0.97 (0.90, 1.06)	0.98 (0.90, 1.06)	0.98 (0.90, 1.07)
COPD	1.02 (0.9, 1.15)	1.02 (0.90, 1.16)	1.02 (0.90, 1.15)	1.02 (0.90, 1.16)

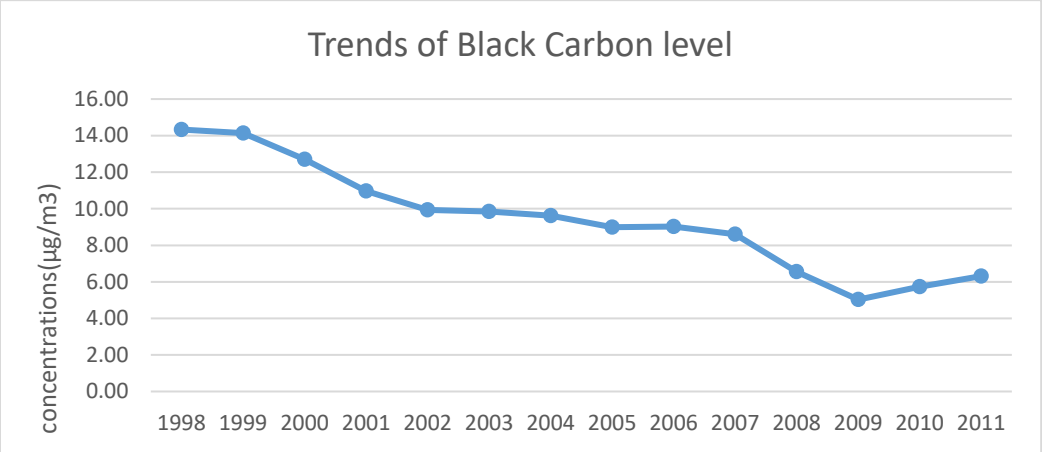
*P<0.05

Table S5. HRs (95%CI) for per IQR elevation of air pollutants in sensitivity analyses for to yearly exposure to different air pollutants, excluding participants who changed their addresses.

Cause of Death	$PM_{2.5}$	BC	NO_2
All natural cause	1.00 (0.98, 1.03)	1.02 (0.99, 1.06)	0.99 (0.96, 1.03)
Cardiovascular	1.02 (0.99, 1.06)	1.09 (1.02, 1.16)*	0.99 (0.94, 1.05)
IHD	0.98 (0.92, 1.05)	1.07 (0.96, 1.19)	1.08 (0.99, 1.18)
Cerebrovascular	1.02 (0.97, 1.10)	1.07 (0.96, 1.20)	0.99 (0.9, 1.08)
Respiratory	0.99 (0.94, 1.04)	0.96 (0.89, 1.04)	0.99 (0.92, 1.06)
Pneumonia	0.98 (0.92, 1.04)	0.95 (0.86, 1.06)	0.97 (0.91, 1.06)
COPD	1.02 (0.92, 1.10)	0.94 (0.81, 1.09)	1.02 (0.90, 1.16)

*P<0.05





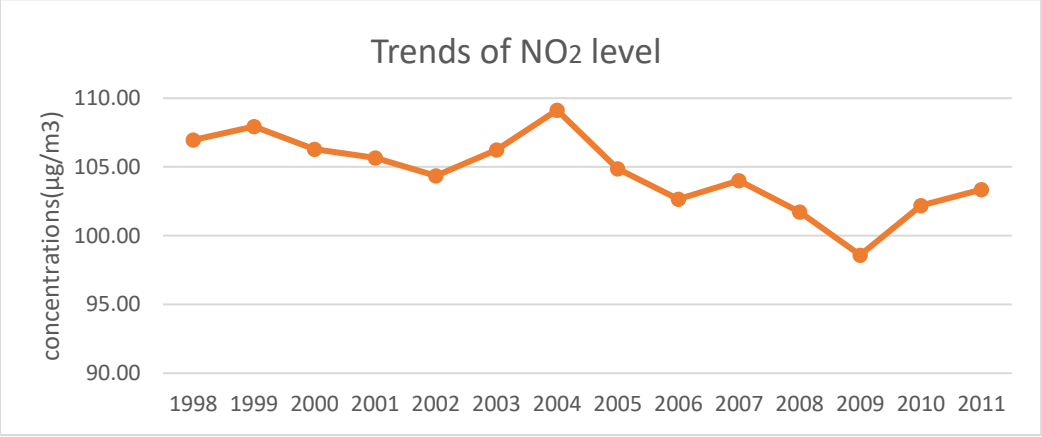


Figure S1. The trends of $PM_{2.5}$, BC, and NO_2 across the whole study period.