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Cigarette smoking increases deaths associated with air pollution in Hong Kong

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HIGHLIGHTS

- Ever-smokers are more susceptible to short-term air pollution exposure.
- The higher risks due to smoking are stronger among males, overweight elders, or elders with worse health.
- Tobacco control can reduce health burdens attributable to air pollution.

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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 examine 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 (ΔER%) 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 greater ERs % associated with air pollutants among current- and ex-smokers relative to never-smokers. We found ΔER% 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

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[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.

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 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 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 season 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, 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 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 1–3 days ($lag_{1\text{-}3}$) 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 (ORs) and 95% confidence intervals (CIs) 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 ($lag_{0\text{-}1}$).

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 ($\leq$25 kg/m^2 versus >25 kg/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 males or those who consumed alcohol (Table 1).

The daily mean concentration of air pollutants on the day of death was 37.6 μg/m^3 for $PM_{2.5}$, 52.5 μg/m^3 for PM_{10}, and 57.6 μg/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 μg/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 ΔER% of air pollutants for current- and ex-smokers relative to never-smokers (Table 3). Although the point estimates of ΔER% for air pollutants were all positive, we found the ΔER% was statistically significant for $PM_{2.5}$ among ex-smokers [2.63% (95% CI: 0.39%, 4.88%) per 10 μg/m^3 increase at lag_1] and PM_{10} among current-smokers [2.21% (95% CI: 0.08%, 4.33%) per 10 μg/m^3 increase at lag_1] and ex-smokers [1.96% (95% CI: 0.26%, 3.65%) per 10 μg/m^3 increase at lag_1].

In secondary analyses, we evaluated whether the ΔER% of current- and ex-smokers relative to never-smokers differed by personal characteristics (Fig. 3). We found the ΔERs% 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 ΔER% per 10 μg/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 $\leq$ 25 kg/m^2 for PM_{10} at lag_1, and 2.80% (95% CI: 0.45%, 5.15%) among current-

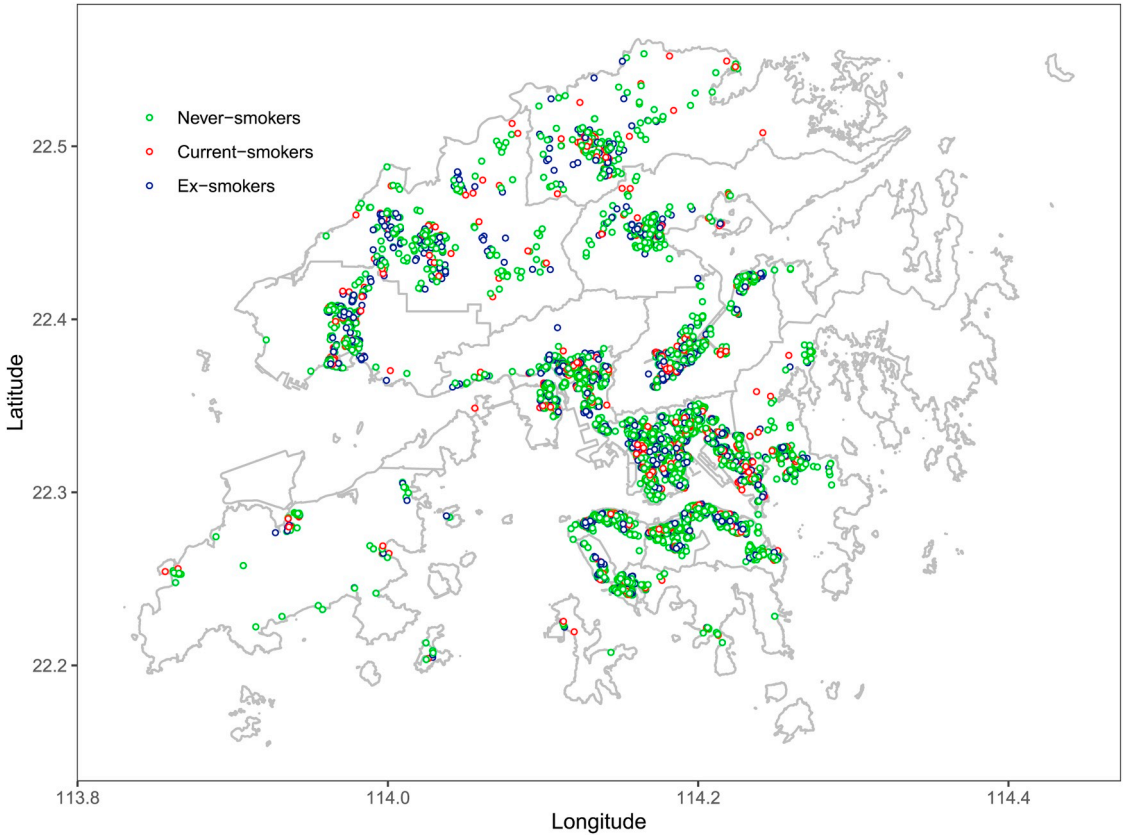

Fig. 1. Spatial distribution of the deceased current-smokers (n = 2,327), ex-smokers (n = 4,402), and never-smokers (n = 9,561) in the Chinese Elderly Health Service Cohort.

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 [≥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 [≥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
$PM_{2.5}$ (μg/m^3)	37.6 ± 21.8	1.00	0.92	0.77	−0.38	−0.42
PM_{10} (μg/m^3)	52.5 ± 28.6		1.00	0.70	−0.37	−0.46
NO_2 (μg/m^3)	57.6 ± 20.3			1.00	−0.39	−0.35
Temperature (°C)	23.1 ± 5.2				1.00	0.28
Relative humidity (%)	77.6 ± 10.6					1.00

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

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 lag_1. We also found greater ΔERs% of ever-smokers versus never-smokers in the warm seasons (Table S1).

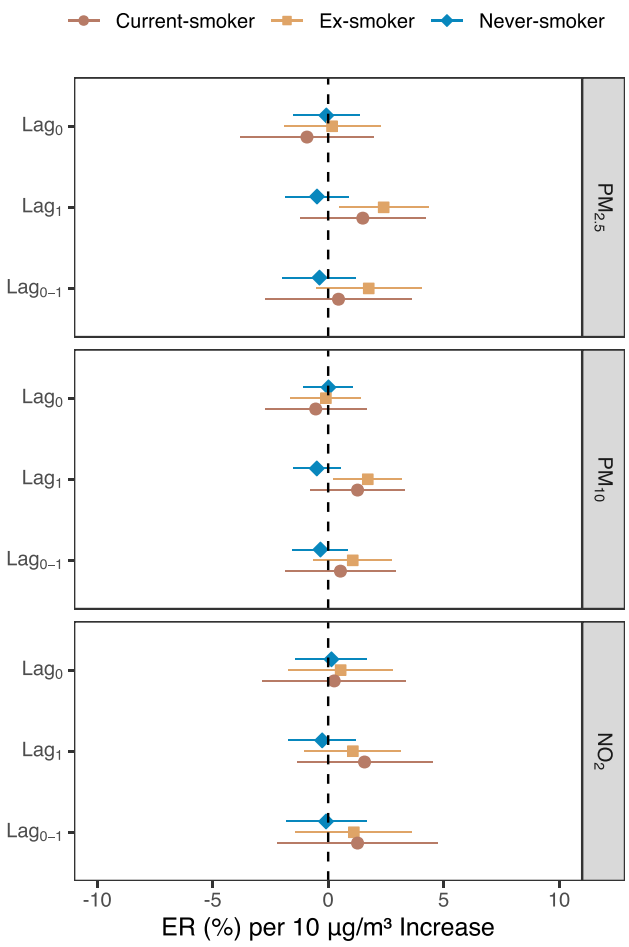

Fig. 2. Excess Risk (%) and 95% confidence interval (CI) of mortality associated with air pollutants per 10 μg/m^3 increase in current-, ex-, and never-smokers. Abbreviations: ER% = percent excess risk; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10} = particulate matter with aerodynamic diameter less than 10 μm; and 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 2.5 μm; PM_{10} = particulate matter with aerodynamic diameter less than 10 μm; NO_2 = nitrogen dioxide.

4. Discussion

Among 16,290 deaths occurring in this Elderly Health Service Cohort of Chinese elders, we found that smokers were more susceptible to short-term air pollution exposure than never-smokers. We also found that the increased susceptibility associated with cigarette smoking was more pronounced among males, overweight or obese elders, elders with poor

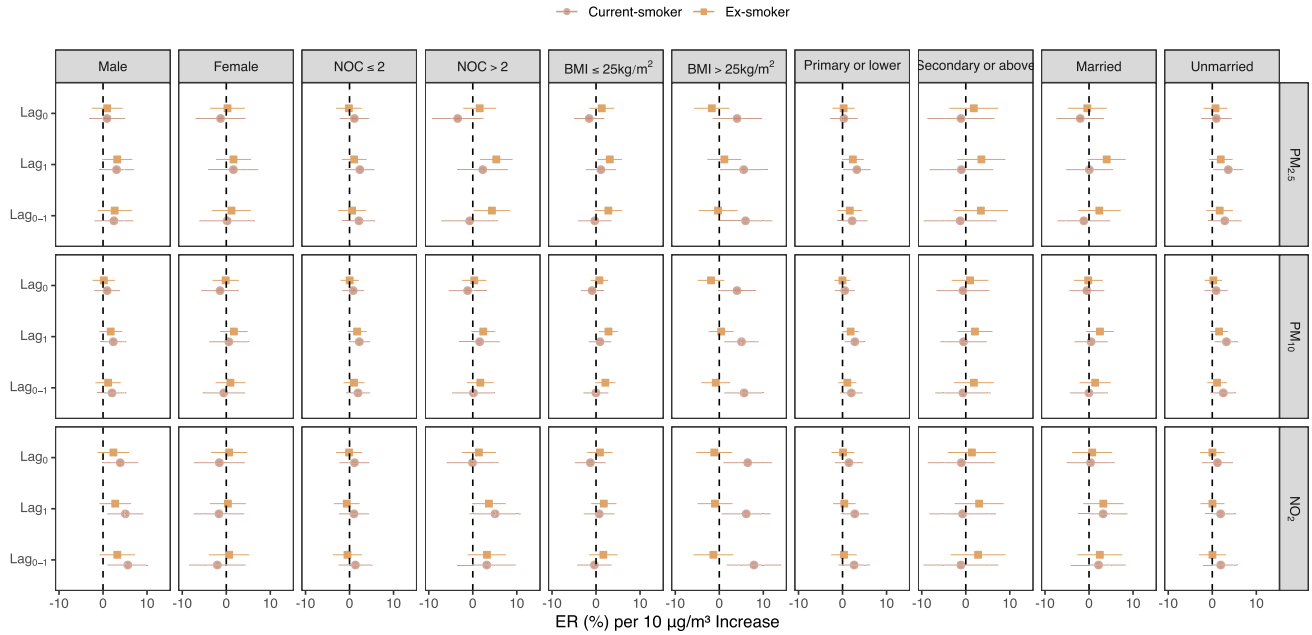

Fig. 3. The additional excess risk (%) of mortality associated with air pollution per 10 μg/m^3 increase in current- and ex-smokers relative to never-smokers by personal characteristics. Abbreviation: NOC = number of comorbidities; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm; PM_{10} = particulate matter with aerodynamic diameter less than 10 μm; and NO_2 = nitrogen dioxide.

health conditions, or elders received primary or lower education. Our findings suggest that tobacco control can reduce the health burdens attributable to air pollution.

Our finding of a positive ΔER% associated with air pollution among current- and ex-smokers compared with never-smokers was consistent with prior studies (Canova et al., 2012; Wong et al., 2007). For example, a London, UK study reported that a 10 μg/m^3 increase in PM_{10} was associated with an 87% increase in the risk of airway exacerbation among smokers, whereas no excess risks were observed among never- and ex-smokers (Canova et al., 2012). A Hong Kong study among 10,833 men aged 30 years or above found that the ΔER% of all-natural mortality per 10 μg/m^3 increase in PM_{10} among smokers was 2.2% (95% CI: −0.4%, 4.8%) compared with never-smokers, which was generally consistent with our findings (Wong et al., 2007). Compared with the Hong Kong study (Wong et al., 2007), our study had two major improvements. We collected information on smoking habits directly from participants themselves instead of asking this information from relatives of the deceased people, which could minimize the misclassification of smoking status. Also, we collected detailed information on smoking status (i.e., current-, ex-, and never-smokers), which allows us to examine the ΔER% 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 et al., 2001; Mortensen et al., 1994). 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 and 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., 1994), 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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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Shengzhi Sun: Conceptualization, Methodology, Software, Writing - original draft. **Wangnan Cao:** Writing - original draft, Writing - review & editing. **King-Pan Chan:** Resources, Data curation, Writing - review & editing. **Jinjun Ran:** Software, Validation, Writing - review & editing. **Yunquan Zhang:** Writing - review & editing. **Yilin Feng:** Writing - review & editing. **Ruby Siu-yin Lee:** Resources, Writing - review & editing. **Chit-Ming Wong:** Writing - review & editing, Supervision, Conceptualization. **Linwei Tian:** Supervision, Conceptualization, Writing - review & editing, Funding acquisition. **Yujie Lei:** Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2020.117266.

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