Cigarette Smoking Increases Deaths Associated with Air Pollution in Hong Kong

Shengzhi Sun[a,b,c,1], Wangnan Cao[d,1], King-Pan Chan[a], Jinjun Ran[a], Yang Ge[e], Yunquan Zhang[f], Yilin Feng[g], Qiang Zeng[h], Ruby Siu-yin Lee[i], Chit-Ming Wong[a], Linwei Tian[a,*], and Yujie Lei[j,*]

Author affiliations

[a] School of Public Health, The University of Hong Kong, Hong Kong SAR, China

[b] Department of Epidemiology, Brown University School of Public Health, Providence, RI 02912, USA

[c] Department of Environmental Health, Boston University School of Public Health, 715 Albany Street, Boston, MA 02118, USA

[d] Center for Evidence Synthesis in Health, Brown University School of Public Health, Providence, RI 02912, USA

[e] School of Public Health, Department of Epidemiology and Biostatistics, University of Georgia, USA

[f] Hubei Providence Key Laboratory of Occupational Hazard Identification and Control, School of Public Health, Wuhan University of Science and Technology, Wuhan 430065, China; Department of Preventive Medicine, School of Health Sciences, Wuhan University, Wuhan 430071, China.

[g] University of Michigan Medical School, Ann Arbor, MI.

[h] Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China

[i] Elderly Health Service, Department of Health, Hong Kong Special Administrative Region, China

[j] Department of Thoracic Surgery I, The Third Affiliated Hospital of Kunming Medical University/Yunnan Cancer Hospital, Yunnan Cancer Center, The International Cooperation Key Laboratory of Regional Tumor in High Altitude Area, Kunming, China

[1] These two authors contributed equally to this work.

[*]**Address correspondence to:**

Dr. Linwei Tian, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong. Phone: (+852) 3917 6351; Fax: (+852) 2855 9528; Email: linweit@hku.hk.

Dr. Yujie Lei, Department of Thoracic Surgery I, The Third Affiliated Hospital of Kunming Medical University/Yunnan Cancer Hospital, Yunnan Cancer Center, The International Cooperation Key Laboratory of Regional Tumor in High Altitude Area, Kunming, China. Phone: (+86) 871 6817 3640; Fax: (+86) 871 6818 5730; Email: 583271025@qq.com

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Abstract

Background: Ambient air pollution and cigarette smoking are two significant risk factors for mortality; however, less is known about their interaction.

Objectives: We aimed to assess effect modification of cigarette smoking on the association between short-term exposure to air pollution and mortality in the Chinese Elderly Health Service Cohort in Hong Kong.

Methods: We included 16,290 Chinese elders aged 65 years or older who died between 1 July 1998 and 31 December 2011. Smoking history was collected through face-to-face interviews by registered nurses or doctors using a standardized structured questionnaire when they were recruited into the cohort. We used a time-stratified case-crossover approach to estimate the percent excess risk (ER%) of all-natural mortality per 10 $\mu g/m^3$ increase in fine particulate matter ($PM_{2.5}$), respirable particulate matter (PM_{10}), and nitrogen dioxide (NO_2) among current-, ex-, and never-smokers, and to estimate the additional percent excess risk (DER%) for current- and ex-smokers relative to never-smokers. We performed secondary analysis to assess whether the estimated additional risks varied by personal characteristics.

Results: There were a greater ER % associated with air pollutants among current- and ex-smokers relative to never-smokers. We found DER% per 10$\mu g/m^3$ increase in air pollutants was statistically significant for $PM_{2.5}$ among ex-smokers [2.63% (95% CI: 0.39%, 4.88%) at 1 day prior to death (lag_1)], and PM_{10} among current-smokers [2.21% (95% CI: 0.08%, 4.33%) at lag_1] and ex-smokers [1.96% (95% CI: 0.26%, 3.65%) at lag_1]. The increased risks associated with cigarette smoking were more pronounced among males, overweight or obese elders, elders with three or more comorbidities, or elders received primary or lower education.

Conclusion: Ever-smokers were more susceptible to excess mortality risk associated with daily air pollution, especially for males, overweight or obese elders, and those with poor

health conditions or received lower educational attainment. Tobacco control can reduce the health burdens attributable to air pollution.

Keywords: Air pollution; Cigarette smoking; Interaction; Mortality; Case-crossover study

1. Introduction

Air pollution and cigarette smoking are both significant risk factors for mortality and are two leading preventable causes of death (Brunekreef and Holgate 2002; Chang et al. 2015). It is estimated that one in five deaths were related to cigarette smoking in the United States (US), and one in eight deaths were attributable to air pollution globally (Centers for Disease Control and Prevention 2017; World Health Organization 2014). Although it has been well documented that air pollution and cigarette smoking are both associated with adverse health outcomes, evidence on their synergistic effects is scarce, and findings are mixed (Hoek et al. 2013; Krzyzanowski and Wojtyniak 1982; Lin et al. 2017; Neupane et al. 2010; Pope III et al. 2004; Wong et al. 2007; Xu and Wang 1998). For example, a study of 65,893 women in 36 US metropolitan found that the association of cardiovascular events with long-term fine particulate matter exposure was stronger among current-smokers [hazard ratio (HR): 1.68 (95% CI: 1.06, 2.66)] than never-smokers [HR: 1.18 (95% CI: 0.99, 1.40)] per 10 $\mu g/m^3$ increase in fine particulate matter. However, an analysis of the National Institutes of Health-AARP cohort among 517,041 participants failed to find any difference among associations between ever-smokers and never-smokers (Thurston et al. 2015).

Most prior studies examined whether cigarette smoking intensified the long-term effects of air pollution on diseases development (Hoek et al. 2013; Krzyzanowski and Wojtyniak 1982; Lin et al. 2017; Neupane et al. 2010; Pope III et al. 2004; Thurston et al. 2015; Wong et al. 2007; Xu and Wang 1998); evidence of whether cigarette smoking might amplify the short-term effects of air pollution on triggering diseases is limited. Also, most prior studies investigated smoking status as a confounder instead of further investigating its effect modification on the deleterious effects of air pollution (Filleul et al. 2003; Wong et al. 2015).

Accordingly, we sought to examine whether current- and ex-smokers, compared to never-smokers, were more susceptible to short-term exposure to air pollution in a large prospective Chinese elderly cohort. To identify susceptible subgroups, we also examined whether the increased susceptibility associated with cigarette smoking varied by seasons and personal characteristics of sex, baseline health conditions, body mass index, educational attainment, and marital status.

2. Materials and methods

2.1. Study population

The Chinese Elderly Health Service Cohort in Hong Kong is a prospective cohort, which was initiated by the Elderly Health Service of the Hong Kong Department of Health. All Hong Kong residents aged 65 years or above were eligible to enrol. From 1998 to 2001, 66,820 elders, about 9% of Hong Kong elderly, were recruited into the cohort and were followed up until 31st December 2011. Information on lifestyle habits (e.g., smoking status) and socio-economic conditions (e.g., educational attainment) were collected by face-to-face interview when participants were first enrolled. Details of data collection have been described elsewhere (Lam et al. 2007; Schooling et al. 2006). To ascertain death of participants, we linked the cohort with the death registration database by the unique Hong Kong identity card number. All-natural deaths were coded according to the International Classification of Diseases, Ninth Revision (ICD-9): 1-799 or Tenth Revision (ICD-10): A00-R99. A total of 16,290 elders died of all-natural causes during the follow-up period, and the spatial distribution of the deceased elders was shown in **Fig. 1**. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

2.2. Smoking status

We collected individual's baseline smoking status through face-to-face interviews by registered nurses and doctors using a standardized structured questionnaire. We defined current-smokers as those who had ever smoked (i.e., smoked at least one cigarette a day continuously for at least one year) and were still smoking at baseline, and ex-smokers as those who had ever smoked but had quit smoking at baseline (Lam et al. 2007). We defined never-smokers as those who had not continuously smoked more than one cigarette a day for at least one year.

2.3. Air pollution and meteorological data

We obtained daily average concentrations of fine particulate matter ($PM_{2.5}$), respirable particulate matter (PM_{10}), and nitrogen dioxide (NO_2) between 1998 and 2011 from ten general monitoring stations in Hong Kong (**Fig. S1**). We then created a time-series of territory-wide daily average concentrations of air pollutants by averaging concentrations of air pollutants across the ten air monitoring stations (Sun et al. 2019). We also obtained daily mean ambient temperature (°C) and daily mean relative humidity (%) from the Hong Kong Observatory.

2.4. Statistical analysis

We used a case-crossover study design to estimate the association between day-to-day variation in ambient air pollutants and the relative risk of all-natural deaths. The case-crossover design is commonly used to study the effects of transient exposures on the relative risk of acute events (Carracedo-Martínez et al. 2010; Janes et al. 2005; Levy et al. 2001). With this study design, each participant experiencing a health event of interest serves as his/her control, and the inference is based on comparing exposures over time within the same

person (Carracedo-Martínez et al. 2010). In the present study, we compared concentrations of air pollutants on the event day or prior days (i.e., case period) to concentrations of air pollutants on other days when participants did not experience the event (i.e., control periods). We used a time-stratified approach to select the control periods which were the same year, month, and day of the week as the case period to control for seasonality, long-term trends, and other potential measured or unmeasured confounders that vary relatively slowly over time (Janes et al. 2005; Levy et al. 2001). We adjusted for time-varying confounders including ambient temperatures of the same-day and the moving average of the previous 1 to 3 days (lag_{1-3}) with natural cubic splines with three degrees of freedom each simultaneously in the model to control for both immediate and delayed effects of temperature (Orazzo et al. 2009; Tian et al. 2017), relative humidity using a natural cubic spline with three degrees of freedom, and public holidays.

We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals associated with a 10 $\mu g/m^3$ increase in each air pollutant. We expressed results as percent excess risk (ER%) calculated as (OR-1)´ 100%. As the health effects of air pollutants were usually immediate (Di et al. 2017; Wong et al. 2008), we estimated the association of all-natural mortality with air pollutants at the event day (lag_0), 1 day prior to the event day (lag_1), and the moving average of the current and previous one day (lag_{0-1}).

To estimate additional percent excess risk (ΔER%) associated with air pollutants among current- and ex-smokers relative to never-smokers, we added an interaction term to the models which was the product of air pollutant and the smoking status with never-smoker as the reference group (Bhaskaran et al. 2011; Forastiere et al. 2008; Lee et al. 2018).

In secondary analyses, we also examined whether the increased susceptibility associated with cigarette smoking varied by season (cool versus warm) and personal characteristics of sex (male versus female), baseline health conditions (participants with 0-2 versus 3-8 comorbidities), body mass index (£25kg/m^2 versus >25kg/m^2), educational attainment (primary or lower versus secondary or above), and marital status (married versus unmarried).

All analyses were conducted in R software version 3.5.1 with the "Survival" package version 2.42-6 for the conditional logistic regression.

3. Results

Among 66,820 enrolled participants in the Chinese Elderly Health Service Cohort, a total of 16,290 deaths were recorded between enrolment and 31st December 2011. Among the 16,290 deaths, 9,561 deaths were never-smokers, followed by ex-smokers (4,402), and current-smokers (2,327). Compared with never-smokers, ever-smokers were more likely to be male or those who consumed alcohol **(Table 1**).

The daily mean concentration of air pollutants on the day of death was 37.6 mg/m^3 for $PM_{2.5}$, 52.5 mg/m^3 for PM_{10}, and 57.6 mg/m^3 for NO_2 (**Table 2**). The Pearson correlations among air pollutants were generally high (r>0.5). The Pearson correlations of air pollutants with ambient temperature and relative humidity were generally moderate to low (r<0.5).

Fig. 2 shows the ER% of mortality associated with air pollutants per 10 mg/m^3 increase among current-, ex-, and never-smokers. Although most of the associations were not statistically significant, we observed a statistically significant association for $PM_{2.5}$ at lag_1

(ER%=2.40%; 95% CI: 0.46%, 4.35%), and PM_{10} at lag_1 (ER%=1.72%; 95% CI: 0.24%, 3.20%) among ex-smokers.

To examine whether ever smoking might intensify the mortality effects of air pollution, we further estimated the DER% of air pollutants for current- and ex-smokers relative to never-smokers (**Table 3**). Although the point estimates of DER% for air pollutants were all positive, we found the DER% was statistically significant for $PM_{2.5}$ among ex-smokers [2.63% (95% CI: 0.39%, 4.88%) per 10 $\mu g/m^3$ increase at lag_1] and PM_{10} among current-smokers [2.21% (95% CI: 0.08%, 4.33%) per 10 $\mu g/m^3$ increase at lag_1] and ex-smokers [1.96% (95% CI: 0.26%, 3.65%) per 10 $\mu g/m^3$ increase at lag_1].

In secondary analyses, we evaluated whether the DER% of current- and ex-smokers relative to never-smokers differed by personal characteristics (**Fig. 3**). We found the DERs% of ever-smokers versus never-smokers for the three air pollutants were generally stronger among males, overweight or obese elders, elders with poor health conditions, or elders received primary or lower education than their counterparts. For example, the DER% per 10 $\mu g/m^3$ in air pollutants was 5.07% (95% CI: 0.96%, 9.18%) among male current-smokers versus -1.67% (95% CI: -7.42%, 4.08%) among female current-smokers for NO_2 at lag_1, 5.34% (95% CI: 1.65%, 9.03%) among ex-smokers with three or more comorbidities versus 1.06% (95% CI: -1.78%, 3.89%) among ex-smokers with two or less comorbidities for $PM_{2.5}$ at lag_1, 5.05% (95% CI: 1.15%, 8.95%) among current-smokers with BMI >25 kg/m^2 versus 0.90% (95% CI: -1.67%, 3.47%) among current-smokers with BMI £ 25 kg/m^2 for PM_{10} at lag_1, and 2.80% (95% CI: 0.45%, 5.15%) among current-smokers with primary or lower education versus -0.51% (95% CI: -5.79%, 4.77%) among elders with secondary or above for PM_{10} at

221 lag_1. We also found greater DERs% of ever-smokers versus never-smokers in the warm
222 seasons (**Table S1**).
223
224 **4. Discussion**
225 Among 16,290 deaths occurring in this Elderly Health Service Cohort of Chinese elders, we
226 found that smokers were more susceptible to short-term air pollution exposure than never-
227 smokers. We also found that the increased susceptibility associated with cigarette smoking
228 was more pronounced among males, overweight or obese elders, elders with poor health
229 conditions, or elders received primary or lower education. Our findings suggest that tobacco
230 control can reduce the health burdens attributable to air pollution.
231
232 Our finding of a positive DER% associated with air pollution among current- and ex-smokers
233 compared with never-smokers was consistent with prior studies (Canova et al. 2012; Wong et
234 al. 2007). For example, a London, UK study reported that a 10 mg/m^3 increase in PM_{10} was
235 associated with an 87% increase in the risk of airway exacerbation among smokers, whereas
236 no excess risks were observed among never- and ex-smokers (Canova et al. 2012). A Hong
237 Kong study among 10,833 men aged 30 years or above found that the DER% of all-natural
238 mortality per 10 mg/m^3 increase in PM_{10} among smokers was 2.2% (95% CI: -0.4%, 4.8%)
239 compared with never-smokers, which was generally consistent with our findings (Wong et al.
240 2007). Compared with the Hong Kong study (Wong et al. 2007), our study had two major
241 improvements. We collected information on smoking habits directly from participants
242 themselves instead of asking this information from relatives of the deceased people, which
243 could minimize the misclassification of smoking status. Also, we collected detailed
244 information on smoking status (i.e., current-, ex-, and never-smokers), which allows us to
245 examine the DER% for current- and ex-smokers separately.

It is biologically plausible for the positive interaction between short-term exposure to air pollution and cigarette smoking, although the exact underlying mechanism is not clear yet. The increased deposition of air pollutants and decreased clearance among ever-smokers may play a role. The airways and lungs of ever-smokers are already damaged (Heijink et al. 2012; Hoffmann et al. 2013), which is likely to make them especially vulnerable to the adverse effects of air pollutants. Prior studies reported structurally damaged airway epithelial barrier and increased airway epithelial permeability among ever-smokers (Heijink et al. 2012; Jones et al. 1980), which could facilitate the penetration of inhaled particles into the systemic circulation (Nemmar et al. 2002). Increased mucus production and depressed ciliary and macrophage activity were also observed among smokers (Mehta et al. 2008), which could result in a decrease of lung's ability to clear the penetrated pollutants. This has been confirmed by most previous human studies suggesting the mucociliary clearance was faster in non-smokers than smokers (Möller 2001; Mortensen et al. 1994b). The serum levels of antioxidants were also found to be lower among smokers (Dietrich et al. 2003; Wei et al. 2001), which in turns renders smokers more susceptible to oxidative stress induced by air pollutants (Minuz et al. 2006).

One novel finding of this study was that we found cigarette smoking significantly intensified the mortality effect of air pollution among elders with worse health status. People with worse health conditions were consistently associated with a greater susceptibility to short-term air pollution exposure (Qiu et al. 2015; Zanobetti and Schwartz 2002; Zeka et al. 2006). For example, Zanobetti and Schwartz (2002) conducted a study in four US cities and found that the association between particulate matter and cardiovascular admission was doubled among diabetes than non-diabetes (Zanobetti and Schwartz 2002). Studies also suggested that

smokers with poor health, higher body mass index had a greater risk of morbidity or mortality (Freedman et al. 2006; Lou et al. 2018; Solberg et al. 2004). For example, a study among 39,887 Chinese adults found that the odds ratio of incident stroke was 3.45 (95% CI: 2.30, 5.16) among smokers with type 2 diabetes, but was only 2.00 (95% CI: 1.56, 2.56) among type 2 diabetes patients or 1.65 (95% CI: 1.36, 2.00) among smokers (Lou et al. 2018). People with worse health may already have an inflamed airway and their clearance for particles may also be impaired (Brown et al. 2002). Smoking may further introduce inflammatory response and exacerbate oxidative stress and weaken the function of epithelial cells and alveolar macrophages, which thus substantially increased the susceptibility to short-term air pollution.

Our data did not support a beneficial effect of quitting smoking on the excess mortality risk of air pollution. The exact length of quitting smoking was not considered in our study, which could limit us to identify the beneficial effect of quitting smoking. However, previous studies suggested that the retarded mucociliary clearance could only partially improve among smokers who stopped smoking (Camner et al. 1973; Mortensen et al. 1994a), which could support our finding. Our findings could also be partly explained by worse health among ex-smokers than current- and never-smokers (**Table 1**), which might imply that poor health could be a contributor to their smoking cessation.

To our best knowledge, this is the first study with detailed individual characteristics to examine the interaction between cigarette smoking and short-term air pollution exposure on mortality. This study also has some limitations. First, there was a lack of measurement of individual exposure to air pollution. The true intake fraction may depend on the local pollutant concentrations and personal habits such as time spent outdoors, especially near

pollutant sources and level of physical activity. However, studies on short-term effects of air pollution may reduce individual's exposure misclassification error as the assessment is based on temporal variations instead of spatial variations in pollutant concentrations. Second, our samples may not be representative of the general Hong Kong older population as the Elderly Health Centre clients are more health-conscious than the general population, which may attenuate the strength of our observations. Finally, smoking status was recorded at baseline, and the participants might change their smoking habits during their follow-up, which might influence our findings. It is likely that a current-smoker would quit smoking at an older age, thus findings for the baseline current-smokers need to be interpreted cautiously.

5. Conclusions

Ever-smokers are more susceptible to the excess mortality risk of short-term air pollution exposure among Chinese elders. Tobacco control can reduce the health burdens attributable to air pollution.

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Table 1. Summary of the baseline characteristics of participants who died during the follow-up period by smoking status (n=16,290).

Variable	Never-smokers (n=9,561)	Current-smokers (n=2,327)	Ex-smokers (n=4,402)
Age [years, mean (SD)]	82.5 (6.9)	80.6 (6.3)	82.4 (6.5)
Sex			
Male	2145 (22.4)	1,764 (75.8)	3,287 (74.7)
Female	7,416 (77.6)	563 (24.2)	1,115 (25.3)
No. of comorbidities			
0-2	6,217 (65.0)	1,753 (75.3)	2,806 (63.7)
3-11	3,344 (35.0)	574 (24.7)	1,596 (36.3)
BMI quartile, n (%)			
Underweight [<19.0 kg/m^2]	885 (9.3)	451 (19.4)	560 (12.7)
Normal [19.0-25.0 kg/m^2]	4,910 (51.4)	1,329 (57.1)	2,340 (53.2)
Overweight [25.0-30.0 kg/m^2]	3,105 (32.5)	477 (20.5)	1,336 (30.3)
Obese [³ 30.0 kg/m^2]	661 (6.9)	70 (3.0)	166 (3.8)
Exercise			
Days per week [mean (SD)]	5.6 (2.6)	4.8 (3.1)	5.5 (2.7)
Education			
Uneducated	5,196 (54.3)	848 (36.4)	1,527 (34.7)
Primary	3,037 (31.8)	1,120 (48.1)	1,991 (45.2)
Secondary	1,030 (10.8)	285 (12.2)	698 (15.9)
Post-secondary	298 (3.1)	74 (3.2)	186 (4.2)
Marital status			
Married	1,891 (19.8)	769 (33.0)	1,349 (30.6)
Unmarried	7,670 (80.2)	1,558 (67.0)	3,053 (69.4)
Alcohol consumption			
Never drink	8,180 (85.6)	1,119 (48.1)	1,974 (44.8)
Former drink	522 (5.5)	444 (19.1)	1,364 (31.0)
Social/seasonal drinker	708 (7.4)	426 (18.3)	802 (18.2)
Regular drinker	151 (1.6)	338 (14.5)	262 (6.0)
Expenses/month in USD			
Low [<128]	1,647 (17.2)	309 (13.3)	692 (15.7)
Medium [128-384]	6,587 (68.9)	1,602 (68.8)	3,002 (68.2)
High [³ 385]	1,327 (13.9)	416 (17.9)	708 (16.1)

Abbreviations: SD=standard deviation; BMI=body mass index

Table 2. Air pollutant and weather conditions on the day of death, and Pearson correlation coefficients between air pollutants and weather conditions.

Variable	Mean±SD	Pearson correlation				
		$PM_{2.5}$	PM_{10}	NO_2	Temperature	Relative humidity
$PM_{2.5}$ ($\mu g/m^3$)	37.6±21.8	1.00	0.92	0.77	-0.38	-0.42
PM_{10} ($\mu g/m^3$)	52.5±28.6		1.00	0.70	-0.37	-0.46
NO_2 ($\mu g/m^3$)	57.6±20.3			1.00	-0.39	-0.35
Temperature (°C)	23.1±5.2					0.28
Relative humidity	77.6±10.6					1.00

Abbreviations: SD=standard deviation; $PM_{2.5}$= particulate matter with aerodynamic diameter ≤ 2.5μm; PM_{10}= particulate matter with aerodynamic diameter ≤ 10μm; NO_2=nitrogen dioxide.

Table 3. Additional percent excess risk (%) of mortality per 10 μg/m^3 increase in air pollution stratified by smoking status.

Air pollutant	Lag day	Current-smokers	Ex-smokers
$PM_{2.5}$	0	0.08 (-2.83, 2.98)	0.49 (-1.80, 2.78)
	1	2.53 (-0.34, 5.39)	**2.63 (0.39, 4.88)**
	0-1	1.62 (-1.59, 4.84)	1.98 (-0.56, 4.52)
PM_{10}	0	0.36 (-1.78, 2.49)	0.10 (-1.56, 1.76)
	1	**2.21 (0.08, 4.33)**	**1.96 (0.26, 3.65)**
	0-1	1.59 (-0.78, 3.97)	1.25 (-0.62, 3.12)
NO_2	0	1.07 (-1.88, 4.02)	0.41 (-1.94, 2.76)
	1	2.22 (-0.73, 5.16)	0.93 (-1.40, 3.25)
	0-1	2.05 (-1.25, 5.35)	0.84 (-1.78, 3.47)

Abbreviations: $PM_{2.5}$= particulate matter with aerodynamic diameter less than 2.5μm; PM_{10}= particulate matter with aerodynamic diameter less than 10μm; NO_2=nitrogen dioxide.

Figure Legends

Fig. 1. Spatial distribution of the deceased current-smokers (n=2,327), ex-smokers (n=4,402), and never-smokers (n=9,561) in the Chinese Elderly Health Service Cohort.

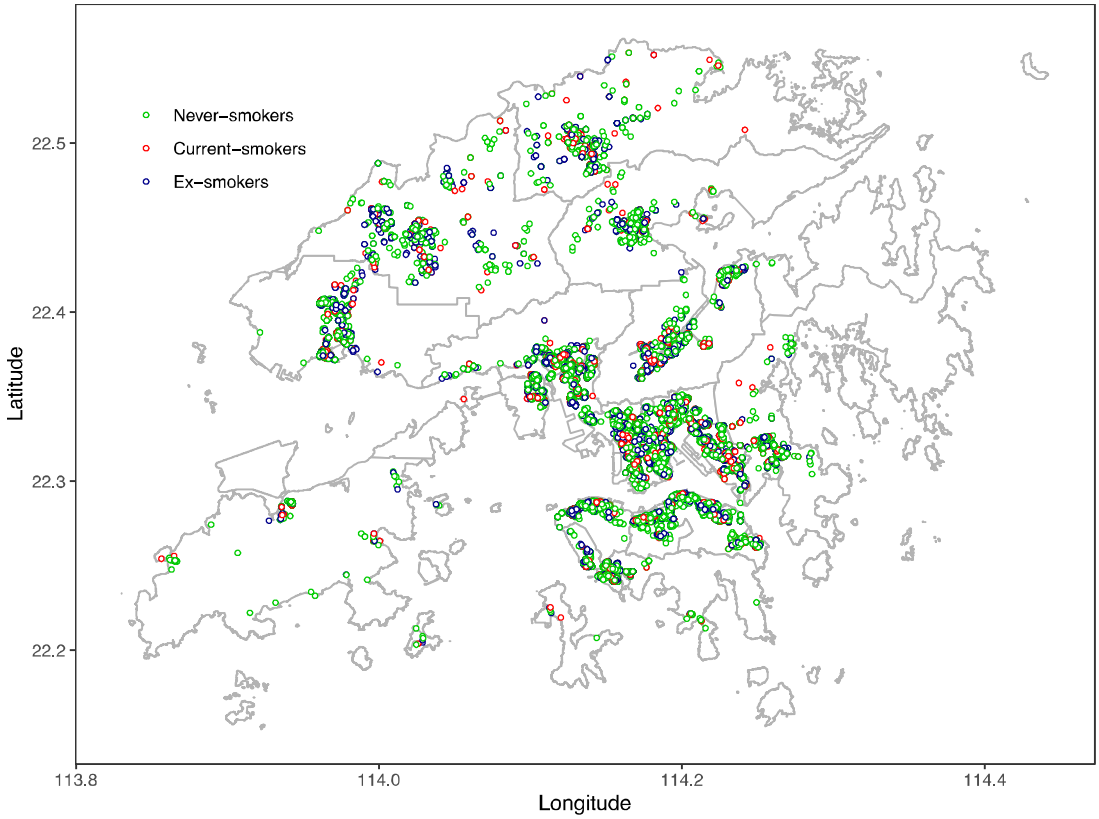
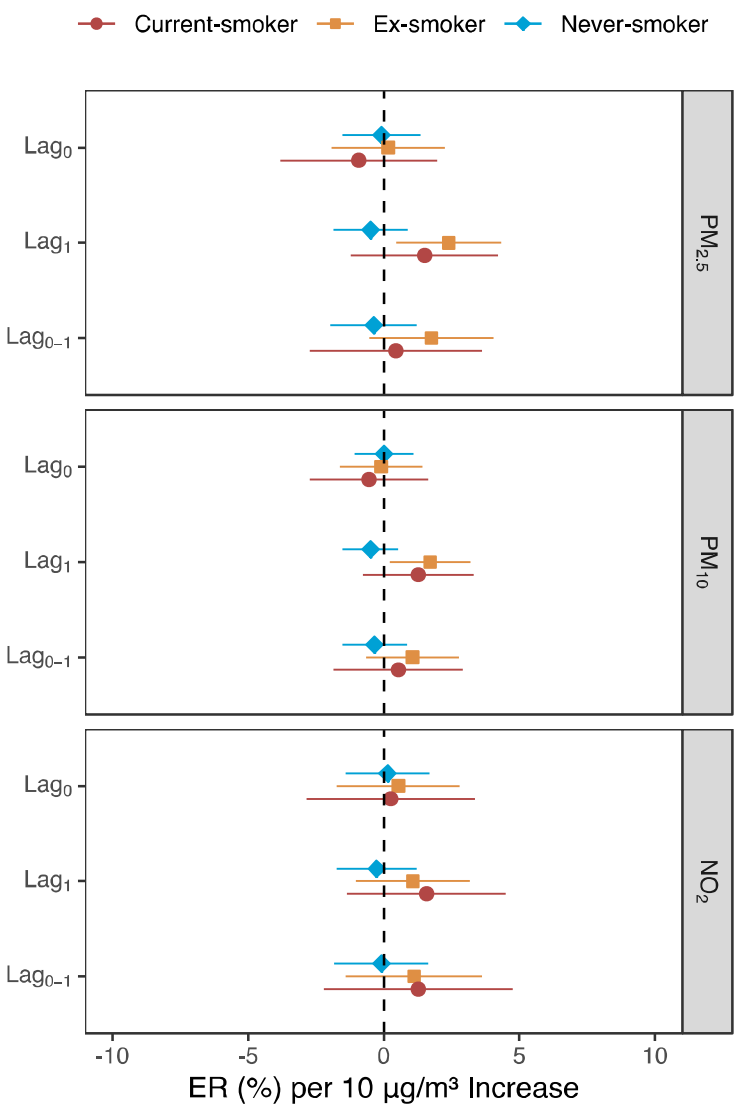
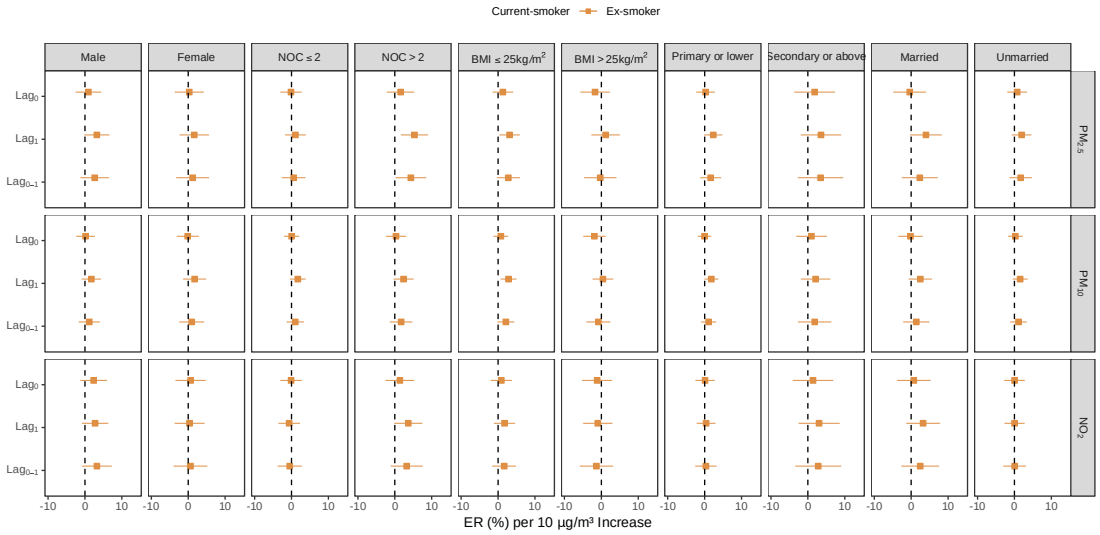


Fig. 2. Excess Risk (%) and 95% confidence interval (CI) of mortality associated with air pollutants per 10 $\mu g/m^3$ increase in current-, ex-, and never-smokers.



Abbreviations: ER%=percent excess risk; $PM_{2.5}$= particulate matter with aerodynamic diameter less than 2.5µm; PM_{10}= particulate matter with aerodynamic diameter less than 10µm; and NO_2=nitrogen dioxide.

Fig. 3. The additional excess risk (%) of mortality associated with air pollution per 10㎍/m^3 increase in current- and ex-smokers relative to never-smokers by personal characteristics.



Abbreviation: NOC=number of comorbidities; $PM_{2.5}$= particulate matter with aerodynamic diameter less than 2.5μm; PM_{10}= particulate matter with aerodynamic diameter less than 10μm; and NO_2=nitrogen dioxide.