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Mortality and morbidity burden associated with smoking: evidence from a 1.6 million cohort in Hong Kong

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Abstract

Background

Existing evidence on the disease burden of smoking is often outdated and incomprehensive, particularly in Asia, which plays a pivotal role in the global tobacco control community. This study aimed to provide an updated and comprehensive estimate of the mortality and morbidity burden associated with smoking in Hong Kong.

Methods

This retrospective cohort study included adults with smoking status information recorded in the Hong Kong Hospital Authority database between 1 January 2008 and 31 December 2012. Subjects were classified into never-smokers, ex-smokers and current smokers. The primary outcome was all-cause mortality. Cox proportional hazards regression, adjusted with fine stratification weighting and key baseline characteristics, yielded hazard ratios (HRs) with 95% confidence intervals (CIs) for each outcome.

Results

Of the 1,571,065 individuals analyzed, there were 14.3% current smokers, 11.9% ex-smokers, and 73.8% never-smokers. After a median follow-up of 11.7 years, 61,198 current smokers, 45,918 ex-smokers and 220,947 never-smokers died. Significantly higher risks of all-cause mortality were observed among current smokers (HR [95% CI]: 1.53 [1.51-1.56]) and ex-smokers (1.33 [1.31-1.35]) than among never-smokers. Current and ex-smoking were positively associated with the incidences of 76 and 60 out of 115 morbidities, respectively. Strong associations were observed between smoking and increased risks of suicide (intentional self-harm), mental and behavioral disorders due to psychoactive substance use and alcohol use, particularly among current smokers. Notably, these risks were higher in females than in males for all three outcomes. Additionally, females demonstrated higher risks of all-cause mortality, pneumonia, chronic obstructive pulmonary disease, and asthma compared to males.

Conclusions

Smoking remains a substantial burden on the healthcare system in Hong Kong, which may still be underestimated due to Hong Kong's relatively less advanced stage in the tobacco epidemic compared to some Western countries, where the full hazards of smoking have already manifested more prominently.

Keywords: smoking; mortality; disease burden; Hong Kong; cohort study.

Word count: 297

What this study adds?

Most evidence on the disease burden of smoking comes from Western countries. However, evidence from Asia is equally critical given the region's central role in the global tobacco control community.

With a median follow-up of 11.7 years among 1.5 million individuals, the present study confirmed the substantial increased risks of all-cause mortality and a wide range of smoking-related morbidities in current smokers compared to never-smokers, using a territory-wide electronic health record database in Hong Kong. Risks associated with smoking were higher in females than in males for all-cause mortality and some morbidity outcomes, including pneumonia, chronic obstructive pulmonary disease, and asthma. Additionally, smoking showed strong associations with an increased risk of mental and behavioral disorders due to psychoactive substance and alcohol use, as well as intentional self-harm.

Hong Kong occupies a unique position in the global tobacco epidemic. It lies between the advanced stages observed in high-income countries, such as the United States, and Australia, and the earlier stages seen in low- and middle-income countries (LMICs) like Chinese mainland and India. Therefore, the full hazards of smoking may still be underestimated, similar to what was historically observed in high-income countries. Moreover, the findings from Hong Kong can forewarn the potential long-term challenges posed by smoking in Chinese mainland and other LMICs.

Word count: 211

Background

After decades of global effort in tobacco control, smoking remains a leading cause of disease burden globally(1), estimated to account for 7.7 million deaths and 200 million disability-adjusted life years (DALYs) in 2019(2). If current trends continue, smoking is projected to result in approximately 1 billion deaths during this century, primarily in low- and middle-income countries (LMICs), which is roughly ten times the toll it took in the 20th century(3).

While global-level evidence on the disease burden of smoking is well-documented(4, 5), region- or country-specific data are also crucial for accurate estimation of the hazards of smoking and evidence-based tobacco control policies. However, most relevant studies have been conducted in Western countries(6-10), and major evidence gaps exist in other populations with distinctive smoking and disease patterns. Recently, the prospective China Kadoorie Biobank (CKB) Cohort Study investigated the associations of smoking with disease incidence and mortality risks in 0.5 million adults in China(11), the world's largest tobacco consumer and producer. While this study addressed some key knowledge gaps(11), it covered regions at earlier stages of the smoking epidemic, with the "full effects" of smoking yet to be captured until 20-30 years later(12).

Compared to other parts of China (and Asia), with strong and substantial tobacco control policies and effort since the 1980s, Hong Kong moved to a later stage of smoking epidemic more rapidly than Western countries, with daily cigarette smoking in people aged 15 and over dropping from 23.3% to 9.1% between 1982 and 2023. However, substantial knowledge gaps remain, as other studies in Asia often faced further limitations, including the lack of morbidity outcome data(13-18), healthy volunteer bias(19, 20), small sample sizes(16, 21, 22), and the use of cross-sectional or short-term (<6 years) cohort study designs(22-24).

Comprehensive assessment of the disease burden associated with smoking in Hong Kong is not only important to raise awareness and inform policies locally, but also to shed light on future health impact of smoking in other populations moving towards more mature stages of smoking epidemic. Therefore, we conducted a retrospective cohort study to examine the impact of smoking on all-cause mortality and a wide range of morbidity outcomes, using a territory-wide electronic health record (EHR) database.

Methods

Data sources

This study extracted clinical data from the centralized EHR database maintained by the Hospital Authority (HA) of the Hong Kong Special Administrative Region (HKSAR), China. The HA is the statutory organization responsible for the administration of all public hospitals and the majority of public outpatient services in Hong Kong, encompassing 43 public hospitals, 74 General Outpatient Clinics (GOPCs), and 49 Specialist Outpatient Clinics (SOPCs). Since 1999, the HA's Clinical Management System (CMS) has been systematically collecting real-world, up-to-date clinical data generated during routine medical practice(25). This comprehensive database includes detailed information such as patient demographics, clinical diagnoses, prescriptions, laboratory test results, and other relevant medical records. Moreover, mortality data were retrieved from the Hong Kong Death Registry. All databases were linked through anonymized patient identifiers to ensure data integrity and confidentiality. The completeness and coding accuracy of these datasets have been well-documented in previous studies, establishing their reliability for epidemiological research(26, 27). These datasets have been widely employed in numerous high-quality epidemiological studies(28-31).

Study design and participants

This is a retrospective cohort study involving all adults with smoking status information as identified in the HA EHR databases during 1 January 2008 to 31 December 2012. Subjects were classified into three categories based on the earliest smoking record during the inclusion period: current smokers, ex-smokers, and never-smokers. Current smokers were identified based on any of the following criteria: (i) self-reported as a current smoker defined by a data field of the HA database, (ii) a diagnosis coded as International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) code 305.1(tobacco use disorder), (iii) use of smoking cessation medications, including nicotine replacement products, varenicline, bupropion, or nortriptyline, or (iv) utilization of smoking cessation services. Ex-smokers were defined by the following: (i) a diagnosis coded as ICD-9-CM code V15.82 (personal history of tobacco use), or (ii) self-reported as an ex-smoker. Never-smokers were identified based on self-reported status as a never-smoker. The index date for each subject was defined as the date when the corresponding smoking status record was documented. To ensure data accuracy, participants who self-reported as never-smokers but had any of the following records on or before the index date were excluded: (i) a diagnosis coded as ICD-9-CM code 305.1 or V15.82, (ii) self-reported as a current smoker or ex-smoker, (iii) use of smoking cessation medications, or (iv) utilization of smoking cessation services.

Baseline characteristics

Baseline characteristics included age, sex, the year of follow-up initiation, Charlson Comorbidity Index (CCI)(32), the presence of comorbidities (i.e. hypertension, diabetes mellitus, atrial fibrillation, amputation, dementia, respiratory diseases, connective tissue disorders, peptic ulcer disease, coronary heart disease, heart failure, stroke, liver disease, chronic kidney disease, and cancer), and medication use (i.e. oral antidiabetics, lipid-lowering drugs, and antihypertensives) within 90 days on or before the index date. The Charlson Comorbidity Index is a comprehensive measure used to quantify a patient's severity of comorbid conditions. It is calculated based on age, as well as the presence of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia or paraplegia, diabetes mellitus, renal disease, liver disease, peptic ulcer disease, rheumatologic disease, malignancy, human immunodeficiency virus/acquired immunodeficiency syndrome(33). These comorbidities were identified using diagnostic codes from ICD-9-CM and/or the International Classification of Primary Care, Second Edition (ICPC-2). Information on medication use was identified based on the British National Formulary (BNF) coding system. Detailed definitions of these variables are provided in **Additional file 1: S. Table 1-2**.

Outcomes

The primary outcome of this study was all-cause mortality. Secondary outcomes were defined as cause-specific incidences of 115 morbidities including a broader range of health conditions defined according to ICD-9-CM. Detailed definitions of the outcomes are provided in **Additional file 1: S. Table 3**. Eligible participants were followed from the index date until the earliest occurrence of the outcome event (when the outcome was a disease), death, or the end of the study period (31 December 2022). The end of follow up was defined separately for each outcome.

Statistical analysis

Baseline characteristics were summarized as mean and standard deviation (SD) for continuous variables and as count and proportion for categorical variables. To ensure balance among the three comparison groups, the fine stratification weighting approach was applied(34, 35). This approach involved assigning weights to each individual to create a pseudo-population, ensuring that the distribution of covariates was balanced across groups. Specifically, fine stratification weights were estimated using multinomial logistic regression, where smoking status served as the dependent variable. The model included all the baseline characteristics mentioned previously. After applying the weights, the standardized mean difference

(SMD) of each baseline variables across the three groups was calculated to assess balance. Variables with an SMD of less than 0.1 were considered to indicate sufficient balance between groups.

To evaluate the risk of outcomes for the smoking population compared to never-smokers, the incidence rate of each outcome with 95% confidence intervals (CIs) was calculated based on the Poisson distribution. During the analysis of each outcome, individuals with a history of the specific outcome at baseline were further excluded to reduce potential bias. Cox proportional hazards regression, adjusted with the fine stratification weighting, was applied to estimate the hazard ratios (HRs) with 95% CIs for each outcome. The population-attributed fraction (PAF) for all-cause mortality was estimated with the formula P (HR − 1) / HR, where P is the proportion of ex-smokers or current smokers among subjects who died during the follow-up period(11, 36). Subgroup analyses, stratified by sex (male and female), age (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥ 80 years), and Charlson Comorbidity Index (CCI; 0–2, and >2)(32), were conducted for all-cause mortality and diseases with compelling evidence suggesting the association with smoking, such as site-specific cancer, cardiovascular diseases, and diseases of the respiratory system, to explore potential heterogeneity of the association across subgroups(37). A CCI score of 0–2 reflects the absence of comorbidity or a low level of comorbidity, while a score greater than 2 indicates a high level of comorbidity(32). The P-value for heterogeneity was assessed by adding an interaction term between smoking status and the subgroup category into the Cox model. For the age-stratified subgroup analysis, a chi-square test for trend was performed instead of the heterogeneity test to investigate the trend in the differences of subgroup-specific relative risks(38). Additionally, several sensitivity analyses were performed to assess the robustness of the results: (i) competing risk model using the

Fine and Gray method was applied to account for death as a competing event(39); (ii) inverse probability of treatment weighting (IPTW) was used as an alternative to fine stratification weighting to control confounding bias(40); (iii) Cox model adjusted for all baseline characteristics was applied instead of adjusting all baseline characteristics and fine stratification weights; (iv) selected baseline characteristics (i.e., age, CCI, sex, oral antidiabetic drugs, lipid-lowering drugs, and antihypertensive agents) and fine stratification weighting were adjusted in Cox model; (v) patients with outcomes occurring within the first three years after the index date were excluded; (vi) patients with less than one year of follow-up were excluded; (vii) subjects were followed from the index date until the occurrence of the outcome of interest (when the outcome was a disease), death, a change in smoking status, or the end of the study period (31 December 2022), whichever occurred first; (viii) current smokers and ex-smokers were combined into a single group for comparison with never-smokers; and (ix) false discovery rate (FDR)-adjusted p-values were calculated using the Benjamini-Hochberg procedure to reduce probability of false positives arising from multiple comparisons(41, 42).

All significance tests were two-tailed and a significance level of less than 0.05 was considered statistically significant. The statistical analyses were carried out using R version 4.4.2 and Stata 16.1. To ensure the quality of the analysis, two investigators (BW and MHL) independently performed the statistical analyses.

Results

From 1 January 2008 to 31 December 2012, a total of 1,571,103 adults with smoking status information was identified, including 224,223 current smokers, 186,976 ex-smokers, and 1,159,904 never-smokers. Following the application of exclusion criteria, 38 individuals were excluded, including 6 subjects who were recorded as never-smokers but had a history of nicotine dependence on or before the index date, and 32 subjects who were recorded as never-smokers but had used smoking cessation medications or services on or before that date. The final study cohort consisted of 224,223 (14.3%) current smokers, 186,976 (11.9%) ex-smokers, and 1,159,866 (73.8%) never-smokers (**Figure 1**), of whom 81.6%, 88.4%, and 31.8%, respectively, were males. The distribution of baseline characteristics across the three before fine stratification weighting is presented in **Additional file 1: S. Table 4**. Compared to never-smokers and current smokers, ex-smokers were older (mean age, years: current smokers: 52.88; ex-smokers: 65.58; never-smokers: 56.22), and had higher CCI scores (mean CCI: current smokers: 1.67; ex-smokers: 3.30; never-smokers:1.85). After applying fine stratification weighting, the SMDs for all baseline characteristics were less than 0.1, indicating good balance across the three groups (**Table 1**).

Figure 2 illustrates the risk of all-cause mortality and all morbidity outcomes among never-smokers, ex-smokers, and current smokers. The incidence rates (IRs) per 1, 000 person-years for all-cause mortality, along with their 95% confidence intervals (95% CI), were 25.35 (25.15-25.55) for current smokers, 22.19 (21.98-22.39) for ex-smokers, and 16.69 (16.62-16.76) for never-smokers. Regarding relative risks, both current and ex-smokers exhibited significantly higher risks of mortality compared to never-smokers, with HRs of 1.53 (95% CI: 1.51-1.56) for current smokers and 1.33 (95% CI: 1.31-1.35) for ex-smokers. The PAF calculated for all-cause mortality was 6.49% in current smokers and 3.47% in ex-smokers. Similarly, smoking is significantly associated with an increased risk of a wide range of morbidities. Specifically, current smokers and ex-smokers demonstrated significantly higher risk of 76 and 60 out of 115 morbidities, respectively, compared to never-smokers. For example, the HRs (95% CIs) for current compared to never-smokers were 3.35 (3.16-3.55) for lung cancer, 2.45 (2.07-2.91) for oesophagus cancer, 1.40 (1.22-1.61) for stomach cancer, 1.14 (1.05-1.23) for colorectal cancer, 1.07 (1.04-1.10) for diabetes mellitus, 1.41 (1.23-1.62) for major cardiovascular diseases, 1.10 (1.00-1.21) for hypertension, 1.34 (1.15-1.55) for atherosclerotic cardiovascular disease, 1.29 (1.24-1.33) for stroke, 3.54 (3.34-3.76) for chronic obstructive pulmonary disease (COPD), 1.46 (1.41-1.52) for pneumonia, and 1.54 (1.36-1.74) for asthma. Meanwhile, although the HRs for ex-smokers were relatively lower compared to current smokers, significantly higher risks for the aforementioned outcomes were still observed, except the risk for stomach cancer. The significant HRs (95% CIs) for ex-smokers ranged from 1.07 (1.03-1.11) for diabetes mellitus to 2.11 (1.94-2.29) for COPD, reflecting the long-term adverse effects after smoking cessation. Notably, substantially higher risks associated with smoking were observed in both ex- and current smokers for mental and behavioral disorders due to psychoactive substance use (HRs [95% CIs]: current smokers: 24.27 [22.71-25.94]; ex-smokers: 4.75 [4.16-5.43]), mental and behavioral disorders due to use of alcohol (HRs [95% CI]: current smokers: 5.52 [4.92-6.20]; ex-smokers: 2.81 [2.28-3.47]), and suicide (intentional self-harm) (HRs [95% CI]: current smokers: 4.46 [4.03-4.93]; ex-smokers: 2.25 [1.83-

2.76]). Moreover, significant inverse associations were observed for several outcomes, such as breast cancer (HRs [95% CIs]: current smokers: 0.86 [0.75–0.98]; ex-smokers: 0.72 [0.59–0.88]), prostate cancer (current smokers: 0.71 [0.66–0.77]; ex-smokers: 0.87 [0.81–0.93]), and brain cancer (current smokers: 1.07 [0.64–1.80]; ex-smokers: 0.36 [0.22–0.57]).

Subgroup analysis results stratified by sex, CCI, and age, are illustrated in **Figure 3** and **Additional file 1: S. Figure 1**. The P values for heterogeneity test and trend test are provided in **Additional file 1: S. Table 5**. Mortality risks associated with smoking were significantly higher in individuals with CCI scores of 2 or less compared to those with CCI scores greater than 2. Specifically, the hazard ratios (HRs) and 95% confidence intervals (CIs) for current smokers were 2.11 (2.06-2.17) vs. 1.57 (1.54-1.59) for current smokers ($P_{heterogeneity} < 0.0001$), and for ex-smokers, the HRs (95% CIs) were 1.42 (1.35–1.48) versus 1.32 (1.30–1.34) ($P_{heterogeneity} < 0.0001$). Furthermore, smoking was significantly associated with an increased mortality risk across all age subgroups, while a significant decreasing trend in size of the effect was observed with increasing baseline age (P_{trend} < 0·0001 for both current smokers vs· never-smokers, and ex-smokers vs· never-smokers)· Among individuals aged <30 years, the HRs (95% CIs) for all-cause mortality were 2·30 (1·97–2·69) for current smokers and 1·56 (1·08–2·25) for ex-smokers, whereas among those aged ≥ 80 years, the HRs (95% CIs) decreased to 1·34 (1·29–1·38) and 1·21 (1·18–1·24), respectively· For morbidity outcomes, the HRs (95% CIs) for lung cancer was significantly higher in males compared to females· Among current smokers, the HRs (95% CIs) were 4·38 (4·14–4·64) in males and 2·76 (2·44–3·11) in females ($P_{heterogeneity} < 0.0001$). Similarly, for ex-smokers, the HRs (95% CIs) were 2.07 (1.94–2.21) in males and 1.92 (1.65–2.24) in females ($P_{heterogeneity} < 0.05$). Additionally, the HRs (95% CIs) for lung cancer was also significantly higher in individuals with CCI scores greater than 2 compared to those with CCI scores of 2 or less. For current smokers, the HRs (95% CIs) were 4.10 (3.79–4.44) in those with CCI scores greater than 2 and 2.97 (2.74–3.23) in those with CCI scores of 2 or less ($P_{heterogeneity} < 0.0001$). For ex-smokers, the HRs (95% CIs) were 2.40 (2.20–2.62) for subjects with CCI scores greater than 2 and 1.42 (1.22–1.65) for those with CCI scores of 2 or less ($P_{heterogeneity} < 0.0001$). Results for other morbidity outcomes were consistent across subgroups. Sensitivity analyses, as shown in **Additional file 1: S. Figures 2–10**, demonstrated similar results to the main analysis, indicating the robustness of the findings.

Discussion

This study offers comprehensive and up-to-date evidence on the disease burden associated with smoking in Hong Kong, using a territory-wide retrospective cohort. Both current and ex-smokers were associated with significantly higher risks of all-cause mortality and some smoking-related morbidities compared to never-smokers. Moreover, current smokers face higher risks than ex-smokers, underscoring the health benefits of smoking cessation. Specifically, 11.0% of male and 2.9% of female deaths were attributed to current smoking. Current smoking was positively associated with 76 out of 115 assessed morbidities. Specifically, smoking primarily contributed to disease burdens in infectious diseases (7.9%), the digestive system (7.9%), the respiratory systems (9.2%), neoplasm (13.2%), the circulatory systems (15.8%) and injuries (19.7%). Collectively, these categories accounted for 73.7% of the 76 smoking-associated morbidities.

For all-cause mortality, the observed hazard ratio (HR [95% CI]) of 1.54 (1.52, 1.57) for current smokers in this study was lower than the HRs typically reported in Western countries, where estimates are closer to 3(43-46). One possible explanation is that smokers in high-income countries, such as the United States and Australia, typically initiate smoking at younger ages, smoke more heavily, are further along in the tobacco epidemic(1, 47), and the full risks of smoking are more evident in regions at advanced epidemic stages where decades of high tobacco consumption have already taken their toll(20). Despite being a developed economy for decades, Hong Kong remains at a less advanced stage of the smoking pandemic compared to Western countries(48). Specifically, Hong Kong lags behind the United States by approximately 20 years, but is 20 years ahead of Chinese Mainland in terms of mean cigarette consumption and smoking-attributable mortality(48). For instance, in 2008, 4.7% of smokers in Hong Kong consumed more than 20 cigarettes per day, whereas 10.1% of smokers in the United States smoked more than 24 cigarettes daily(49, 50). By 2023, this proportion had declined to 2.1% in Hong Kong, while in the United States, it decreased to 8.1% by 2022(49, 50). Another possible explanation is that the study population consisted of patients, including never-smokers as the reference group. This may have led to underestimation of mortality risks compared to other studies in which the study population is drawn from the general population. Moreover, Hong Kong's public healthcare system, which is heavily subsidized by the Government, provides broad coverage and ensures that even individuals with low socioeconomics status have access to appropriate care(51), an advantage less common in many Western countries(52). However, our findings were comparable to the evidence from Asia(18). A prior pooled analysis of 21 cohorts from 7 Asian countries or regions reported an HR (95% CI) of 1.48 (1.38, 1.58) among ever smokers, with slightly higher risks observed in Singapore, Japan, Korea and Taiwan than Chinese mainland and India(18). We found a considerably stronger HR compared to the findings from the China

Kadoorie Biobank study, which reported an HR (95% CI) of 1.36 (1.32, 1.39) for ever-smokers(11). Nonetheless, the HR (95% CI) of 1.54 (1.52, 1.57) for all-cause mortality among current smokers in our study was slightly lower than the HR (95% CI) of 1.89 [1.81, 1.98] reported by Lam *et al* for the elderly aged ≥ 65 in Hong Kong a decade ago(20). A possible explanation for this difference is that the 1998 cohort in Lam *et al*'s study likely smoked more heavily than the 2008 cohort, as the average number of cigarettes consumed per day in Hong Kong has been decreasing over the past four decades(50), given the Government's comprehensive tobacco control strategies over the years. While Hong Kong is at a relatively less advanced stage of the tobacco epidemic compared to Western countries, its position approximately two decades ahead of Chinese mainland offers valuable insights for policymakers in Chinese mainland and other LMICs(48). The full hazards of smoking may remain underestimated due to the time lag between peak cigarette consumption and the emergence of smoking-related health outcomes.

This study confirmed significant associations between smoking and the incidence of some smoking-related morbidities, including lung cancer, COPD and major cardiovascular diseases, aligning with global evidence(53-60). For example, smoking was strongly linked to lung cancer incidence, as supported by prior research(54, 56, 57). Similarly, the association with COPD(53, 59, 60) and cardiovascular diseases(55, 58) corroborated previous findings. Regarding the sex-specific difference, higher smoking-associated risks of all-cause mortality, pneumonia, COPD, and asthma were observed in females compared to males, consistent with prior evidence(11, 61-63). Potential reasons could be that female smokers may be more susceptible to smoking's effects despite lower exposure levels(64, 65). Additionally, traditional gender roles in East Asian societies may expose women to household air pollution, increasing their risk of respiratory diseases(66, 67). Exposure to secondhand smoke at home is another potential explanation for the higher risks of all-cause mortality, pneumonia, COPD, and asthma observed among women in the present study(68). Furthermore, women are at greater risk of secondhand smoke infiltration due to the high prevalence of multiunit housing in Hong Kong, where secondhand smoke can diffuse from one unit to another(69). However, this study yielded higher relative risks of lung cancer in males, echoing earlier findings(48, 70). It is noteworthy that the tobacco epidemic among women lags several decades behind that of men, potentially underestimating the risks for women(47, 71). Continued monitoring of sex-specific differences in smoking-related risks is warranted.

The present study observed a declining trend in the association of smoking with all-cause mortality among current smokers across age subgroups, consistent with previous studies(72-74). This phenomenon may be explained by survivor effects, where individuals more susceptible to smoking' hazards are more likely to die earlier, leaving a healthier cohort of older smokers.

Large effect sizes were observed between smoking and the risks of mental and behavioral disorders due to psychoactive substance and alcohol use, and suicide (intentional self-harm), particularly among current smokers. Prior studies have reported similar findings(75-77). The results warrant cautious interpretations. In particular, the notably high hazard ratios for the outcome "mental and behavioral disorders due to psychoactive substance use" may suggest confounding by reverse causality, as previous studies have shown that individuals with substance use disorders are also more likely to smoke(76, 78, 79). Furthermore, in alignment with previous studies that indicated a stronger association between smoking and psychosocial or emotional problems in females than in males(80-82), the present study also found a significantly higher risk of these outcomes in females than in males. These outcomes include mental and behavioral disorders due to psychoactive substance and alcohol use, as well as suicide (intentional self-harm). Particularly, among current smokers in the present study, a higher proportion of women exhibited a history of mental and behavioral issues at baseline compared to men. This included overall mental and behavioral disorders (18.8% vs. 12.2%), mental and behavioral disorders due to psychoactive substance use (3.5% vs. 1.7%), and suicide (intentional self-harm) (2.2% vs. 0.6%). While these findings align with prior research(80-82), they should be interpreted with caution due to the potential for reverse causation. Nonetheless, this highlights the strong correlation between tobacco use and mental health issues in Hong Kong, particularly among women. A holistic approach to tobacco control and smoking cessation that incorporates mental health interventions could yield broader public health benefits.

Notably, the present study identified inverse associations between smoking and both breast cancer (BC) and prostate cancer (PCa), an observation that has been debatable in previous research(83-86). The dual carcinogenic and antiestrogenic effects of smoking may largely explain these controversial associations with BC(87, 88), and such associations can vary by pathological subtype and menopausal status. For instance, prior studies have reported that smoking does not affect triple-negative breast cancer incidence(89, 90). One study found that increased risk of premenopausal BC was only observed among women who had smoked for 30 years or more(91). But among postmenopausal women, reduced BC risk was identified only in those who were overweight or obese, with no association observed in those of normal weight(91). Similarly, a systematic and meta-analysis of observational studies showed that smoking increased the risk of premenopausal BC and estrogen receptor-positive (ER+) BC, but had no effect on postmenopausal BC and estrogen receptor-negative (ER-) BC(92). Regarding PCa, the present findings are consistent with the majority of previous studies, which has also demonstrated inverse associations of smoking with prostate cancer risk(93-96). Potential explanations include the lower likelihood of smokers undergoing regular health check-ups and prostate-specific antigen screening. Additionally, smokers face higher risk of mortality from other smoking-related diseases, such as lung cancer and cardiovascular diseases, which may preclude a diagnosis of PCa.

Limitations

This study has several limitations. First, the retrospective cohort design establishes associations rather than causality. Second, as in most previous cohort studies, smoking status was assessed only at baseline in the main analysis. However, the sensitivity analysis in which subjects were additionally censored when their smoking status changed during the follow-up period yielded results similar to the main analysis, supporting the robustness of the main findings of the current study. Third, the unavailability of potential confounders such as alcohol consumption, physical activity, dietary habits, and education attainment limited the ability to adjust for these variables. Fourth, detailed smoking patterns (e.g., type and number of tobacco products used, age of initiation/cessation, and reasons for cessation) were not captured, restricting the ability to estimate the full hazards of smoking and the benefits of quitting. The absence of these key smoking-related variables also constrained our capacity to directly verify the claim that Hong Kong occupies an intermediate position between Western countries and Chinese mainland in terms of the stages in the tobacco epidemic. Fifth, the study population, drawn from adults attending public healthcare facilities in Hong Kong, may not be fully representative of the general population in Hong Kong. For instance, it may disproportionately reflect certain age groups or demographic characteristics. Furthermore, only 6.8% of participants in the present cohort reported a history of overall mental and behavioral disorders, a figure notably lower than those reported in national or territory-wide surveys conducted in Hong Kong and other regions(97-100). For example, the prevalence of mental disorders was 13.3% in Hong Kong between 2010 and 2013 and 22.8% in the United States in 2021(98, 99). Given the well-established correlation between smoking and mental disorders, this discrepancy suggests that the present study may have underestimated the long-term effects of smoking on mental health. Sixth, the potential for misclassification of smoking status (primarily misclassifying smokers as never-smokers) cannot be ruled out, which may have led to underestimation of the risks of smoking-attributable mortality and morbidity.

Conclusions

This study showed significant relative risks associated with smoking in Hong Kong using a territory-wide electronic health record database of Chinese adults with a median follow-up duration of 11 years. Despite the city's low smoking prevalence, the risks observed may still be underestimated due to the time lag between the peak cigarette consumption and the manifestation of smoking-related health outcomes.

Policymakers should remain vigilant and continue monitoring the tobacco epidemic and its associated disease burdens. To further reduce smoking prevalence, policymakers should consider integrating mental health and substance use interventions into broader tobacco control strategies. Furthermore, given the higher risks of mortality and morbidities found in women, including all-cause mortality, respiratory diseases, and mental and behavioral disorders, gender specific smoking cessation interventions should be promulgated to reduce smoking prevalence in this group of smokers. Such a holistic approach could generate additional health gains beyond tobacco-related outcomes. Moreover, Hong Kong's experience as a region at an advanced stage of the tobacco epidemic provides critical insights for Chinese mainland and other LMICs, helping to inform policy and mitigate the global healthcare burden of smoking.

List of all abbreviations

DALYs	Disability-Adjusted Life Years
LMICs	Low- and Middle-Income Countries
CKB	China Kadoorie Biobank
EHR	Electronic Health Record
HA	Hospital Authority
HKSAR	Hong Kong Special Administrative Region
GOPCs	General Outpatient Clinics
SOPCs	Specialist Outpatient Clinics
CMS	Clinical Management System
ICD-9-CM	International Classification of Diseases, Ninth Edition, Clinical Modification
CCI	Charlson Comorbidity Index
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
ICPC-2	International Classification of Primary Care, Second Edition
BNF	British National Formulary
SD	Standard Deviation
SMD	Standardized Mean Difference
CIs	Confidence Intervals
HRs	Hazard Ratios
PAF	Population-Attributed Fraction
IPTW	Inverse Probability of Treatment Weighting
FDR	False Discovery Rate
IRs	Incidence Rates
COPD	Chronic Obstructive Pulmonary Disease
BC	Breast Cancer
PCa	Prostate Cancer
ER+	Estrogen Receptor-Positive

ER-   Estrogen Receptor-Negative

Declarations

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Consent for publication

Not applicable. All patient records were retrieved anonymously from the computerized administrative system of the Hospital Authority.

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Role of the funding source

The funders had no role in the study design, data collection, data analysis, interpretation, and report drafting. The corresponding authors had full access to all the data in the study and took final responsibility for the decision to submit for publication.

Data Availability

The electronic medical records used in this study are held by the Hospital Authority (HA) of Hong Kong and contain sensitive personal information. Due to privacy protection and confidentiality requirements, these data cannot be publicly shared. Access to the data is available upon request to the Hospital Authority of Hong Kong (https://www3.ha.org.hk/data/Provision/Index/).
The Hospital Authority (HA) has in place a mechanism for handling external data requests for academic research - the Central Panel on Administrative Assessment of External Data Requests will consider such requests on a case-by-case basis. Details of the application procedure are provided at https://www3.ha.org.hk/data/Provision/ApplicationProcedure. The timeframe for response to data requests varies depending on the complexity of the request.

Authors' Contributions

The authors' responsibilities were as follows: EYFW and BW conceived and designed the research; EYFW was responsible for data acquisition, administrative, technical, or material support and supervision; BW, MHL and EYFW analyzed and interpreted the data; BW, TC, MHL drafted the manuscript; all authors were responsible for the critical revision of the manuscript for important intellectual content.

All authors read and approved the final manuscript.

Competing Interests

ICKW received research grants from Amgen, Janssen, GSK, Novartis, Pfizer, Bayer and Bristol-Myers Squibb and Takeda, Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, The European Union's Seventh Framework Programme for research, technological development, Research Grants Council Hong Kong and Health and Medical Research Fund Hong Kong; consulting fees from IQVIA and World Health Organization; payment for expert testimony for Appeal Court in Hong Kong; serves on advisory committees for Member of Pharmacy and Poisons Board; is a member of the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization; is a member of the Advisory Panel on COVID-19 Vaccines of the Hong Kong Government; is the non-executive director of Jacobson Pharma Corp. Ltd. in Hong Kong; and is the founder and director of Therakind Limited (UK), Advance Data Analytics for Medical Science (ADAMS) Limited (HK) and OCUS Innovation Limited (HK, Ireland and UK). EYFW has received research grants from the Health Bureau, the Hong Kong Research Grants Council, Narcotics Division, Security Bureau, Social Welfare Department, Labour and Welfare Bureau of the Government of the Hong Kong SAR and National Natural Science Foundation of China; serves on member of Core Team for Expert Group on Drug Registration of Pharmacy and Poisons Board, and is the director of Advance Data Analytics for Medical Science (ADAMS) Limited (HK). These are outside the submitted work. The remaining authors have nothing to disclose.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the Institutional Review Boards of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB; Ref no.: UW 23-352). Individual consent was not required, as all patient records were retrieved anonymously from the computerized administrative system of the Hospital Authority.

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Additional file 1: S. Tables 1.-5. and S. Figures 1.-10.

S. Table 1.— included comorbidities and medications at baseline

S. Table 2.— included comorbidities for CCI calculation

S. Table 3.— morbidity definitions (ICD-9-CM & ICPC-2)

S. Table 4.— unweighted baseline characteristics

S. Table 5.— subgroup heterogeneity and trend tests

S. Figure 1.— disease risks in current and ex-smokers compared to never smokers by sex, CCI and age

S. Figure 2.— disease risks in current and ex-smokers compared to never smokers considering death as a competing event

S. Figure 3.— disease risks in current and ex-smokers compared to never smokers using IPTW

S. Figure 4.— disease risks in current and ex-smokers compared to never smokers adjusted with all baseline characteristics

S. Figure 5.— disease risks in current and ex-smokers compared to never smokers adjusted with age, sex, CCI, use of anti-diabetes drugs, lipid-lowering drugs, anti-hypertension drugs, and fine stratification weighting

S. Figure 6.— disease risks in current and ex-smokers compared to never smokers excluding subjects with corresponding outcome during the first three years of follow-up

S. Figure 7.— disease risks in current and ex-smokers compared to never smokers excluding subjects with less than one year follow-up

S. Figure 8.— disease risks in current and ex-smokers compared to never smokers censoring subjects with a record of smoking status changes

S. Figure 9.— disease risks in ever-smokers compared to never-smokers

S. Figure 10.— disease risks (FDR-adjusted P-values added) in current and ex-smokers compared to never smokers

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Figure 1. Study flow chart.

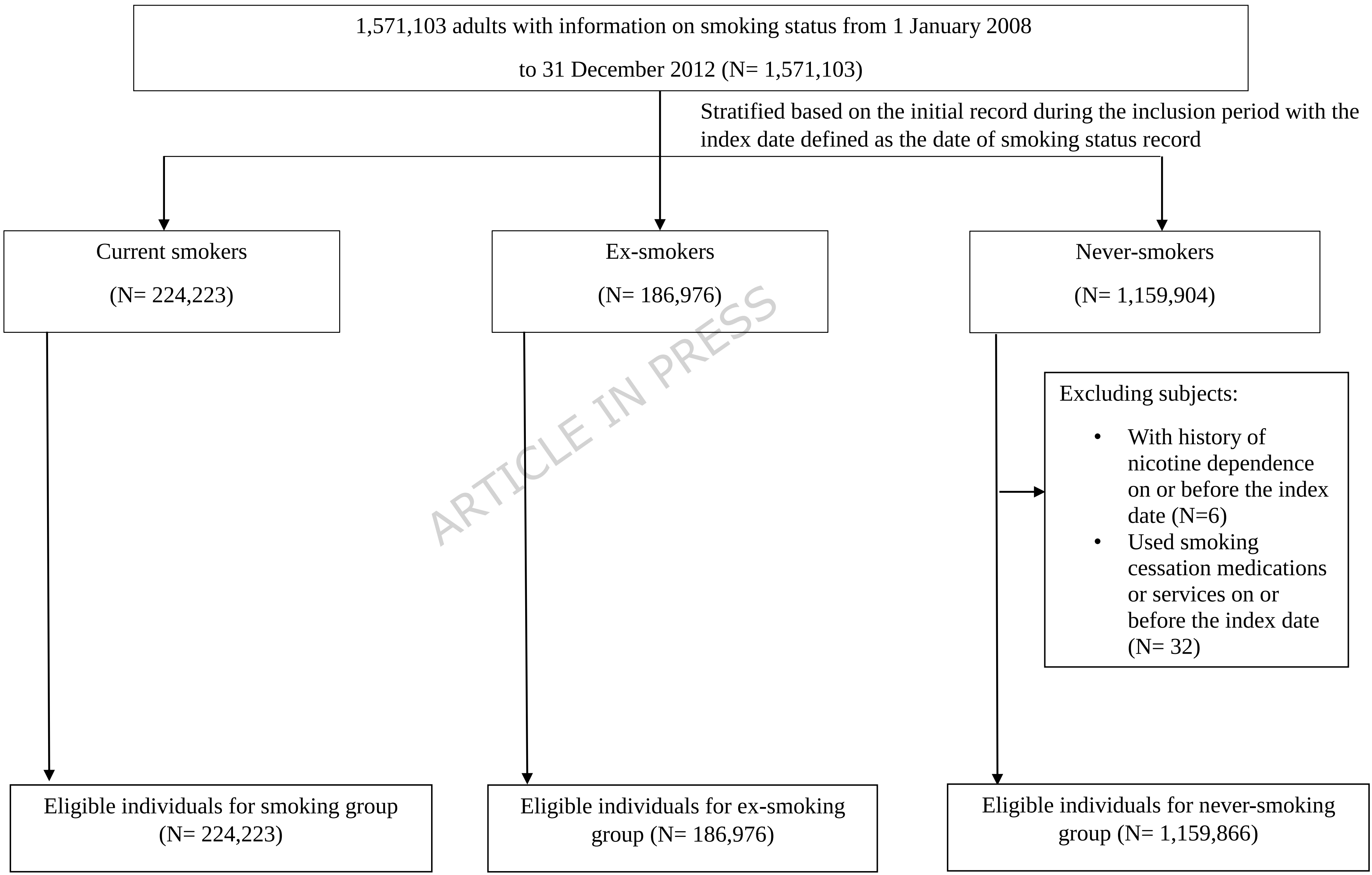


Table 1. Baseline characteristics after fine-stratification.

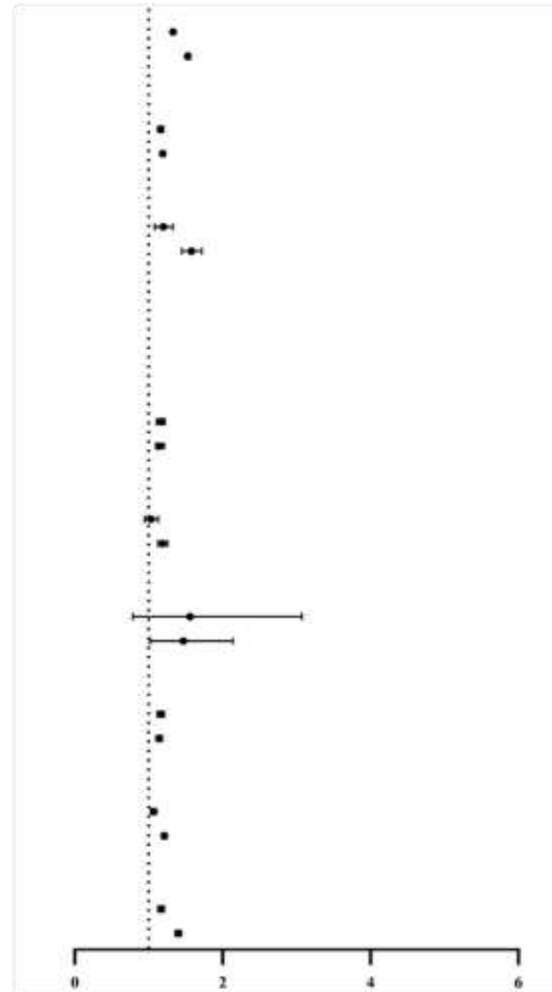
Characteristics	Never-smokers	Ex-smokers	Current smokers	SMD
Participants, n	1,159,866	186,976	224,223	
Age, years (mean (SD))	56.76 (16.89)	56.67 (17.12)	55.83 (17.11)	0.036
Sex, male (no. (%))	529,299 (45.6)	82,679.10 (44.2)	101,958 (45.5)	0.019
Year of inclusion (no. (%))				0.056
2008	247,403 (21.3)	43,073 (23.0)	46,900 (20.9)	
2009	221,659 (19.1)	36,972 (19.8)	41,640 (18.6)	
2010	204,118 (17.6)	33,425 (17.9)	38,820 (17.3)	
2011	276,977 (23.9)	41,333 (22.1)	55,903 (24.9)	
2012	209,709 (18.1)	32,172 (17.2)	40,960 (18.3)	
Charlson Comorbidity Index (mean (SD))	1.99 (2.03)	2.09 (2.07)	1.96 (2.13)	0.040
Comorbidities – no. (%)				
Hypertension	472,353 (40.7)	76,099 (40.7)	90,664 (40.4)	0.004
Diabetes mellitus	238,503 (20.6)	42,235 (22.6)	43,858 (19.6)	0.050
Atrial fibrillation	21,673 (1.9)	3,957 (2.1)	4,266 (1.9)	0.012
Amputation	1,820 (0.2)	301 (0.2)	326 (0.1)	0.003
Dementia	8,653 (0.7)	1,771 (0.9)	2,066 (0.9)	0.015
Respiratory disease	52,847 (4.6)	10,997 (5.9)	10,714 (4.8)	0.040
Connective tissue disorder	4,718 (0.4)	972 (0.5)	1,007 (0.4)	0.011
Peptic ulcer disease	30,209 (2.6)	5,053 (2.7)	5,501 (2.5)	0.010
Coronary heart diseases	59,292 (5.1)	10,266 (5.5)	11,124 (5.0)	0.016
Heart failure	21,608 (1.9)	4,183 (2.2)	4,081 (1.8)	0.020
Stroke	64,307 (5.5)	11,589 (6.2)	11,718 (5.2)	0.028

Liver disease	45,448 (3.9)	7,872 (4.2)	8,806 (3.9)	0.010
Chronic kidney disease	148,147 (12.8)	27,255 (14.6)	30,659 (13.7)	0.035
Cancer	56,470 (4.9)	10,434 (5.6)	11,101 (5.0)	0.021
Medication use within 90 days – no. (%)				
Anti-hypertensive drug	260,224 (22.4)	42,659 (22.8)	49,518 (22.1)	0.012
Oral Antidiabetic drugs	99,386 (8.6)	17,963 (9.6)	18,179 (8.1)	0.035
Lipid lowering drugs	52,949 (4.6)	9,184 (4.9)	9,493 (4.2)	0.022

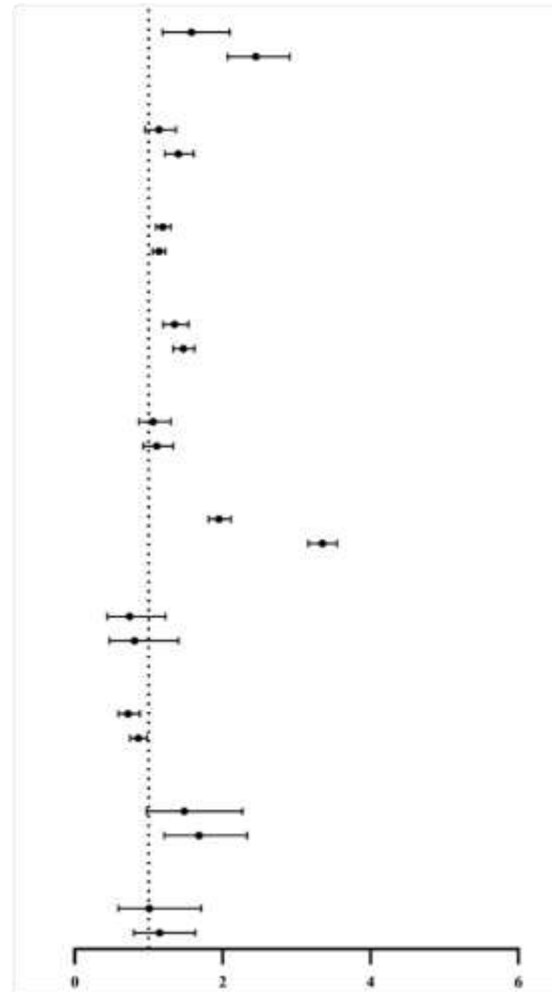
SMD: standardized mean difference; SD: standard deviation.

Figure 2. Risk of all-cause mortality and all outcomes in current smokers and ex-smokers compared to never-smokers.

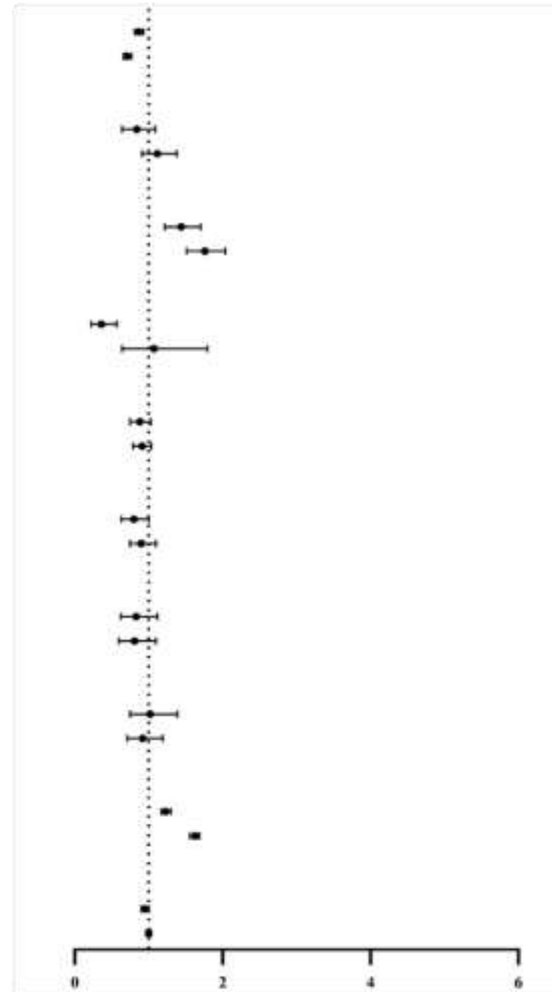
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
All-cause mortality				
Never-smokers	220,947	1,159,866	16.69 (16.62-16.76)	REF
Ex-smokers	45,918	186,976	22.19 (21.98-22.39)	1.33 (1.31-1.35)
Current smokers	61,198	224,223	25.35 (25.15-25.55)	1.53 (1.51-1.56)
Overall - Infectious Disease				
Never-smokers	83,937	1,117,714	6.72 (6.68-6.77)	REF
Ex-smokers	15,143	178,836	7.84 (7.72-7.97)	1.16 (1.13-1.20)
Current smokers	18,025	216,000	7.95 (7.83-8.06)	1.19 (1.16-1.22)
Tuberculosis				
Never-smokers	4,106	1,117,714	0.32 (0.31-0.33)	REF
Ex-smokers	765	178,836	0.38 (0.36-0.41)	1.20 (1.08-1.33)
Current smokers	1,192	216,000	0.51 (0.48-0.54)	1.58 (1.45-1.72)
Meningococcal infection				
Never-smokers	7	1,117,714	NA	NA
Ex-smokers	1	178,836	NA	NA
Current smokers	1	216,000	NA	NA
Septicemia				
Never-smokers	29,916	1,117,714	2.35 (2.32-2.38)	REF
Ex-smokers	5,406	178,836	2.74 (2.66-2.81)	1.17 (1.11-1.22)
Current smokers	6,244	216,000	2.69 (2.62-2.76)	1.15 (1.10-1.21)
Viral hepatitis				
Never-smokers	11,883	1,117,714	0.93 (0.92-0.95)	REF
Ex-smokers	1,919	178,836	0.97 (0.93-1.01)	1.03 (0.95-1.13)
Current smokers	2,619	216,000	1.13 (1.09-1.17)	1.19 (1.13-1.26)
HIV/AIDS				
Never-smokers	217	1,117,714	0.02 (0.01-0.02)	REF
Ex-smokers	53	178,836	0.03 (0.02-0.03)	1.56 (0.79-3.07)
Current smokers	59	216,000	0.03 (0.02-0.03)	1.47 (1.02-2.14)
All other infectious disease				
Never-smokers	57,993	1,117,714	4.61 (4.57-4.64)	REF
Ex-smokers	10,506	178,836	5.39 (5.29-5.49)	1.17 (1.12-1.21)
Current smokers	11,901	216,000	5.19 (5.10-5.29)	1.14 (1.11-1.18)
Overall – Neoplasms				
Never-smokers	83,927	1,104,507	6.85 (6.80-6.90)	REF
Ex-smokers	14,039	178,314	7.30 (7.18-7.42)	1.07 (1.03-1.10)
Current smokers	18,721	214,600	8.32 (8.20-8.44)	1.21 (1.18-1.24)
Cancer				
Never-smokers	53,724	1,104,507	4.31 (4.28-4.35)	REF
Ex-smokers	9,830	178,314	5.04 (4.94-5.14)	1.17 (1.13-1.21)
Current smokers	13,752	214,600	6.02 (5.92-6.12)	1.40 (1.36-1.44)



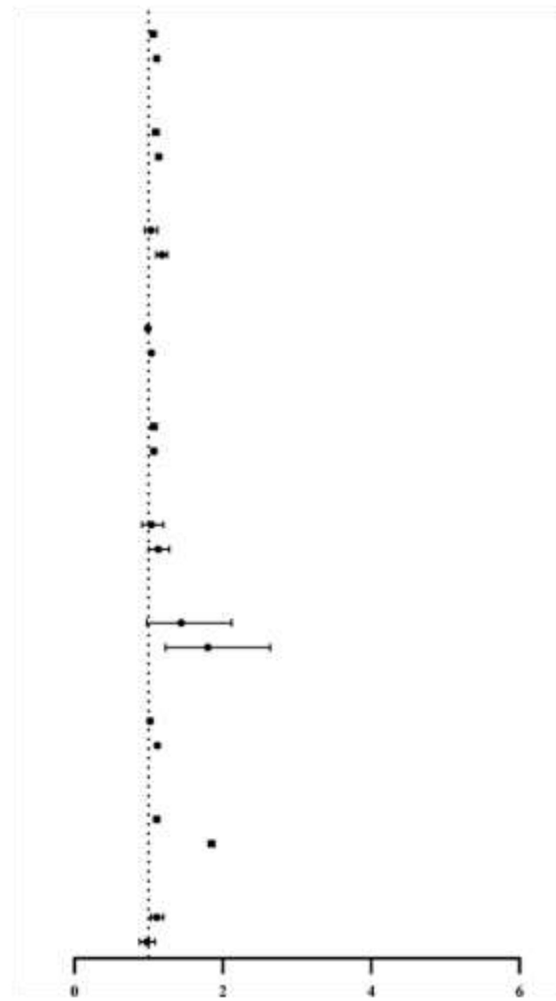
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Cancer of the oesophagus				
Never-smokers	549	1,104,507	0.04 (0.04-0.05)	REF
Ex-smokers	137	178,314	0.07 (0.06-0.08)	1.58 (1.19-2.10)
Current smokers	249	214,600	0.11 (0.09-0.12)	2.45 (2.07-2.91)
Stomach cancer				
Never-smokers	2,123	1,104,507	0.17 (0.16-0.17)	REF
Ex-smokers	379	178,314	0.19 (0.17-0.21)	1.14 (0.95-1.37)
Current smokers	545	214,600	0.23 (0.22-0.25)	1.40 (1.22-1.61)
Colorectal cancer				
Never-smokers	8,562	1,104,507	0.68 (0.66-0.69)	REF
Ex-smokers	1,601	178,314	0.81 (0.77-0.85)	1.19 (1.10-1.30)
Current smokers	1,790	214,600	0.77 (0.74-0.81)	1.14 (1.05-1.23)
Cancer of the liver (and intrahepatic bile ducts)				
Never-smokers	2,982	1,104,507	0.24 (0.23-0.24)	REF
Ex-smokers	633	178,314	0.32 (0.29-0.34)	1.35 (1.20-1.54)
Current smokers	802	214,600	0.34 (0.32-0.37)	1.47 (1.33-1.62)
Pancreatic cancer				
Never-smokers	1,481	1,104,507	0.12 (0.11-0.12)	REF
Ex-smokers	246	178,314	0.12 (0.11-0.14)	1.06 (0.87-1.30)
Current smokers	300	214,600	0.13 (0.12-0.14)	1.11 (0.93-1.33)
Lung cancer				
Never-smokers	6,222	1,104,507	0.49 (0.48-0.50)	REF
Ex-smokers	1,903	178,314	0.96 (0.92-1.00)	1.95 (1.81-2.11)
Current smokers	3,823	214,600	1.65 (1.59-1.70)	3.35 (3.16-3.55)
Skin cancer				
Never-smokers	307	1,104,507	0.02 (0.02-0.03)	REF
Ex-smokers	35	178,314	0.02 (0.01-0.02)	0.74 (0.44-1.23)
Current smokers	46	214,600	0.02 (0.01-0.03)	0.81 (0.47-1.40)
Breast cancer				
Never-smokers	5,975	596,680	0.87 (0.85-0.89)	REF
Ex-smokers	697	99,188	0.63 (0.58-0.67)	0.72 (0.59-0.88)
Current smokers	948	116,578	0.74 (0.70-0.79)	0.86 (0.75-0.98)
Cervical cancer				
Never-smokers	593	596,680	0.09 (0.08-0.09)	REF
Ex-smokers	142	99,188	0.13 (0.11-0.15)	1.48 (0.97-2.27)
Current smokers	185	116,578	0.14 (0.12-0.17)	1.68 (1.21-2.33)
Ovarian cancer				
Never-smokers	608	596,680	0.09 (0.08-0.10)	REF
Ex-smokers	98	99,188	0.09 (0.07-0.11)	1.01 (0.59-1.71)
Current smokers	129	116,578	0.10 (0.08-0.12)	1.15 (0.80-1.63)



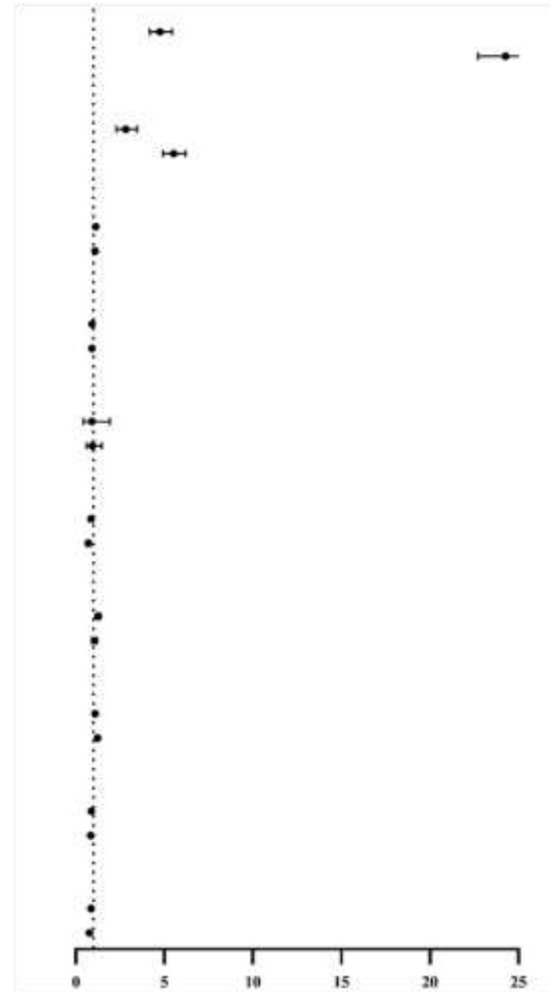
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Prostate cancer				
Never-smokers	4,643	507,827	0.81 (0.79-0.83)	REF
Ex-smokers	608	79,126	0.70 (0.65-0.76)	0.87 (0.81-0.93)
Current smokers	601	98,023	0.58 (0.53-0.62)	0.71 (0.66-0.77)
Cancer of the kidney (and renal pelvis)				
Never-smokers	969	1,104,507	0.08 (0.07-0.08)	REF
Ex-smokers	127	178,314	0.06 (0.05-0.08)	0.84 (0.64-1.09)
Current smokers	200	214,600	0.09 (0.07-0.10)	1.12 (0.91-1.38)
Bladder cancer				
Never-smokers	1,456	1,104,507	0.12 (0.11-0.12)	REF
Ex-smokers	330	178,314	0.17 (0.15-0.18)	1.44 (1.22-1.70)
Current smokers	471	214,600	0.20 (0.18-0.22)	1.76 (1.51-2.04)
Brain cancer (meninges, brain, and other CNS)				
Never-smokers	186	1,104,507	0.01 (0.01-0.02)	REF
Ex-smokers	10	178,314	0.01 (0.00-0.01)	0.36 (0.22-0.57)
Current smokers	36	214,600	0.02 (0.01-0.02)	1.07 (0.64-1.80)
Lymph cancer				
Never-smokers	3,281	1,104,507	0.26 (0.25-0.27)	REF
Ex-smokers	454	178,314	0.23 (0.21-0.25)	0.88 (0.75-1.03)
Current smokers	546	214,600	0.23 (0.22-0.26)	0.91 (0.79-1.04)
Non-Hodgkin's lymphoma				
Never-smokers	1,628	1,104,507	0.13 (0.12-0.13)	REF
Ex-smokers	203	178,314	0.10 (0.09-0.12)	0.80 (0.63-1.00)
Current smokers	270	214,600	0.12 (0.10-0.13)	0.90 (0.75-1.10)
Multiple myeloma				
Never-smokers	825	1,104,507	0.07 (0.06-0.07)	REF
Ex-smokers	107	178,314	0.05 (0.04-0.07)	0.83 (0.62-1.12)
Current smokers	123	214,600	0.05 (0.04-0.06)	0.81 (0.60-1.10)
Leukemia				
Never-smokers	855	1,104,507	0.07 (0.06-0.07)	REF
Ex-smokers	137	178,314	0.07 (0.06-0.08)	1.02 (0.75-1.39)
Current smokers	144	214,600	0.06 (0.05-0.07)	0.92 (0.71-1.19)
All other cancers				
Never-smokers	23,025	1,104,507	1.83 (1.80-1.85)	REF
Ex-smokers	4,434	178,314	2.24 (2.18-2.31)	1.23 (1.17-1.30)
Current smokers	6,861	214,600	2.96 (2.89-3.03)	1.63 (1.56-1.69)
In situ, benign, uncertain, and unknown neoplasms				
Never-smokers	43,303	1,104,507	3.49 (3.46-3.52)	REF
Ex-smokers	6,425	178,314	3.30 (3.22-3.38)	0.95 (0.90-1.00)
Current smokers	7,958	214,600	3.49 (3.41-3.56)	1.00 (0.96-1.04)



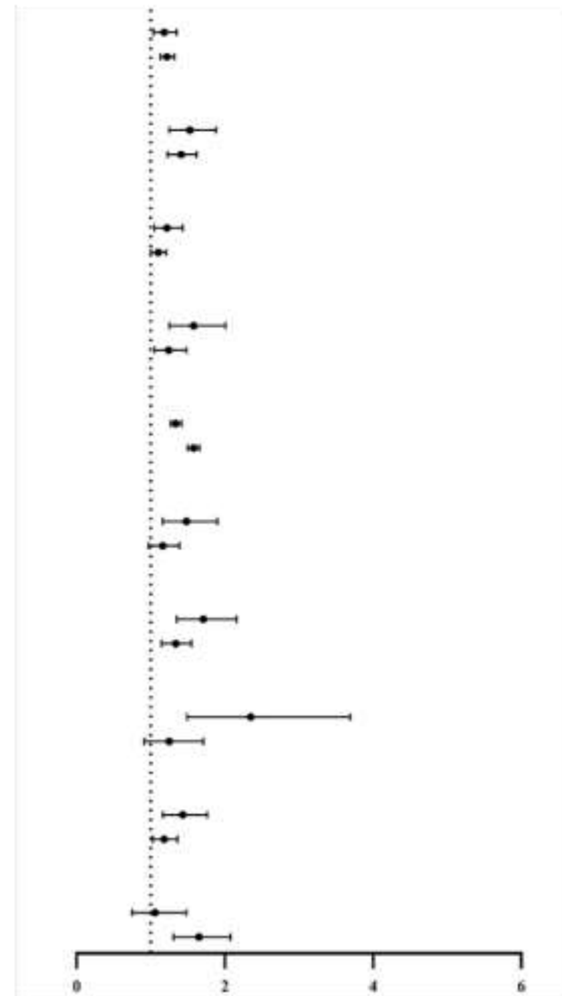
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Overall - Diseases of the blood and certain immune disorders				
Never-smokers	81,945	1,128,906	6.53 (6.49-6.58)	REF
Ex-smokers	13,585	181,375	6.95 (6.83-7.07)	1.06 (1.03-1.10)
Current smokers	16,733	218,461	7.30 (7.19-7.41)	1.11 (1.08-1.14)
Anemias				
Never-smokers	65,477	1,128,906	5.18 (5.14-5.22)	REF
Ex-smokers	11,192	181,375	5.68 (5.58-5.79)	1.10 (1.06-1.14)
Current smokers	13,607	218,461	5.89 (5.79-5.99)	1.14 (1.10-1.17)
All other diseases of the blood				
Never-smokers	10,030	1,128,906	0.78 (0.76-0.79)	REF
Ex-smokers	1,613	181,375	0.80 (0.76-0.84)	1.03 (0.95-1.12)
Current smokers	2,158	218,461	0.92 (0.88-0.96)	1.18 (1.10-1.26)
Overall - Endocrine, nutritional, & metabolic diseases				
Never-smokers	163,383	928,583	17.26 (17.17-17.34)	REF
Ex-smokers	25,205	148,898	17.06 (16.85-17.27)	0.99 (0.96-1.01)
Current smokers	32,232	183,803	18.15 (17.95-18.35)	1.04 (1.02-1.06)
Diabetes mellitus				
Never-smokers	56,073	928,583	5.48 (5.43-5.52)	REF
Ex-smokers	9,326	148,898	5.88 (5.76-6.00)	1.07 (1.03-1.11)
Current smokers	11,358	183,803	5.93 (5.82-6.04)	1.07 (1.04-1.10)
Nutritional deficiencies				
Never-smokers	3,844	928,583	0.36 (0.35-0.37)	REF
Ex-smokers	622	148,898	0.38 (0.35-0.41)	1.04 (0.91-1.20)
Current smokers	804	183,803	0.40 (0.38-0.43)	1.13 (1.00-1.28)
Malnutrition				
Never-smokers	228	928,583	0.02 (0.02-0.02)	REF
Ex-smokers	51	148,898	0.03 (0.02-0.04)	1.44 (0.98-2.12)
Current smokers	78	183,803	0.04 (0.03-0.05)	1.80 (1.23-2.64)
All other endocrine/nutritional/metabolic				
Never-smokers	118,404	928,583	11.61 (11.54-11.68)	REF
Ex-smokers	18,514	148,898	11.69 (11.52-11.86)	1.02 (0.99-1.05)
Current smokers	24,277	183,803	12.76 (12.60-12.92)	1.12 (1.10-1.14)
Overall - Mental and behavioral disorders				
Never-smokers	82,937	1,095,648	6.89 (6.84-6.94)	REF
Ex-smokers	14,026	172,703	7.67 (7.54-7.79)	1.11 (1.07-1.15)
Current smokers	24,160	190,050	12.96 (12.80-13.12)	1.85 (1.81-1.89)
Vascular and unspecified dementia				
Never-smokers	9,652	1,095,648	0.77 (0.76-0.79)	REF
Ex-smokers	1,642	172,703	0.86 (0.82-0.90)	1.11 (1.03-1.20)
Current smokers	1,543	190,050	0.76 (0.72-0.80)	0.98 (0.88-1.09)



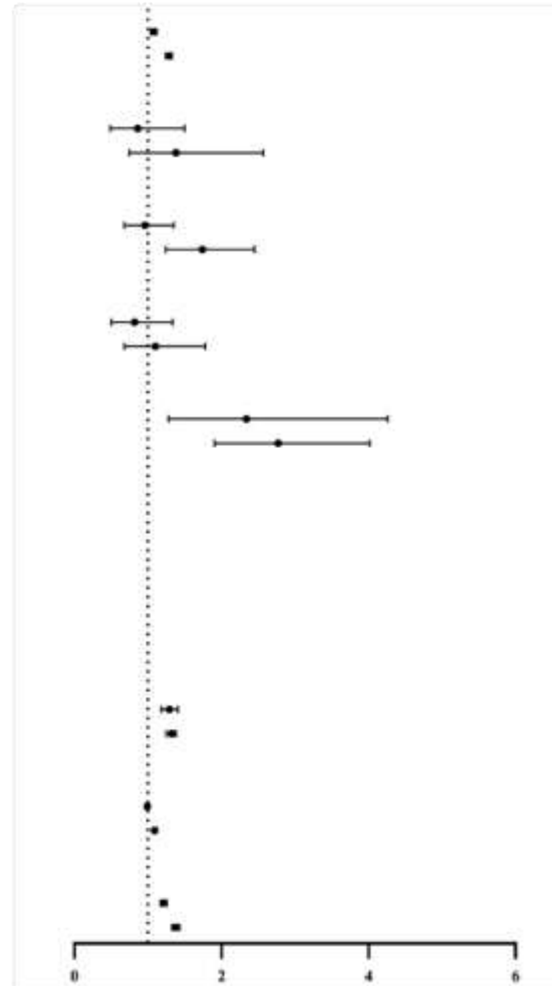
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Mental and behavioral disorders due to psychoactive substance use				
Never-smokers	1,729	1,095,648	0.14 (0.13-0.14)	REF
Ex-smokers	1,234	172,703	0.65 (0.61-0.68)	4.75 (4.16-5.43)
Current smokers	6,567	190,050	3.25 (3.17-3.33)	24.27 (22.71-25.94)
Mental and behavioral disorders due to use of alcohol				
Never-smokers	865	1,095,648	0.07 (0.06-0.07)	REF
Ex-smokers	370	172,703	0.19 (0.17-0.21)	2.81 (2.28-3.47)
Current smokers	775	190,050	0.38 (0.35-0.41)	5.52 (4.92-6.20)
All other mental and behavioral disorders				
Never-smokers	50,584	1,095,648	4.12 (4.08-4.15)	REF
Ex-smokers	8,523	172,703	4.55 (4.46-4.65)	1.11 (1.06-1.15)
Current smokers	8,977	190,050	4.50 (4.41-4.59)	1.09 (1.05-1.13)
Overall - Diseases of the nervous system				
Never-smokers	113,109	1,078,427	9.77 (9.71-9.82)	REF
Ex-smokers	16,399	175,541	8.90 (8.77-9.04)	0.91 (0.88-0.94)
Current smokers	19,299	211,296	8.94 (8.81-9.07)	0.91 (0.89-0.93)
Motor neuron disease				
Never-smokers	157	1,078,427	0.01 (0.01-0.01)	REF
Ex-smokers	23	175,541	0.01 (0.01-0.02)	0.91 (0.43-1.91)
Current smokers	27	211,296	0.01 (0.01-0.02)	0.93 (0.59-1.47)
Parkinson's disease				
Never-smokers	4,013	1,078,427	0.33 (0.32-0.34)	REF
Ex-smokers	542	175,541	0.28 (0.26-0.30)	0.85 (0.75-0.97)
Current smokers	513	211,296	0.23 (0.21-0.25)	0.69 (0.59-0.81)
Alzheimer's disease				
Never-smokers	4,963	1,078,427	0.40 (0.39-0.41)	REF
Ex-smokers	990	175,541	0.51 (0.48-0.54)	1.26 (1.14-1.40)
Current smokers	968	211,296	0.43 (0.40-0.45)	1.05 (0.91-1.21)
All other diseases of the nervous system				
Never-smokers	25,906	1,078,427	2.12 (2.09-2.15)	REF
Ex-smokers	4,449	175,541	2.31 (2.24-2.38)	1.09 (1.03-1.15)
Current smokers	5,833	211,296	2.59 (2.52-2.66)	1.22 (1.16-1.27)
Overall - Diseases of the eye				
Never-smokers	162,826	1,039,547	15.18 (15.11-15.25)	REF
Ex-smokers	23,305	170,522	13.44 (13.27-13.61)	0.88 (0.86-0.91)
Current smokers	26,259	207,460	12.70 (12.55-12.85)	0.83 (0.81-0.85)
Overall - Diseases of the ear				
Never-smokers	68,458	1,114,866	5.58 (5.54-5.63)	REF
Ex-smokers	9,312	180,866	4.80 (4.71-4.90)	0.86 (0.82-0.90)
Current smokers	9,861	218,002	4.32 (4.24-4.41)	0.77 (0.74-0.79)



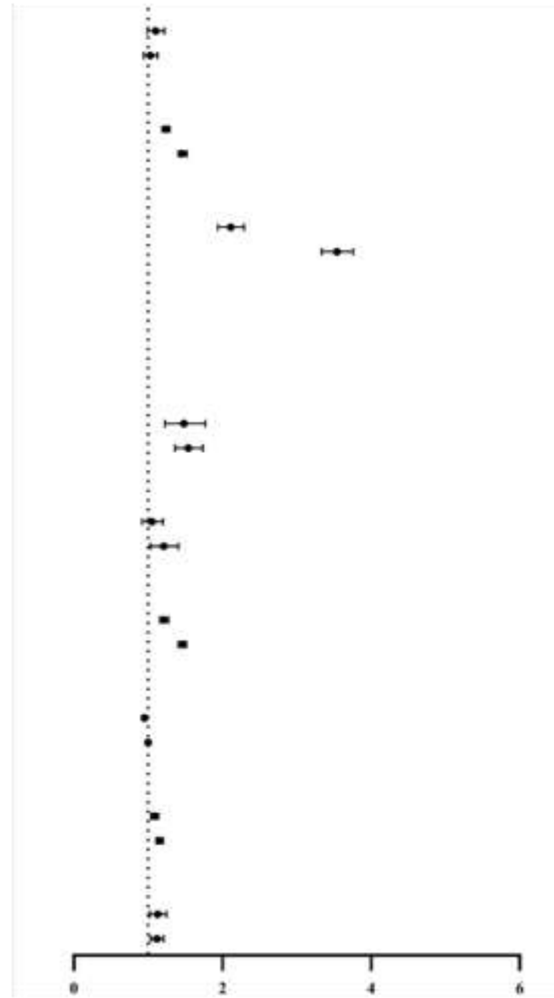
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Overall - Diseases of the circulatory system				
Never-smokers	4,774	554,825	0.75 (0.72-0.77)	REF
Ex-smokers	904	91,143	0.89 (0.83-0.95)	1.18 (1.04-1.35)
Current smokers	1,088	108,707	0.92 (0.87-0.98)	1.22 (1.13-1.32)
Major cardiovascular diseases				
Never-smokers	1,322	554,825	0.21 (0.19-0.22)	REF
Ex-smokers	324	91,143	0.32 (0.28-0.35)	1.53 (1.25-1.88)
Current smokers	343	108,707	0.29 (0.26-0.32)	1.41 (1.23-1.62)
Hypertension				
Never-smokers	3,423	554,825	0.53 (0.52-0.55)	REF
Ex-smokers	670	91,143	0.66 (0.61-0.71)	1.22 (1.05-1.43)
Current smokers	705	108,707	0.59 (0.55-0.64)	1.10 (1.00-1.21)
Ischemic heart diseases				
Never-smokers	786	554,825	0.12 (0.11-0.13)	REF
Ex-smokers	199	91,143	0.19 (0.17-0.22)	1.58 (1.25-2.01)
Current smokers	180	108,707	0.15 (0.13-0.18)	1.24 (1.05-1.48)
Acute Myocardial Infarction (Heart Attack)				
Never-smokers	17,698	554,825	2.77 (2.73-2.81)	REF
Ex-smokers	3,779	91,143	3.72 (3.60-3.84)	1.34 (1.27-1.42)
Current smokers	5,110	108,707	4.35 (4.24-4.47)	1.58 (1.50-1.66)
Other forms of chronic ischemic heart disease				
Never-smokers	678	554,825	0.11 (0.10-0.11)	REF
Ex-smokers	161	91,143	0.16 (0.13-0.18)	1.48 (1.16-1.90)
Current smokers	145	108,707	0.12 (0.10-0.14)	1.16 (0.97-1.39)
Atherosclerotic Cardiovascular Disease				
Never-smokers	893	554,825	0.14 (0.13-0.15)	REF
Ex-smokers	243	91,143	0.24 (0.21-0.27)	1.71 (1.35-2.16)
Current smokers	219	108,707	0.18 (0.16-0.21)	1.34 (1.15-1.55)
Heart failure				
Never-smokers	263	554,825	0.04 (0.04-0.05)	REF
Ex-smokers	99	91,143	0.10 (0.08-0.12)	2.35 (1.49-3.69)
Current smokers	60	108,707	0.05 (0.04-0.06)	1.25 (0.91-1.71)
Diseases of the heart				
Never-smokers	1,382	554,825	0.21 (0.20-0.23)	REF
Ex-smokers	316	91,143	0.31 (0.28-0.34)	1.43 (1.16-1.76)
Current smokers	301	108,707	0.25 (0.23-0.28)	1.18 (1.03-1.36)
Cerebrovascular disease (Stroke)				
Never-smokers	479	554,825	0.07 (0.07-0.08)	REF
Ex-smokers	81	91,143	0.08 (0.06-0.10)	1.06 (0.75-1.48)
Current smokers	144	108,707	0.12 (0.10-0.14)	1.65 (1.31-2.08)



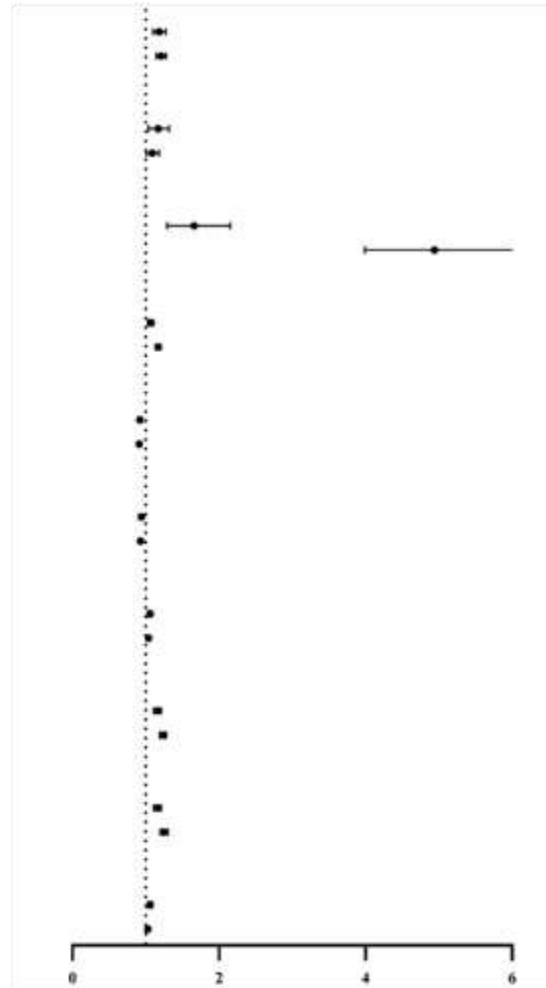
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)		Hazard ratio (95% CI)
Stroke					
Never-smokers	47,335	554,825	7.60 (7.54-7.67)	REF	
Ex-smokers	8,132	91,143	8.20 (8.03-8.38)	1.08 (1.04-1.12)	
Current smokers	11,151	108,707	9.77 (9.59-9.95)	1.29 (1.24-1.33)	
Intracranial haemorrhage					
Never-smokers	108	554,825	0.02 (0.01-0.02)	REF	
Ex-smokers	15	91,143	0.01 (0.01-0.02)	0.86 (0.49-1.50)	
Current smokers	27	108,707	0.02 (0.02-0.03)	1.38 (0.75-2.57)	
Cerebral infarction					
Never-smokers	170	554,825	0.03 (0.02-0.03)	REF	
Ex-smokers	26	91,143	0.03 (0.02-0.04)	0.96 (0.68-1.35)	
Current smokers	54	108,707	0.05 (0.03-0.06)	1.74 (1.24-2.45)	
Stroke, not specified as haemorrhage or infarction					
Never-smokers	85	554,825	0.01 (0.01-0.02)	REF	
Ex-smokers	11	91,143	0.01 (0.01-0.02)	0.82 (0.50-1.34)	
Current smokers	17	108,707	0.01 (0.01-0.02)	1.10 (0.68-1.78)	
Diseases of arteries, arterioles, and capillaries					
Never-smokers	109	554,825	0.02 (0.01-0.02)	REF	
Ex-smokers	41	91,143	0.04 (0.03-0.05)	2.34 (1.28-4.26)	
Current smokers	56	108,707	0.05 (0.04-0.06)	2.77 (1.91-4.02)	
Atherosclerosis (hardening of the arteries)					
Never-smokers	20	554,825	NA	NA	
Ex-smokers	5	91,143	NA	NA	
Current smokers	5	108,707	NA	NA	
Aortic Aneurysm					
Never-smokers	7	554,825	NA	NA	
Ex-smokers	6	91,143	NA	NA	
Current smokers	16	108,707	NA	NA	
All other diseases of the circulatory system					
Never-smokers	10,591	554,825	1.67 (1.64-1.70)	REF	
Ex-smokers	2,199	91,143	2.19 (2.10-2.28)	1.29 (1.18-1.41)	
Current smokers	2,652	108,707	2.27 (2.19-2.36)	1.32 (1.25-1.38)	
Overall - Diseases of the respiratory system					
Never-smokers	148,240	846,978	17.28 (17.19-17.37)	REF	
Ex-smokers	24,137	141,743	17.14 (16.92-17.35)	0.99 (0.96-1.01)	
Current smokers	31,963	173,153	19.28 (19.07-19.49)	1.09 (1.07-1.12)	
Influenza and pneumonia					
Never-smokers	39,734	846,978	4.16 (4.11-4.20)	REF	
Ex-smokers	7,825	141,743	5.04 (4.93-5.15)	1.21 (1.17-1.26)	
Current smokers	10,553	173,153	5.73 (5.62-5.84)	1.38 (1.33-1.43)	



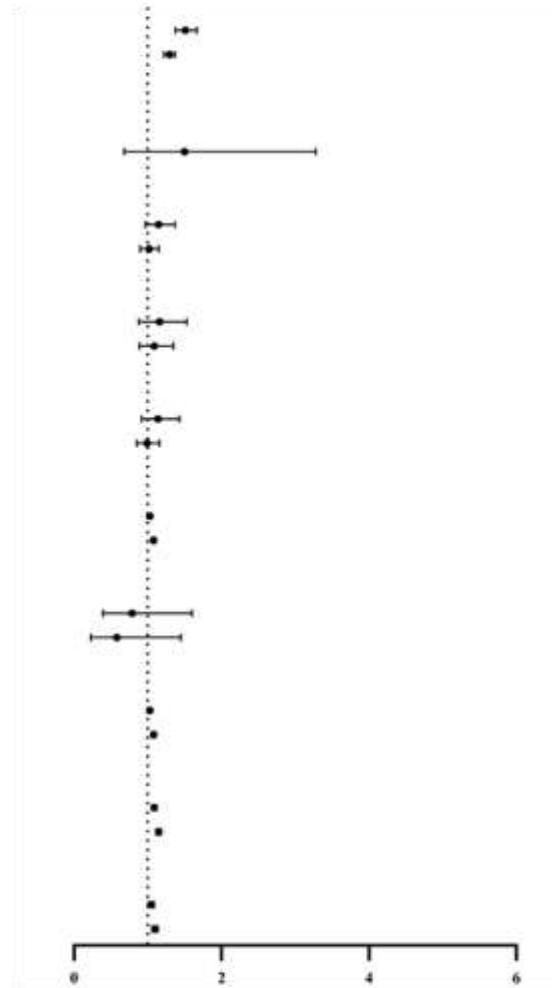
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Influenza				
Never-smokers	7,781	846,978	0.81 (0.79-0.82)	REF
Ex-smokers	1,389	141,743	0.88 (0.84-0.93)	1.10 (0.99-1.22)
Current smokers	1,565	173,153	0.84 (0.80-0.88)	1.03 (0.94-1.13)
Pneumonia				
Never-smokers	34,797	846,978	3.63 (3.59-3.66)	REF
Ex-smokers	7,012	141,743	4.50 (4.39-4.60)	1.24 (1.19-1.29)
Current smokers	9,736	173,153	5.27 (5.16-5.37)	1.46 (1.41-1.52)
Chronic obstructive pulmonary disease (COPD)				
Never-smokers	6,031	846,978	0.62 (0.61-0.64)	REF
Ex-smokers	2,064	141,743	1.32 (1.26-1.37)	2.11 (1.94-2.29)
Current smokers	4,108	173,153	2.22 (2.15-2.28)	3.54 (3.34-3.76)
Emphysema				
Never-smokers	9	846,978	NA	NA
Ex-smokers	15	141,743	NA	NA
Current smokers	30	173,153	NA	NA
Asthma				
Never-smokers	2,822	846,978	0.29 (0.28-0.30)	REF
Ex-smokers	680	141,743	0.43 (0.40-0.47)	1.48 (1.23-1.77)
Current smokers	848	173,153	0.45 (0.42-0.49)	1.54 (1.36-1.74)
Pneumonitis due to solids and liquids (food and vomit)				
Never-smokers	2,763	846,978	0.29 (0.27-0.30)	REF
Ex-smokers	471	141,743	0.30 (0.27-0.33)	1.05 (0.92-1.20)
Current smokers	642	173,153	0.34 (0.32-0.37)	1.21 (1.03-1.41)
All other diseases of the respiratory system				
Never-smokers	35,976	846,978	3.76 (3.72-3.80)	REF
Ex-smokers	7,100	141,743	4.57 (4.46-4.67)	1.21 (1.16-1.27)
Current smokers	9,985	173,153	5.42 (5.31-5.53)	1.46 (1.41-1.51)
Overall - Diseases of the digestive system				
Never-smokers	179,441	941,488	18.80 (18.71-18.89)	REF
Ex-smokers	27,451	153,862	17.94 (17.73-18.16)	0.95 (0.93-0.98)
Current smokers	34,289	187,226	18.98 (18.78-19.18)	1.00 (0.98-1.02)
Other diseases of intestines (vascular, obstruction, diverticular disease) and peritoneum				
Never-smokers	38,038	941,488	3.57 (3.54-3.61)	REF
Ex-smokers	6,527	153,862	3.87 (3.78-3.96)	1.09 (1.04-1.14)
Current smokers	8,144	187,226	4.09 (4.00-4.17)	1.15 (1.11-1.20)
Diverticular disease of intestine				
Never-smokers	7,859	941,488	0.73 (0.71-0.75)	REF
Ex-smokers	1,403	153,862	0.82 (0.78-0.87)	1.13 (1.02-1.25)
Current smokers	1,627	187,226	0.81 (0.77-0.85)	1.12 (1.03-1.21)



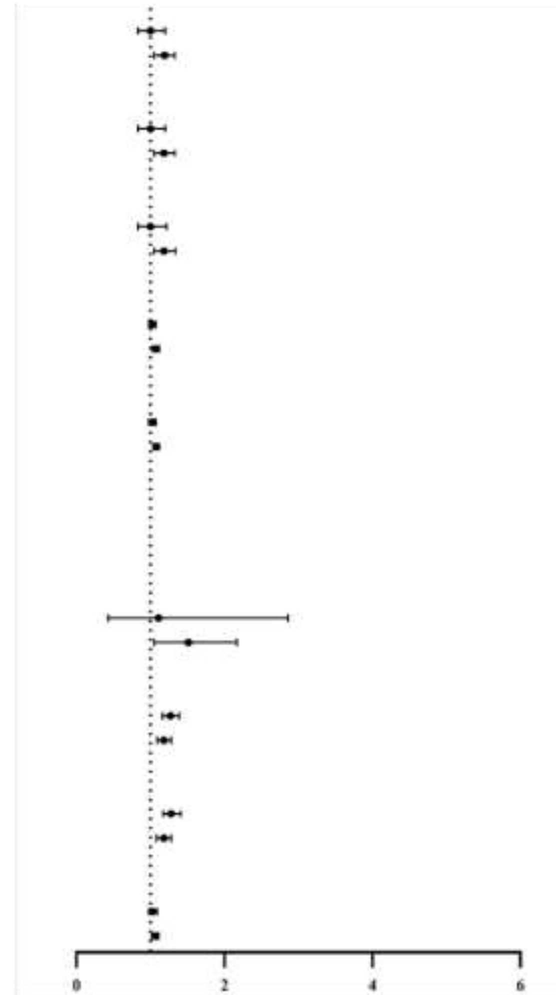
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Diseases of the liver				
Never-smokers	16,205	941,488	1.51 (1.48-1.53)	REF
Ex-smokers	3,026	153,862	1.78 (1.71-1.84)	1.18 (1.10-1.27)
Current smokers	3,641	187,226	1.81 (1.75-1.87)	1.21 (1.15-1.28)
Chronic liver disease and cirrhosis				
Never-smokers	7,467	941,488	0.69 (0.68-0.71)	REF
Ex-smokers	1,380	153,862	0.81 (0.76-0.85)	1.17 (1.04-1.32)
Current smokers	1,495	187,226	0.74 (0.70-0.78)	1.09 (1.01-1.18)
Alcoholic liver disease				
Never-smokers	224	941,488	0.02 (0.02-0.02)	REF
Ex-smokers	59	153,862	0.03 (0.03-0.04)	1.66 (1.29-2.15)
Current smokers	209	187,226	0.10 (0.09-0.12)	4.94 (3.99-6.12)
All other diseases of the digestive system				
Never-smokers	69,965	941,488	6.67 (6.62-6.72)	REF
Ex-smokers	11,809	153,862	7.11 (6.98-7.24)	1.07 (1.03-1.10)
Current smokers	15,176	187,226	7.74 (7.62-7.86)	1.17 (1.14-1.20)
Overall - Diseases of the skin				
Never-smokers	173,102	982,128	17.42 (17.34-17.51)	REF
Ex-smokers	25,957	162,773	16.06 (15.87-16.26)	0.92 (0.90-0.94)
Current smokers	30,610	196,065	16.10 (15.92-16.28)	0.91 (0.89-0.93)
Overall - Diseases of the musculoskeletal system				
Never-smokers	169,265	942,309	17.88 (17.79-17.96)	REF
Ex-smokers	26,022	157,290	16.80 (16.60-17.01)	0.94 (0.91-0.96)
Current smokers	30,564	189,088	16.79 (16.60-16.97)	0.93 (0.91-0.94)
Overall - Diseases of the genitourinary system				
Never-smokers	137,582	1,024,084	12.55 (12.48-12.61)	REF
Ex-smokers	22,723	165,332	13.28 (13.11-13.45)	1.06 (1.03-1.08)
Current smokers	26,643	200,842	13.10 (12.94-13.25)	1.04 (1.02-1.06)
Nephritis and Nephrosis (kidney disease)				
Never-smokers	39,256	1,024,084	3.38 (3.35-3.41)	REF
Ex-smokers	7,104	165,332	3.92 (3.83-4.01)	1.16 (1.11-1.21)
Current smokers	8,877	200,842	4.14 (4.06-4.23)	1.24 (1.19-1.28)
Renal failure				
Never-smokers	30,784	1,024,084	2.63 (2.60-2.66)	REF
Ex-smokers	5,551	165,332	3.04 (2.96-3.12)	1.16 (1.11-1.21)
Current smokers	6,972	200,842	3.23 (3.16-3.31)	1.25 (1.20-1.30)
All other diseases of the genitourinary system				
Never-smokers	105,159	1,024,084	9.38 (9.32-9.43)	REF
Ex-smokers	17,341	165,332	9.91 (9.76-10.06)	1.06 (1.03-1.09)
Current smokers	19,961	200,842	9.61 (9.48-9.75)	1.03 (1.00-1.05)



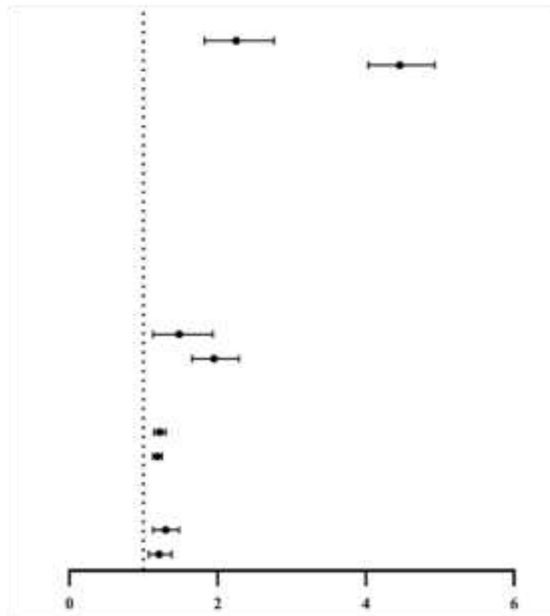
Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Overall - Pregnancy and childbirth				
Never-smokers	10,438	1,131,646	0.81 (0.80-0.83)	REF
Ex-smokers	2,429	179,356	1.24 (1.19-1.29)	1.51 (1.37-1.67)
Current smokers	2,465	215,086	1.08 (1.04-1.12)	1.30 (1.22-1.37)
Overall - Certain conditions of the perinatal period				
Never-smokers	103	1,159,685	0.01 (0.01-0.01)	REF
Ex-smokers	9	186,871	NA	NA
Current smokers	28	224,155	0.01 (0.01-0.02)	1.50 (0.68-3.28)
Overall - Congenital malformations				
Never-smokers	3,481	1,155,421	0.26 (0.26-0.27)	REF
Ex-smokers	628	186,348	0.30 (0.28-0.33)	1.15 (0.97-1.37)
Current smokers	650	223,451	0.27 (0.25-0.29)	1.02 (0.90-1.15)
Congenital malformations of the circulatory system				
Never-smokers	1,131	1,155,421	0.09 (0.08-0.09)	REF
Ex-smokers	206	186,348	0.10 (0.09-0.11)	1.16 (0.88-1.53)
Current smokers	228	223,451	0.09 (0.08-0.11)	1.09 (0.89-1.35)
All other congenital malformations				
Never-smokers	2,379	1,155,421	0.18 (0.17-0.19)	REF
Ex-smokers	426	186,348	0.21 (0.19-0.23)	1.14 (0.92-1.43)
Current smokers	434	223,451	0.18 (0.16-0.20)	0.99 (0.85-1.16)
Overall - Symptoms and signs				
Never-smokers	191,173	1,027,090	17.58 (17.50-17.66)	REF
Ex-smokers	30,021	162,215	18.03 (17.83-18.24)	1.03 (1.00-1.05)
Current smokers	36,915	196,003	18.86 (18.67-19.05)	1.08 (1.06-1.10)
Senility				
Never-smokers	124	1,027,090	0.01 (0.01-0.01)	REF
Ex-smokers	15	162,215	0.01 (0.00-0.01)	0.79 (0.39-1.60)
Current smokers	13	196,003	0.01 (0.00-0.01)	0.58 (0.23-1.45)
All other symptoms and signs				
Never-smokers	191,163	1,027,090	17.58 (17.50-17.66)	REF
Ex-smokers	30,020	162,215	18.03 (17.83-18.24)	1.03 (1.00-1.05)
Current smokers	36,914	196,003	18.86 (18.67-19.05)	1.08 (1.06-1.10)
Overall: External Causes (Injury)				
Never-smokers	99,895	1,089,232	8.31 (8.26-8.36)	REF
Ex-smokers	16,738	173,482	9.04 (8.90-9.17)	1.09 (1.06-1.12)
Current smokers	20,383	205,977	9.56 (9.43-9.69)	1.15 (1.12-1.18)
Unintentional Injury (accidents)				
Never-smokers	66,122	1,089,232	5.42 (5.38-5.46)	REF
Ex-smokers	10,699	173,482	5.67 (5.56-5.78)	1.05 (1.01-1.09)
Current smokers	12,864	205,977	5.92 (5.81-6.02)	1.10 (1.06-1.13)



Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Transport accidents				
Never-smokers	2,685	1,089,232	0.21 (0.21-0.22)	REF
Ex-smokers	415	173,482	0.21 (0.19-0.24)	1.00 (0.83-1.20)
Current smokers	567	205,977	0.25 (0.23-0.28)	1.19 (1.05-1.33)
Land transport accidents				
Never-smokers	2,678	1,089,232	0.21 (0.21-0.22)	REF
Ex-smokers	414	173,482	0.21 (0.19-0.24)	1.00 (0.83-1.20)
Current smokers	566	205,977	0.25 (0.23-0.28)	1.18 (1.05-1.33)
Motor vehicle accidents				
Never-smokers	2,457	1,089,232	0.20 (0.19-0.20)	REF
Ex-smokers	381	173,482	0.20 (0.18-0.22)	1.00 (0.83-1.22)
Current smokers	520	205,977	0.23 (0.21-0.25)	1.18 (1.05-1.34)
Falls, including fracture cause unspecified				
Never-smokers	52,871	1,089,232	4.30 (4.27-4.34)	REF
Ex-smokers	8,377	173,482	4.41 (4.32-4.51)	1.03 (0.98-1.07)
Current smokers	10,056	205,977	4.59 (4.50-4.68)	1.07 (1.03-1.12)
Falls, excluding cause unspecified				
Never-smokers	49,934	1,089,232	4.06 (4.02-4.10)	REF
Ex-smokers	7,910	173,482	4.16 (4.07-4.25)	1.03 (0.98-1.07)
Current smokers	9,527	205,977	4.35 (4.26-4.43)	1.08 (1.04-1.12)
Accidental drowning				
Never-smokers	22	1,089,232	NA	NA
Ex-smokers	1	173,482	NA	NA
Current smokers	6	205,977	NA	NA
Exposure to smoke, fire and flames				
Never-smokers	136	1,089,232	0.01 (0.01-0.01)	REF
Ex-smokers	23	173,482	0.01 (0.01-0.02)	1.11 (0.43-2.86)
Current smokers	37	205,977	0.02 (0.01-0.02)	1.51 (1.05-2.17)
Accidental poisoning				
Never-smokers	8,322	1,089,232	0.67 (0.65-0.68)	REF
Ex-smokers	1,638	173,482	0.85 (0.81-0.89)	1.27 (1.16-1.39)
Current smokers	1,751	205,977	0.79 (0.75-0.82)	1.18 (1.09-1.28)
Accidental poisoning by drugs				
Never-smokers	7,945	1,089,232	0.64 (0.62-0.65)	REF
Ex-smokers	1,575	173,482	0.82 (0.78-0.86)	1.28 (1.17-1.41)
Current smokers	1,665	205,977	0.75 (0.71-0.78)	1.18 (1.08-1.28)
All other unintentional injury				
Never-smokers	34,013	1,089,232	2.75 (2.72-2.78)	REF
Ex-smokers	5,418	173,482	2.84 (2.76-2.91)	1.03 (0.98-1.09)
Current smokers	6,424	205,977	2.92 (2.85-2.99)	1.07 (1.02-1.11)



Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
Suicide (Intentional self-harm)				
Never-smokers	1,594	1,089,232	0.13 (0.12-0.13)	REF
Ex-smokers	554	173,482	0.29 (0.26-0.31)	2.25 (1.83-2.76)
Current smokers	1,267	205,977	0.57 (0.54-0.60)	4.46 (4.03-4.93)
Suicide by exposure to gases & vapours (incl CO)				
Never-smokers	44	1,089,232	NA	NA
Ex-smokers	3	173,482	NA	NA
Current smokers	18	205,977	NA	NA
Suicide by hanging, stangulation, suffocation				
Never-smokers	24	1,089,232	NA	NA
Ex-smokers	1	173,482	NA	NA
Current smokers	6	205,977	NA	NA
Homicide (assault)				
Never-smokers	959	1,089,232	0.08 (0.07-0.08)	REF
Ex-smokers	219	173,482	0.11 (0.10-0.13)	1.48 (1.13-1.94)
Current smokers	334	205,977	0.15 (0.13-0.17)	1.95 (1.66-2.29)
Complications of medical and surgical care				
Never-smokers	21,874	1,089,232	1.76 (1.74-1.78)	REF
Ex-smokers	4,121	173,482	2.15 (2.08-2.22)	1.22 (1.15-1.30)
Current smokers	4,625	205,977	2.09 (2.03-2.15)	1.19 (1.13-1.25)
All other injury				
Never-smokers	3,692	1,089,232	0.30 (0.29-0.30)	REF
Ex-smokers	745	173,482	0.39 (0.36-0.41)	1.30 (1.13-1.48)
Current smokers	814	205,977	0.37 (0.34-0.39)	1.21 (1.07-1.38)



Incidence rate (cases/1000 person-years) with 95% confidence interval based on Poisson distribution. Hazard ratio with 95% confidence interval was obtained by Cox regression adjusted with fine stratification weighting. CI = confidence interval; REF = reference level; NA = not applicable due to insufficient number of cases; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; CNS = central nervous system; incl CO = including carbon monoxide.

Figure 3. Risk of all-cause mortality in current smokers and ex-smokers compared to never-smokers by sex, Charlson Comorbidity Index and age.

Outcomes	Events	Subjects	Incidence rate(95% CI) (per 1000 person years)	Hazard ratio (95% CI)
All-cause mortality				
Sex				
Male				
Never-smokers	82,409	369,083	19.89 (19.76-20.03)	REF
Ex-smokers	43,004	165,286	23.86 (23.64-24.09)	1.20 (1.19-1.22)
Current smokers	58,242	183,039	30.24 (29.99-30.48)	1.53 (1.51-1.55)
Female				
Never-smokers	128,784	790,783	14.08 (14.00-14.15)	REF
Ex-smokers	5,001	21,690	20.80 (20.23-21.38)	1.49 (1.45-1.53)
Current smokers	10,434	41,184	23.19 (22.75-23.64)	1.67 (1.62-1.71)
Charlson Comorbidity Index				
0-2				
Never-smokers	38,420	808,379	3.90 (3.86-3.93)	REF
Ex-smokers	5,229	77,499	5.55 (5.40-5.70)	1.42 (1.35-1.48)
Current smokers	16,078	166,703	8.12 (8.00-8.25)	2.11 (2.06-2.17)
>2				
Never-smokers	168,511	351,487	48.77 (48.54-49.00)	REF
Ex-smokers	62,827	109,477	63.66 (63.16-64.16)	1.32 (1.30-1.34)
Current smokers	36,691	57,520	74.55 (73.79-75.32)	1.57 (1.54-1.59)
Age				
<30				
Never-smokers	567	88,443	0.53 (0.49-0.58)	REF
Ex-smokers	30	2,970	0.83 (0.57-1.17)	1.56 (1.08-2.25)
Current smokers	271	18,402	1.23 (1.09-1.38)	2.30 (1.97-2.69)
30-39				
Never-smokers	1,516	102,696	1.22 (1.16-1.28)	REF
Ex-smokers	137	6,584	1.72 (1.45-2.02)	1.41 (1.17-1.69)
Current smokers	1,014	30,208	2.80 (2.63-2.97)	2.29 (2.10-2.50)
40-49				
Never-smokers	6,383	186,676	2.79 (2.73-2.86)	REF
Ex-smokers	715	15,066	3.92 (3.64-4.21)	1.41 (1.26-1.57)
Current smokers	2,845	42,342	5.56 (5.36-5.77)	1.99 (1.88-2.11)
50-59				
Never-smokers	19,626	288,488	5.59 (5.51-5.67)	REF
Ex-smokers	3,187	34,284	7.75 (7.49-8.02)	1.39 (1.30-1.49)
Current smokers	7,489	55,775	11.43 (11.17-11.69)	2.06 (1.98-2.14)
60-69				
Never-smokers	35,790	224,724	13.49 (13.35-13.63)	REF
Ex-smokers	10,049	45,848	19.24 (18.87-19.62)	1.44 (1.38-1.51)
Current smokers	11,809	41,513	25.67 (25.21-26.14)	1.93 (1.87-2.00)
70-79				
Never-smokers	74,229	173,076	40.81 (40.52-41.10)	REF
Ex-smokers	26,700	51,304	53.42 (52.78-54.06)	1.34 (1.31-1.37)
Current smokers	16,093	26,444	66.88 (65.85-67.92)	1.71 (1.66-1.76)
≥80				
Never-smokers	74,027	95,763	103.94 (103.19-104.69)	REF
Ex-smokers	25,627	30,920	123.12 (121.62-124.64)	1.21 (1.18-1.24)
Current smokers	8,209	9,539	133.94 (131.06-136.86)	1.34 (1.29-1.38)