

Supplementary materials

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Online Tables

Online Table S1. Definitions of covariates

| Diagnosis | ICD-10-CM code and definition | Diagnostic definition |
|-------------------------------------|---|---|
| Inclusion/exclusion criteria | | |
| Atrial fibrillation | I48.0-48.4, I48.9 | Admission \geq 1 or outpatient department \geq 2 |
| Valvular atrial fibrillation | I05.0, I05.2, I05.9, Z95.2-Z95.4 | Admission or outpatient department \geq 1 |
| Ischemic stroke | I63, I64 | Admission or outpatient department \geq 1 |
| Comorbidities | | |
| Hypertension | I10-I13, I15; and minimum 1 prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker). | Admission \geq 1 or outpatient department \geq 2 |
| Diabetes mellitus | or systolic/diastolic blood pressure \geq 140/90 mmHg E11-E14; and minimum 1 prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α -glucosidase inhibitors, and insulin). | Based on the results of 2 nd health exam Admission \geq 1 or outpatient department \geq 2 |
| Dyslipidemia | or fasting glucose level \geq 126 mg/dL E78 or Total cholesterol \geq 240 mg/dL | Based on the results of 2 nd health exam Admission or outpatient department \geq 1 Based on the results of 2 nd health exam |
| Heart failure | I50 | Admission or outpatient department \geq 1 |
| Vascular disease | | |
| Prior MI | I21, I22 | Admission or outpatient department \geq 1 |
| PAD | I70, I73 | Admission or outpatient department \geq 2 |
| CKD | eGFR $<$ 60ml/min/1.73m ² | Based on the results of 2 nd health exam |
| COPD | J41-44 | Admission \geq 1 |
| Cancer | C00-97 and RID code (V193) | Admission or outpatient department \geq 1 |
| Health exam questionnaire | | |
| Alcohol consumption | Mild to moderate drinker: alcohol consumption $>$ 0g to $<$ 30g per day Heavy drinker: alcohol consumption \geq 30g per day | Based on the results of 2 nd health exam |
| Regular exercise | Performing a moderate physical activity more than 30 minutes at least 5 times per week or strenuous | Based on the results of 2 nd health exam |

physical activity more than 20 minutes at least 3 times per week.

Low income

Income lowest 20% and medical aid

Scores

CHA₂DS₂-VASc score Heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes (1 point), previous stroke/systemic embolism/transient ischemic attack (2 points), vascular disease (prior MI or PAD, 1 point) and female sex (1 point)

Clinical outcome

| | | |
|--|----------|--|
| Ischemic stroke | I63, I64 | Admission ≥ 1 and brain imaging (CT or MRI) ≥ 1 |
| Fatal ischemic stroke | I63, I64 | Ischemic stroke event that led to death within 30-day of its occurrence |
| Death from cerebrovascular events | I60-69 | Any cerebrovascular events that led to death within 30-day of its occurrence |

Abbreviation: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance image; PAD, peripheral artery disease.

Online Table S2. Hazard ratios of ischemic stroke and all-cause death: unadjusted and model 1

| Smoking status | Unadjusted HR (95% CI) | Model 1 HR (95% CI) |
|------------------------|-------------------------------|----------------------------|
| Ischemic stroke | P=0.051 | P=<0.001 |
| Never smoker | 1 (reference) | 1 (reference) |
| Ex-smoker | 0.959 (0.881-1.044) | 1.022 (0.917-1.139) |
| Quitter | 0.914 (0.789-1.059) | 1.228 (1.046-1.441) |
| Current smoker | 1.102 (0.997-1.218) | 1.750 (1.551-1.973) |
| All-cause death | P=<0.001 | P=<0.001 |
| Never smoker | 1 (reference) | 1 (reference) |
| Ex-smoker | 1.298 (1.215-1.387) | 1.138 (1.049-1.236) |
| Quitter | 1.473 (1.330-1.632) | 1.831 (1.637-2.048) |
| Current smoker | 1.226 (1.310-1.331) | 1.895 (1.723-2.084) |

Model 1: age and sex-adjusted

Abbreviation: CI, confidence interval; HR, hazard ratio.

Online Table S3. The proportion of patients treated with antiarrhythmic drugs and undergoing AF ablation

| | Total (n=97,637) | Never smokers (n=50,036) | Ex- smokers (n=26,621) | Quitters (n=6768) | Current smokers (n=14,212) | p- value |
|--------------------|-----------------------------|---|---------------------------------------|------------------------------|---|---------------------|
| AAD use | 23,409 (24.0) | 11,273 (22.5) | 7328 (27.5) | 1760 (26.0) | 3048 (21.4) | <0.001 |
| Class Ic | 15,587 (16.0) | 7613 (15.2) | 4861 (18.3) | 1033 (15.3) | 2080 (14.6) | <0.001 |
| Class III | 8045 (8.2) | 3763 (7.5) | 2533 (9.5) | 754 (11.1) | 995 (7.0) | <0.001 |
| AF ablation | 1145 (1.2) | 477 (1.0) | 450 (1.7) | 110 (1.6) | 108 (0.8) | <0.001 |

AAD was defined as class Ic and III drugs.

Abbreviation: AAD, antiarrhythmic drugs; AF, atrial fibrillation.

Online Table S4. Hazard ratios of primary and secondary outcomes after additionally adjusting whether performing early rhythm control by antiarrhythmic drugs or AF catheter ablation

| | HR (95% CI) | p-value | HR* (95% CI) | p-value |
|--|---------------------|---------|---------------------|---------|
| Ischemic stroke | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.593 (0.525-0.671) | <0.001 |
| Ex-smoker | 1.022 (0.917-1.140) | | 0.607 (0.541-0.680) | |
| Quitter | 1.191 (1.014-1.399) | | 0.707 (0.599-0.834) | |
| Current smoker | 1.685 (1.491-1.904) | | 1 (reference) | |
| All-cause death | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.585 (0.532-0.645) | <0.001 |
| Ex-smoker | 1.112 (1.024-1.206) | | 0.651 (0.595-0.711) | |
| Quitter | 1.454 (1.299-1.628) | | 0.851 (0.756-0.958) | |
| Current smoker | 1.708 (1.551-1.881) | | 1 (reference) | |
| Fatal ischemic stroke | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.452 (0.335-0.612) | <0.001 |
| Ex-smoker | 1.063 (0.809-1.396) | | 0.481 (0.360-0.642) | |
| Quitter | 1.014 (0.651-1.581) | | 0.459 (0.290-0.726) | |
| Current smoker | 2.211 (1.635-2.989) | | 1 (reference) | |
| Death from cerebrovascular events | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.521 (0.400-0.678) | <0.001 |
| Ex-smoker | 1.071 (0.850-1.349) | | 0.558 (0.434-0.718) | |
| Quitter | 1.290 (0.919-1.809) | | 0.672 (0.470-0.960) | |
| Current smoker | 1.919 (1.475-2.497) | | 1 (reference) | |

*HRs are presented the reference group as the current smoker. Abbreviation: AF, atrial fibrillation.

Online Table S5. The proportion of patients with obstructive sleep apnea

| | Total (n=97,637) | Never smokers (n=50,036) | Ex- smokers (n=26,621) | Quitters (n=6768) | Current smokers (n=14,212) | p- value |
|------------|-----------------------------|---|---------------------------------------|------------------------------|---|---------------------|
| OSA | 361 (0.4) | 133 (0.3) | 125 (0.5) | 37 (0.5) | 66 (0.5) | <0.001 |

Abbreviation: OSA, obstructive sleep apnea.

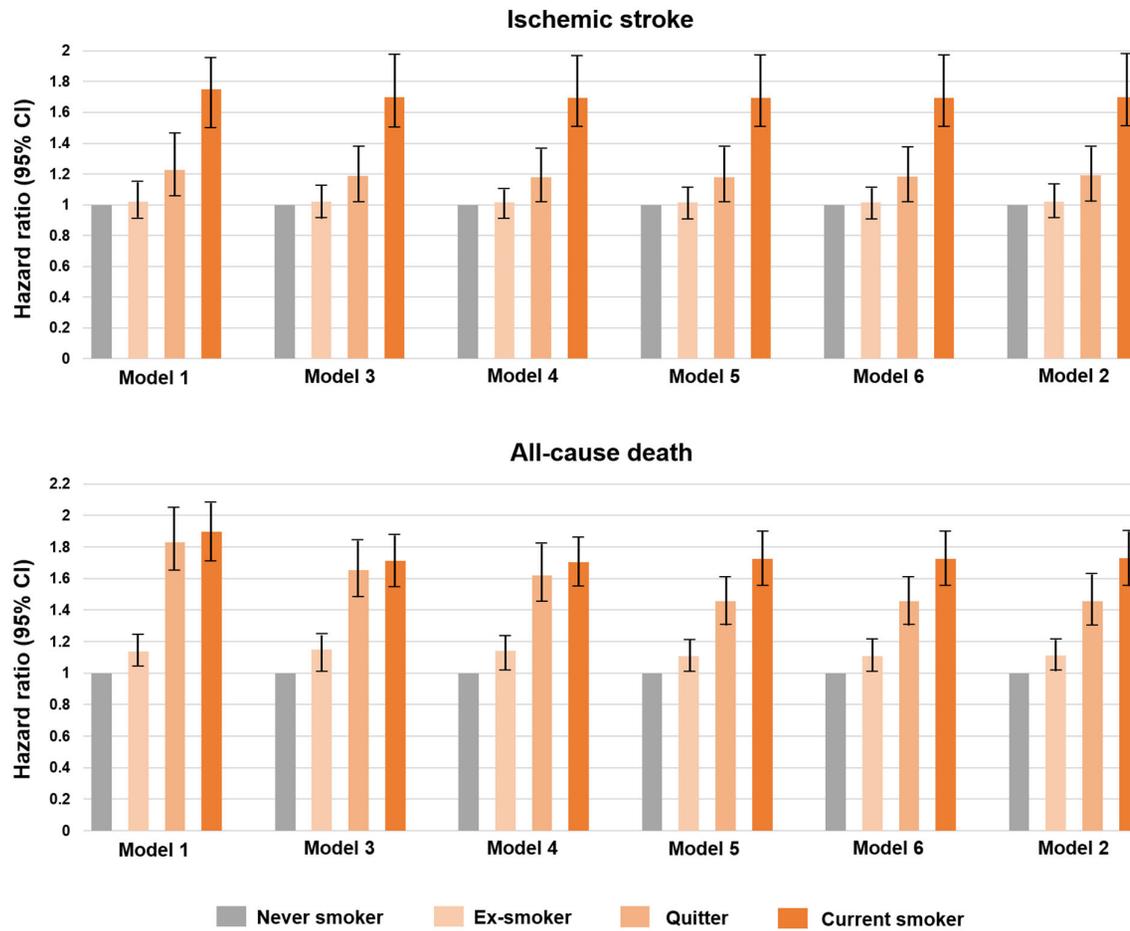
Online Table S6. Hazard ratios of primary and secondary outcomes after additionally adjusting obstructive sleep apnea

| | HR (95% CI) | p-value | HR* (95% CI) | p-value |
|--|---------------------|---------|---------------------|---------|
| Ischemic stroke | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.591 (0.523-0.668) | <0.001 |
| Ex-smoker | 1.022 (0.916-1.139) | | 0.604 (0.539-0.677) | |
| Quitter | 1.194 (1.017-1.403) | | 0.706 (0.599-0.832) | |
| Current smoker | 1.692 (1.497-1.912) | | 1 (reference) | |
| All-cause death | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.581 (0.528-0.640) | <0.001 |
| Ex-smoker | 1.110 (1.023-1.205) | | 0.645 (0.590-0.705) | |
| Quitter | 1.455 (1.300-1.629) | | 0.846 (0.752-0.952) | |
| Current smoker | 1.720 (1.562-1.894) | | 1 (reference) | |
| Fatal ischemic stroke | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.449 (0.332-0.606) | <0.001 |
| Ex-smoker | 1.061 (0.808-1.394) | | 0.476 (0.357-0.635) | |
| Quitter | 1.009 (0.647-1.573) | | 0.453 (0.286-0.717) | |
| Current smoker | 2.229 (1.649-3.013) | | 1 (reference) | |
| Death from cerebrovascular events | | | | |
| Never smoker | 1 (reference) | <0.001 | 0.516 (0.396-0.671) | <0.001 |
| Ex-smoker | 1.068 (0.848-1.346) | | 0.551 (0.428-0.708) | |
| Quitter | 1.285 (0.916-1.804) | | 0.663 (0.464-0.947) | |
| Current smoker | 1.940 (1.491-2.523) | | 1 (reference) | |

*HRs are presented the reference group as the current smoker

Online Figures

Online Figure S1. Hazard ratios for the risk of ischemic stroke and all-cause death in sequentially adjusted multivariable models



Abbreviation: CI, confidence interval.

Model 1: age and sex

Model 3: age, sex, baseline body mass index, heavy drinker, regular exercise, low income, and CHA₂DS₂-VASc score

Model 4: age, sex, baseline body mass index, heavy drinker, regular exercise, low income, comorbidities including hypertension, diabetes mellitus, dyslipidemia,

heart failure, prior myocardial infarction, and peripheral artery disease.

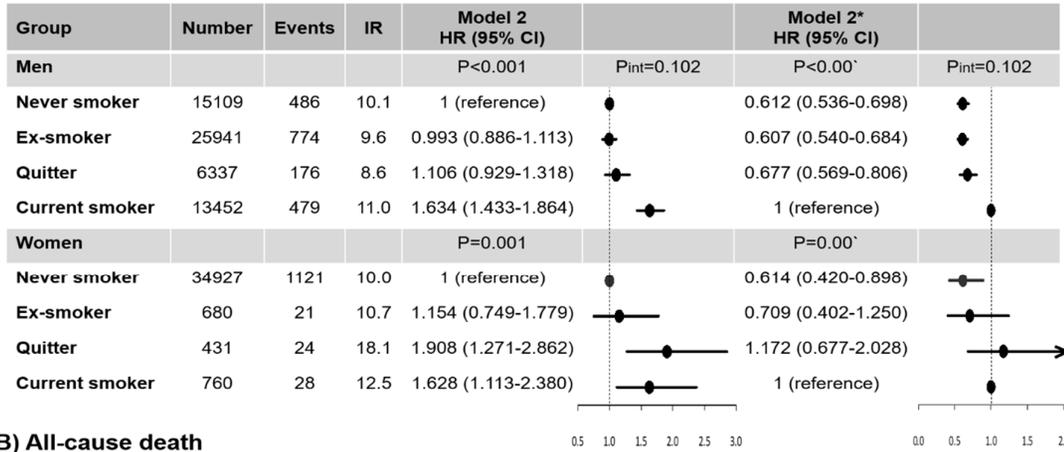
Model 5: model 4 + comorbidities including chronic kidney disease, chronic obstructive pulmonary disease and cancer.

Model 6: model 5 + CHA₂DS₂-VASc score

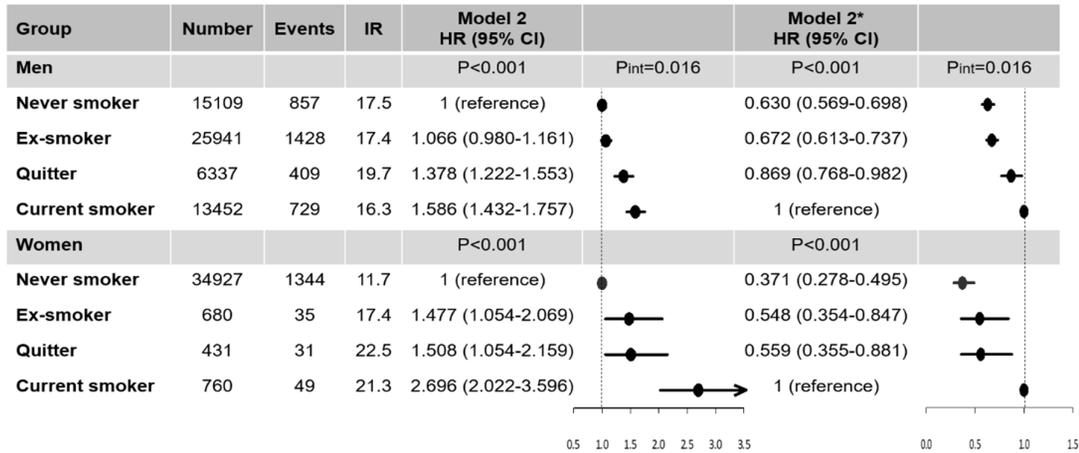
Model 2: model 6 + baseline medications including OACs, aspirin, P2Y₁₂ inhibitor and statin

Online Figure S2. Hazard ratios of smoking status on the risk of ischemic stroke and all-cause death in men and women

(A) Ischemic stroke



(B) All-cause death



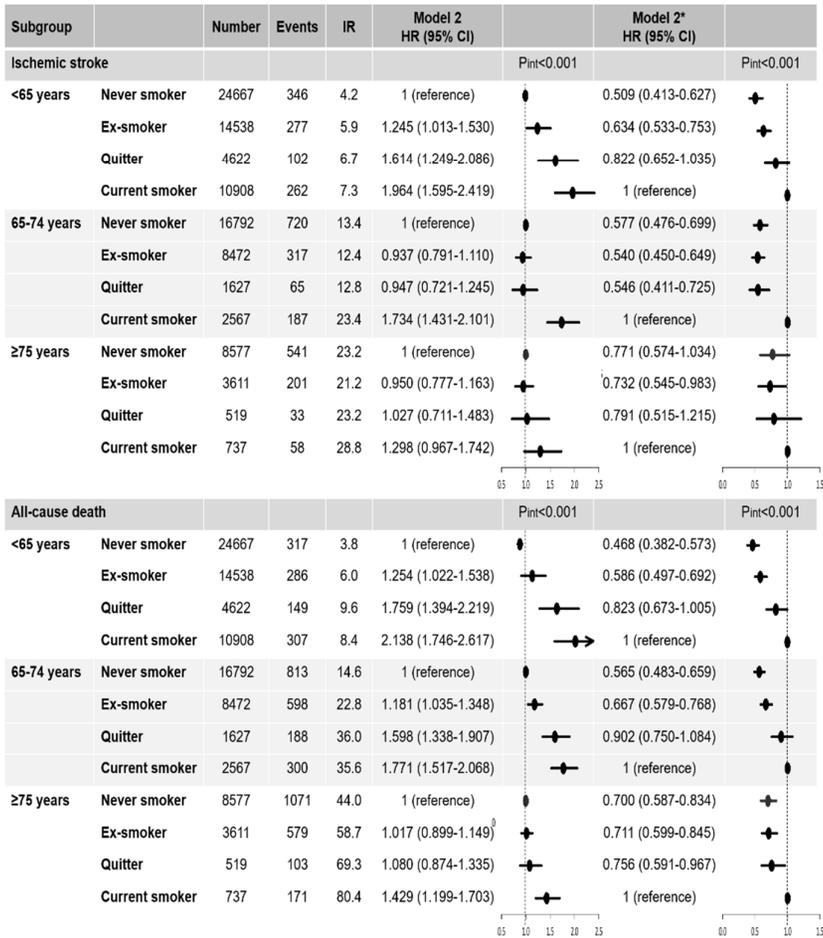
* With current smokers as the reference group

IR, per 1000 person-years

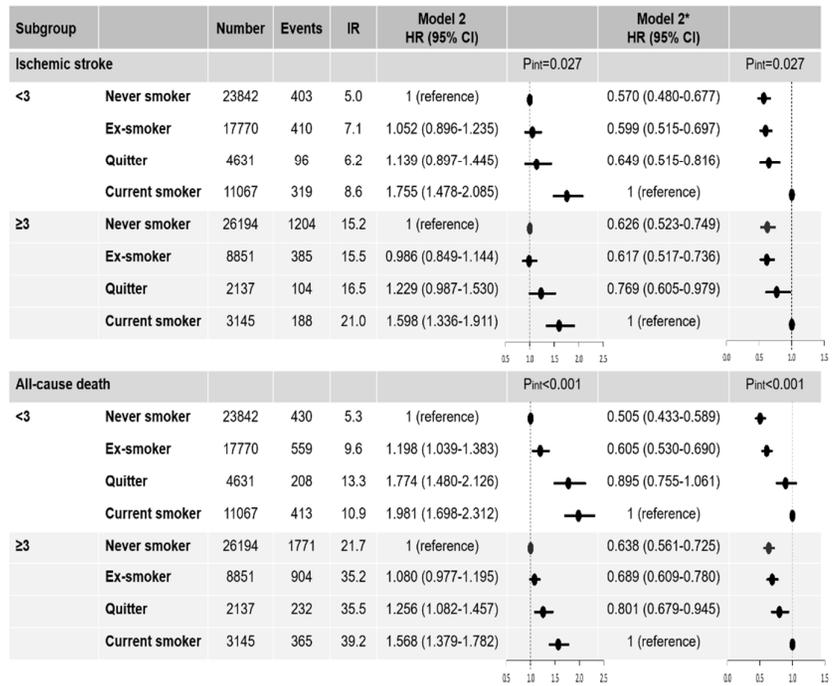
Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate; P_{int}, p for interaction.

Online Figure S3. Subgroup analyses by age (<65 years, 65 to 74 years, and ≥75 years) and CHA₂DS₂-VASc score (<3 and ≥3)

(A) Age



(B) CHA₂DS₂-VASc score



* With current smokers as the reference group

IR, per 1000 person-years

Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate; P_{int}, p for interaction.