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Original Article

Cigarette smoking as a risk factor for influenza-associated mortality: evidence from an elderly cohort

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Background The effects of individual lifestyle factors on the mortality risk after influenza infection have not been explored.

Objectives In this study, we assessed the modifying effects of cigarette smoking on mortality risks associated with influenza in a cohort of Hong Kong elders with a follow-up period of 1998–2009.

Methods We used the Cox proportional hazards model with time-dependent covariates of weekly proportions of specimens positive for influenza (termed as influenza virus activity), to calculate the hazard ratio of mortality associated with a 10% increase in influenza virus activity for never, ex- and current smokers. Other individual lifestyle and socioeconomic factors as well as seasonal confounders were also added into the models.

Results The overall hazard ratio associated with influenza was 1·028 (95% confidence interval, 1·006, 1·051) for all natural cause mortality and 1·035 (1·003, 1·068) for cardiovascular and respiratory mortality. We found that influenza-associated hazard ratio was greater in current and ex-smokers than in never smokers for mortality of all natural causes, cardiovascular and respiratory diseases.

Conclusions The findings suggest that smoking might increase influenza-associated mortality risks among elders.

Keywords Cohort, Cox model, influenza, mortality, smoking.

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Introduction

The World Health Organization (WHO)[1] estimated that 5 million severe cases and 250 000–500 000 deaths were attributed to annual seasonal influenza epidemics worldwide. The disease burden of influenza is particularly heavy in the elders. Influenza was estimated to be associated with more than 1000 deaths each year in Hong Kong and around 90% occurred in those aged over 65 years.[2] Vaccination remains as the most important prevention measure for the elders, because there is ample evidence to suggest that it could effectively reduce the incidence of influenza infection and decrease the risk of hospitalization and mortality.[3] However, the time delay of vaccine production results in occasional mismatch between vaccines and circulating strains. Annual vaccination campaign is also hampered by the concerns over the potential side effects.[4] Therefore, it is necessary to encourage the elders to adopt other prevention approaches such as improving personal hygiene and maintaining healthy life style that can be enhanced before or at the very early stage of pandemics.

Animal studies have demonstrated that cigarette smoking was associated with increased susceptibility to influenza viruses, probably by down-regulating the primary inflammatory response of the host.[5] An early study in the human population found that during the 1968 pandemic the incidence rates of both symptomatic and asymptomatic infections were the highest in the current smokers among a cohort of male college students.[6] Similar findings were also reported in a sero-epidemiology study in the elders.[7] However, there have been very few studies that have explored the impact of smoking on mortality risks specifically associated with influenza, despite the fact that the increased mortality risk of pneumonia and influenza among smokers has been widely reported.[8] The reason could be that it is difficult to identify people who die from influenza, as influenza

infection does not cause any specific symptoms and most cases are not diagnosed by laboratory tests. Furthermore, people infected by influenza could die from exacerbation of their pre-existing conditions or secondary bacterial pneumonia. To quantify the mortality risks of influenza, many ecological studies used regression models to assess the baseline levels when influenza virus circulation is absent or at a low level, and then defined the influenza-associated excess mortality as the sum of the differences between the observed death numbers and modeled derived baseline numbers.[2,9] However, individual risk factors could not be examined in such ecological studies. In the present study, we applied a Cox proportional hazards model with time-dependent covariates, which has been adopted to estimate the effects of air pollution on mortality,[10] with the aim to estimate the influenza-associated mortality in a cohort of older Chinese in Hong Kong. This model also allowed us to assess the effect modification of smoking on mortality risks associated with influenza while controlling for potential individual confounders.

Methods

The elderly cohort

In Hong Kong, 18 Elderly Health Centers (EHC) managed by the Department of Health provide health examination and primary health care service to people aged 65 years or over living in the community. This study covered 66 820 elders who enrolled to the EHC during July 1, 1998–December 31, 2001. The subjects were similar to the general population in age distribution, socioeconomic status and smoking status, except that more women were enrolled than men.[11]

The procedures for collecting baseline data have been described in a previous study.[11] Briefly, information on lifestyle habits (smoking history, exercise frequency and alcohol drinking) and socioeconomic status (housing type, education and monthly expenditure) of all the subjects was collected by trained nurses and doctors using a standardized questionnaire at their first visits to the EHC. The health status was assessed through a clinical examination and chronic conditions were recorded. The subjects were divided into three groups: never, ex- and current smokers, according to their smoking history. Current smokers were defined as those who were still smoking at baseline. Never smokers were those who never smoked and ex-smokers were those who had ever smoked but quitted smoking for at least 1 year.

The death registration data were linked to the cohort baseline by the Department of Health using the unique Hong Kong identity card number. One hundred and ninety-four subjects were excluded owing to unknown date or cause of deaths. Three subjects with an unknown smoking status were also excluded. A final sample of 66 623 subjects were included in this study, among them 14 090 subjects died from all natural causes whose underlying causes of death were coded by the International Classification of Diseases, Ninth Revision (ICD-9) before 2001 and Tenth Revision (ICD-10) afterward. There were 367 subjects who died from accidents or injuries, and they were treated as censored at the date of deaths. Five disease categories were considered in estimating the overall disease burden of influenza: all natural causes (ICD-9, 001-799, ICD-10, A00-R98, Z00-Z99), cardiovascular and respiratory diseases (CRD, ICD-9, 390-519, ICD-10, I00-J99), pneumonia and influenza (P&I, ICD-9 codes 480-487; ICD-10 codes J10-J18), chronic obstructive pulmonary disease (COPD, ICD-9 codes 490-496; ICD-10 codes J40-J47) and ischemic heart disease (IHD, ICD-9 codes 410-414; ICD-10 codes I20-I25). To ensure a sufficient power, only all natural cause and CRD mortality were included to assess effect modification of smoking.

Influenza virology data and meteorology data

Influenza virology data were obtained from the microbiology laboratory of Queen Mary Hospital (QMH). This laboratory routinely collected nasopharyngeal samples from patients who were admitted with respiratory symptoms of fever (temperature >38°C), cough or sore throat, to test for influenza virus and respiratory syncytial virus (RSV) as well as other respiratory viruses. Although the virology data were obtained from only one major hospital, such data have been found to highly correlate with the virology data from the whole territory of Hong Kong in terms of magnitude and seasonal variations.[12] Meteorology data of temperature and relative humidity were obtained from the Hong Kong Observatory.

Statistical analysis

The Cox proportional hazards model with time-dependent covariates was adopted to estimate the cause-specific hazard ratios of influenza-associated mortality for all natural cause and CRD mortality.[13] This model simultaneously adjusted for multiple time variant seasonal confounders, including temperature, humidity and co-circulation of other viruses. As many other previous studies on influenza disease burden,[9,14] we adopted the weekly proportions of specimens positive for influenza (or RSV) as a proxy variable for influenza (or RSV) virus activity. By integrating influenza virology data as a continuous time-dependent variable into the model, the effect of influenza could be assessed by the ratio of mortality hazards when influenza activity was high relative to those when influenza activity was low.[15] This model avoids the subjective definition for epidemic and non-epidemic periods and thereby is particularly suitable for the subtropical and tropical regions

such as Hong Kong, where influenza can be active throughout the year (Appendix 1). The model has the form of

$$h_i(t) = h_0(t)\exp[\sum_j \gamma_j X_{ji} + \sum_k \gamma_k Z_{ki}(t) + \beta flu_i(t)] \quad (1)$$

where the week number t = 1,2,…608 is the indicator of time for the study period of July 1, 1998–December 31, 2009, $h_i(t)$ is the hazard rate for subject i at week t, and $h_0(t)$ is unspecified baseline hazard rate. $flu_i(t)$ denotes a time-dependent covariate of weekly proportions of specimens positive for influenza virus type A or B, termed as influenza virus activity in this article. X_{ji} denotes the j^{th} time-independent variables of age, sex, comorbidity score, receiving public assistance, housing types and education for subject i, where both age and comorbidity score were entered as continuous variables. $Z_{ki}(t)$ is the k^{th} time-dependent variables of seasonal and long-term trends, temperature, humidity, concentration of ambient air pollutants and proportions of specimens positive for RSV. The comorbidity score was defined as the count of chronic conditions including heart diseases, stroke, diabetes, COPD (and/or asthma), and hypertension, to adjust for the preexisting conditions of subjects before enrollment. Influenza-associated mortality risk was measured by the hazard ratio associated with every 10% increase of influenza virus activity, by the formula HR = exp(0·1*β) where β was estimated from equation (1).

Effect modification of smoking was assessed by the Cox proportional hazards model with interaction terms defined as the product of influenza virus activity variables and dummy variables for smoking status. Never smokers were the reference group in this model. A typical model is:

$$h_i(t) = h_0(t)\exp[\sum_j \gamma_j X_{ji} + \sum_k \gamma_k Z_{ki}(t) + \beta_1 flu_i(t) + \beta_2 flu_i(t) * \text{exsmoker} + \beta_3 flu_i(t) * \text{currentsmoker}]$$

where dummy variable exsmoker = 1 indicates ex-smokers and 0 otherwise; currentsmoker = 1 indicates the current smoker group and 0 otherwise. The statistical significance of coefficients β_2 (or β_3) from equation (2) indicated whether the influenza-associated mortality risk was significantly different between ex-smokers (or current smokers) and never smokers. Stratified analyses were separately performed for never, ex- and current smoker groups, regardless of statistical significance of the interaction terms in the models. Gender difference in influenza-smoking association was tested by the likelihood ratio test between the models with or without three-way interaction terms of sex, smoking group and influenza proxy variable. In this study, statistical significance was defined as two-sided $P < 0{\cdot}05$. All the analyses were conducted in STATA 10.0 (STATA Corporation, College Station, TX, USA) and r package version 2.5.1 (R Development Core Team, Vienna, Austria).

Ethics approval was obtained from the ethics committee of the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number UW 09-079).

Results

At baseline, over 80% of never smokers were woman, whereas over 70% of ex-smokers or current smokers were man (Table 1). The ex-smokers were slightly older than never and current smokers and more likely to have more than two underlying chronic conditions, and current smokers were more likely to receive public assistance and less likely to have self-owned houses compared with the other groups (Table 1). The crude mortality rates of all natural causes were higher in current smokers compared to the other two groups, but the mortality rates of CRD were higher in ex-smokers (Table 2).

Influenza-associated mortality risk

The death rates of cohort subjects tended to reach two peaks each year, a pattern similar to influenza virus activity in Hong Kong (Appendix 1). After adjusting for potential confounders, the hazard ratio of mortality associated with per 10% increase in influenza virus activity was 1·028 (95% CI, 1·006, 1·051), 1·035 (1·003, 1·068), 1·036 (0·971, 1·105),1·044 (0·956, 1·140), and 1·061 (0·997,1·130), for all natural causes, CRD, IHD, COPD and P&I, respectively.

Effect modification of smoking on mortality risks associated with influenza

Compared to never smokers, ex-smokers and current smokers had higher hazard ratio of mortality associated with influenza, although all the interaction terms of smoking status and influenza virus activity were found not significant ($P > 0{\cdot}05$). Stratified analyses by smoking status showed an increasing trend of hazard ratio for all-cause mortality from never smokers (1·013), ex-smokers (1·048) and current smokers (1·053), but the estimates were only significant ($P < 0{\cdot}05$) in ex-smokers. Similar results were also found for CRD, with the estimates of 1·029, 1·032 and 1·073 for never, ex- and current smokers for CRD (Figure 1). For the analyses further stratified by sexes, a similar trend was also found for woman, with the significant estimates in current smokers; but for man, a similar trend was not observed and the hazard ratios in current smokers were the lowest and closest to unity among all categories of smoking for both all-cause and CRD mortality (Appendix 2). However, the interaction between gender, influenza and smoking was not significant for all-cause ($P = 0{\cdot}38$) nor for CRD mortality ($P = 0{\cdot}14$).

Table 1. Baseline characteristics of the elderly cohort by smoking status

	Never smoker	Ex-smoker	Current smoker	*P**
Persons (*n*)	47 477	12 776	6370	
Person-years	441 089	109 594	54 068	
Average follow-up (weeks)				
65–74	497·3	471·0	460·6	
75–84	458·1	412·3	396·0	
85+	367·8	319·6	325·1	
Sex (%)				
Women	81·8	26·8	27·8	<0·001
Men	18·2	73·2	72·2	
Age (%)				
65–74	74·5	65·9	74·7	<0·001
75–84	22·7	30·4	23·3	
85+	2·8	3·7	1·9	
Comorbidity score (%)**				
0	50·7	45·8	59·5	<0·001
1	33·2	34·7	28·9	
2–5	16·1	19·5	11·6	
Alcohol drinking (%)***				
Never	83·4	43·4	48·3	<0·001
Former	4·9	25·8	14·6	
Social/regular	11·7	30·8	37·0	
Exercise (%)†				
Sedentary	14·1	14·8	25·6	<0·001
Moderate	34·1	33	33·9	
Frequent	51·8	52·2	40·5	
On public assistance (%)				
Yes	15·4	20·6	21·9	<0·001
No	84·6	79·4	78·1	
Housing (%)				
Self-owned	50·6	45·4	40·5	<0·001
Other	49·4	54·6	59·5	
Education (%)				
None	51·3	32·1	35·8	<0·001
Primary	32·8	46·6	46·1	
Secondary	12·3	17·0	14·6	
Tertiary	3·6	4·4	3·5	

*P-value of χ^2 test.
**Comorbidity score is defined as the number of chronic conditions including heart diseases, stroke, diabetes, chronic obstructive pulmonary disease (and/or asthma), and hypertension.
***Never drinkers were those who had never drunk; regular or social drinkers were defined as persons who drank on 4 or more days or <4 days per week, respectively. Former-drinkers were social or regular drinkers before but had already quitted drinking.
†Sedentary subjects were those who did not do any exercise at all. Moderate exercise was defined as not doing exercise everyday or <30 minutes each time and frequent exercise as doing exercise more than 30 minutes everyday.

Sensitivity analysis

From May to December 2009, a novel influenza virus H1N1 caused a worldwide pandemic.[16] This pandemic virus attacked more children and young adults, a pattern different from seasonal influenza whose attack rate was higher in the elders.[17] We therefore excluded the pandemic period by censoring the data at May 1, 2009. The estimates were slightly larger than those of whole study period, but the pattern across smoking strata was consistent between two sets of estimates (Appendix 3).

To test the sensitivity of adjustment for comorbidity in our model, we changed the definition of comorbidity scores by adding three extra items related to the fragile conditions into the model: any hospital admissions in the last year, unintentional loss of more than 4·5 kg weight and more than two falls in the last half year. Another sensitivity analysis was to add the pre-existing chronic status of heart diseases, stroke, diabetes, COPD (and/or asthma), and hypertension as five separate time-independent variables into the model. Both analyses returned very similar results to the main analysis (data not shown).

Table 2. Crude death numbers (rates per 100 000 person-years) of the elderly cohort by lifestyle factors

Disease	Gender	Both	Men	Women
All natural cause	Never	8935 (2025·7)	1952 (2491·2)	6983 (1925·1)
	Ex	4198 (3830·5)	3126 (3933·8)	1072 (3558·2)
	Current	2244 (4150·3)	1702 (4426·5)	542 (3470·5)
CRD	Never	4312 (977·6)	963 (1229·0)	3349 (923·3)
	Ex	2218 (2023·8)	1643 (2067·6)	575 (1908·5)
	Current	993 (1836·6)	735 (1911·5)	258 (1652·0)

CRD, cardiovascular and respiratory diseases.

Discussion

We found an increasing trend of mortality hazard ratio across never, ex- and current smokers, which demonstrated that smoking is a risk factor for the mortality risks associated with influenza. The association of smoking with respiratory infections has long been established.[18] However, evidence in the literature on smoking and influenza is far from convincing. Some studies reported increased incidence of influenza-like symptoms in young smokers,[19,20] but several community based cohort studies did not detect a significant effect of smoking on influenza transmission in community or within households.[21,22] To our best knowledge, the effects of smoking on influenza-attributable mortality have never been reported. The difficulty in the assessment may be due to the mild and non-specific symptoms of influenza, which makes laboratory tests necessary for the diagnosis of influenza. Nevertheless, the resources needed for large-scale and comprehensive laboratory screening for influenza cases could be enormous. The few fatal cases of influenza infections (most likely due to underdiagnosis of clinical influenza) make the

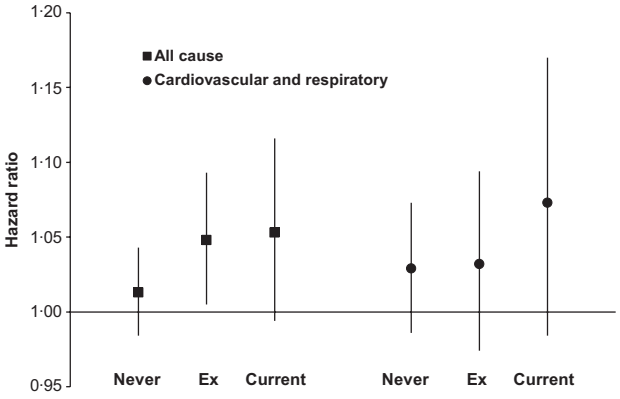

Figure 1. Hazard ratio of all natural causes (square) and cardiovascular/respiratory diseases (CRD, circle) that are associated with 10% increase in influenza virus activity. The subjects were stratified by smoking status: never smokers (Never), ex-smokers (Ex), current smokers (Current).

direct evaluation of influenza-associated mortality even more difficult. In this study, we utilized a large elderly cohort featured with a long follow-up period to assess the mortality risks associated with influenza, which were measured by the hazard ratio of mortality when influenza virus became active in the community relative to that when virus was assumed absent. The results demonstrated significant mortality risks associated with influenza in all-cause and CRD mortality, which were consistent with our previous findings.[2,12] The results were robust to exclusion of the data during the 2009 pandemic year, and to the use of different definitions for comorbidity in the sensitivity analyses. Our study found much higher mortality risks associated with influenza among current smokers compared to those who never smoked. This is consistent with the finding of a previous study using the same cohort, which reported much higher relative risks of respiratory mortality in ex- or current smokers than never smokers.[23] There is ample evidence that has linked smoking with increased risks of viral and bacterial respiratory infections.[24] Smoking can cause structural changes in respiratory epithelial cells and suppress both cell- and humoral-mediated immunity response against infections of influenza and other respiratory viruses.[15,25] Exposure to cigarette smoke was found to alter platelet-activating factors and enhance the adherence of pneumococcal bacteria to influenza-infected respiratory cells,[26–28] which may explain why smokers were more likely to develop more severe symptoms after influenza infection, more prone to secondary bacterial infections[19,20] and had a higher risk of deaths after influenza infection.[29]

An important confounder of vaccination remains unadjusted in our study, because vaccination history is unknown for individual subjects of our elderly cohort. A telephone survey conducted in 2006 collected the vaccination history during 2003–2005 from a sample of 207 subjects from this same cohort.[30] The results showed that the vaccination rates of current smokers were slightly lower than those of never and ex-smokers (43·3% versus 46·5% and 52·7%), but the difference was not statistically significant (Appendix 4). Also, the annual vaccination rate of 57·6% in 2005 from this survey was similar to the rate of 64·5% reported by a study on community-dwelling elders recruited from the general outpatient clinics.[31] Taken together, the difference of influenza-associated mortality risks between smoking groups was unlikely the result of different vaccination rates among these groups. Nevertheless, we may obtain the vaccination status for each subject in the future follow-up. Further studies on interaction between influenza and lifestyle factors with adjustment for vaccination history are warranted.

Gender difference in influenza infections has been noticed in previous studies, but the male/female ratio of influenza mortality or infection risk varied between countries.[32] Women and men may have an unequal risk of influenza infection because of their different social behavior and immune response. Gender heterogeneity in health seeking behavior and pre-existing conditions may also greatly affect the outcome of infection.[32] It is of note that our estimates of hazard ratio could not differentiate the impact on exposure risk and severity of infection. In this study, we found a significant interaction between effects of smoking and influenza on mortality in females, but not in males. However, none of the estimates for influenza effects in male never, ex- and current smokers were statistically significant, suggesting that the sample size of male subjects in our cohort was too small to detect any meaningful pattern of smoking effects. The possibility of survival effects among the male subjects could not be ruled out as women tend to live longer than men. Future studies with a large sample size are needed to further assess the gender difference in smoking effects.

The effect modification of smoking cessation on influenza-associated mortality was not consistent between all natural cause and CRD mortality. Compared to never smokers, the influenza-associated hazard ratio in ex-smokers was elevated for all natural cause mortality, but only slightly elevated for CRD mortality, although none of these estimates were statistically significant. A previous study based on the same cohort reported a higher risk of respiratory mortality in ex-smokers than in current smokers for both men and women.[23] The inconsistent results in ex-smokers may be due to the ill-quitter effect that some unadjusted chronic conditions had forced ex-smokers to quit smoking, or other uncontrolled factors such as time since quitting.

Our estimation of the cause-specific hazard ratio for CRD is subject to the competing events of other causes, and a competing risk analysis can be conducted.[33] Therefore, we did a competing risk analysis for CRD mortality by choosing lung cancer, a leading cause of mortality in Hong Kong, as a competing event. The estimates from the competing risk method are slightly smaller than those from

the traditional censoring method, for all the gender-disease categories, but these two sets of estimates show the same pattern and yield the same conclusion that current smokers tend to have a higher mortality risk of influenza-associated CRD than never smokers (Appendix 5). However, for all natural cause of mortality we did not do any competing risk analyses because of the difficulty in finding a competing event, given that in theory influenza infections unlikely affect the risk of mortality owing to accidental cause, the only potential competing event for all natural causes.

There are limitations in our study. First, our estimates for influenza effects were based on modeling the association between influenza activity and incidence of deaths, which is an indirect method to assess whether death rates increased along with the increase of influenza virus activity. The deaths caused by influenza infection can only be confirmed by extensive laboratory tests, but given the costs of such tests, it would be unrealistic to collect such data. Even if this can be done, it would be even more difficult to assess the number of people who had died from exacerbation of previous conditions and secondary bacterial infections after influenza infection. Second, the subjects were recruited through their voluntary visits to the EHC, therefore they tend to be healthier and more health conscious than those dwelling in the community but had never visited the EHC. Nevertheless, comparison with the survey data of Hong Kong general population shows that our cohort is representative with regard to the lifestyle and socioeconomic factors.[11] Third, in this study the effect of influenza was measured by the relative increase or decrease in mortality risks (hazard ratio) when influenza increases by 10%. It could be problematic if we compare hazard ratio across different disease categories because of the differences in the baseline levels. Nevertheless, this study aimed to assess the modification effects of lifestyle factors, which should be adequately revealed by the difference in hazard ratio estimates. Fourth, only the baseline information was collected for the subjects, but their behavior might have changed during the follow-up period. The change in behavior would introduce misclassification that in the case of changing into healthier lifestyle, could have biased the estimates of effect modification toward the null. Furthermore, we did not take account of the past exposure to smoking before recruitment, such as the years of smoking or quitting, as this information was not available in our cohort. This might have also introduced confounding to our risk estimates. Last but not least, none of the interaction terms in our models were statistically significant. Although this is not unusual in the assessment of effect modification in the studies designed to explore the main effects,[34] our results require cautious interpretation.

Given the concern over concurrent smoking epidemics and influenza epidemics, it is urgent for the government to adopt more stringent tobacco control policies for the health benefit of general population. Smokers shall be added into the priority group of annual influenza vaccination campaign to lower their risks of mortality associated with influenza.

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Conflict of interests

JSMP served as *ad hoc* consultant to pharmaceutical firms Crucell MV and Sanofi Pasteur. Others declared no conflict of interests.

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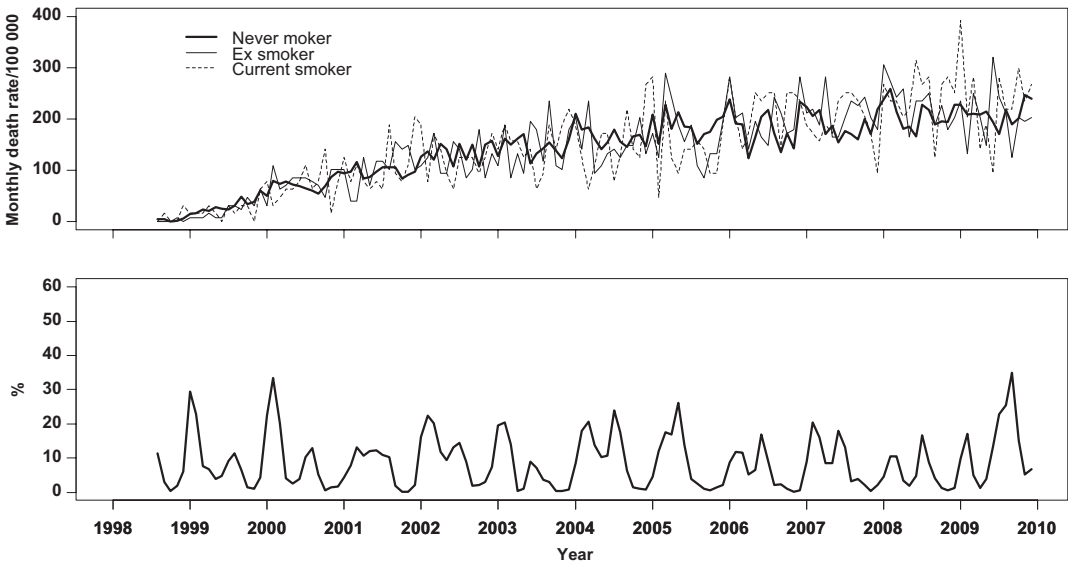
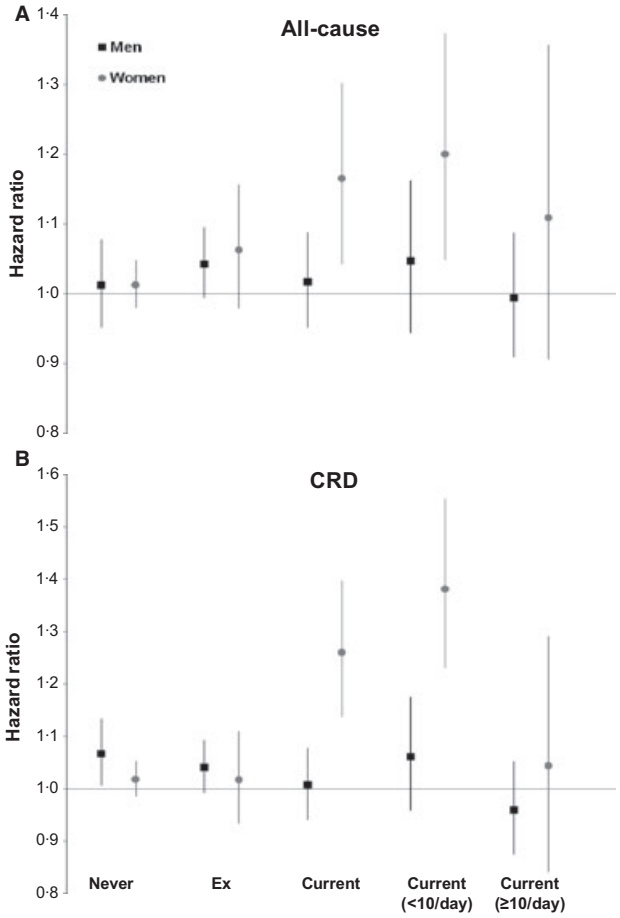
Appendix 1

Monthly mortality rate of cohort subjected by smoking groups and proportions of specimens positive for influenza during the study period. Note: monthly proportions of influenza positive specimens were obtained from the Department of Health, Hong Kong Special Administrative Region.



Appendix 2

Hazard ratio of all-cause and CRD mortality associated with 10% increase in influenza virus activity in men (black square) and women (gray circle). The subjects were stratified into never smokers (Never), ex-smokers (Ex) and current smokers (Current).



Appendix 3

Hazard ratio (HR) of mortality risks associated with every 10% increase in influenza virus activity, stratified by smoking groups. Only the data during the interpandemic periods of May 1998 – April 2009 were included

Cause	Smoking	Both	Men	Women
		HR (95%CI)	HR (95%CI)	HR (95%CI)
All natural cause	Never	1·012 (0·977, 1·048)	1·030 (0·956, 1·110)	1·007 (0·967, 1·048)
	Ex	1·059 (1·008, 1·113)	1·050 (0·991, 1·112)	1·084 (0·983, 1·196)
	Current	1·094 (1·022, 1·171)	1·066 (0·986, 1·154)	1·184 (1·032, 1·357)*

(Continued)

Cause	Smoking	Both	Men	Women
		HR (95%CI)	HR (95%CI)	HR (95%CI)
CRD	Never	1·034 (0·983, 1·088)	1·105 (0·994, 1·229)	1·014 (0·957, 1·075)
	Ex	1·041 (0·972, 1·115)	1·046 (0·966, 1·134)	1·032 (0·902, 1·180)
	Current	1·111 (1·004, 1·231)	1·031 (0·913, 1·165)	1·342 (1·112, 1·620)*

CRD, cardiovascular and respiratory diseases.
*$P < 0·05$ in interaction models with never smokers as reference group.

Appendix 4

Vaccination rates by smoking status, from a survey of 207 subjects sampled form the elderly cohort. Subjects were selected from the elderly cohort by stratified sampling to achieve the equal age, sex and smoking history. Details are described in reference 30

Smoking	Vaccination in 2003–2005		P*
	Yes	No	
Never smoker (%)	40 (46·5)	46 (53·5)	0·58
Ex-smoker (%)	49 (52·7)	44 (47·3)	
Current smoker (%)	13 (43·3)	17 (56·7)	
Total (%)	102 (48·8)	107 (51·2)	

**P*-value of Chi square test.

Appendix 5

Hazard ratio of mortality risks (HR) for cardiovascular and respiratory diseases associated with every 10% increase in influenza virus activity

Model	Smoking	Both	Men	Women
		HR (95%CI)	HR (95%CI)	HR (95%CI)
Censoring method	Never	1·029 (0·987, 1·074)	1·069 (0·980, 1·165)	1·018 (0·970, 1·068)
	Ex	1·033 (0·975, 1·094)	1·041 (0·973, 1·113)	1·017 (0·909, 1·139)
	Current	1·073 (0·984, 1·170)	1·008 (0·909, 1.118)	1·258 (1·074, 1·473)
Competing risk method*	Never	1·025 (0·983, 1·069)	1·066 (0·979, 1·161)	1·013 (0·965, 1·064)
	Ex	1·027 (0·969, 1·087)	1·034 (0·967, 1·106)	1·012 (0·905, 1·131)
	Current	1·067 (0·980, 1·161)	1·002 (0·905, 1·109)	1·251 (1·073, 1·458)

*Lung cancer was the event competing with cardiovascular and respiratory diseases.