

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Data Source and Covariates

Data Source

In brief, the government provides mandatory health insurance coverage to the entire Korean population, approximately 50 million people. The Korean NHIS database contains demographic data as well as information about enrollees' medical expenses, such as diagnoses, examinations, prescription dispensing records, and inpatient and outpatient procedure records.^{1,2} The International Classification of Diseases, Tenth Revision, Clinical Modification codes were used to classify diagnoses. Additionally, enrollees aged 40 years or older are recommended to undergo a biannual health screening conducted by the Korean National Health Insurance Corporation. The health examination consists of anthropometric measurements, blood pressure, a laboratory examination, and a chest X-ray, as well as a self-reported questionnaire on health behaviors such as smoking, alcohol consumption, and physical activity. In 2014, 75% of participants participated.² These data are linked with the Korean NHIS database as a National Health Screening database.

Covariates

Comorbidities included hypertension, diabetes mellitus, dyslipidemia, heart failure, prior myocardial infarction (MI), peripheral artery disease (PAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and cancer.³⁻⁶ The CHA₂DS₂-VASc score for assessing stroke risk was calculated combining covariate information (**Online Table 1**).⁷ Baseline medications, including OACs (i.e. warfarin or direct oral anticoagulants, DOACs), aspirin, P2Y₁₂ inhibitors, and statin, were identified between the date of AF diagnosis and the date of the second health examination. As patients' baseline variables, body mass index, waist circumference, systolic and diastolic blood pressure, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate at the second health examination were collected. Alcohol consumption was categorized into non-drinker, mild to moderate drinker (>0g/day to <30 g/day), and heavy drinker (≥30 g/day). Regular exercise was defined as performing >30 minutes of moderate physical activity ≥5 times a week or >20 minutes of strenuous physical activity ≥5 times per week. Low income was defined as having income in lower 20% among the entire Korean population of subjects supported by the Medical Aid program.

eTable 1. 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 |
| Dementia | F00-03, F107, G30, G231, G310, G311, G318 and prescription of medication for dementia, including galantamine, rivastigmine, donepezil, or memantine | 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 |
| | or systolic/diastolic blood pressure \geq 140/90 mmHg | Based on the results of 2 nd health exam |
| Diabetes mellitus | E11-E14; and minimum 1 prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α -glucosidase inhibitors, and insulin). | Admission \geq 1 or outpatient department \geq 2 |

| | | |
|----------------------------------|---|---|
| | or fasting glucose level \geq 126 mg/dL | Based on the results of 2 nd health exam |
| Dyslipidemia | E78 | Admission or outpatient department \geq 1 |
| | or Total cholesterol \geq 240 mg/dL | 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 < 60 ml/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 | Based on the results of 2 nd health exam |
| | Heavy drinker: alcohol consumption \geq 30g per day | |

| | | |
|---|---|---|
| Regular exercise | Performing a moderate physical activity more than 30 minutes at least 5 times per week or strenuous physical activity more than 20 minutes at least 3 times per week. | Based on the results of 2 nd health exam |
| 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 | | |
| Dementia | F00-03, F107, G30, G231, G310, G311, G318 and prescription of medication for dementia, including galantamine, rivastigmine, donepezil, or memantine | Admission or outpatient department ≥ 1 |
| Alzheimer Disease | F00, G30 and prescription of medication for dementia, including galantamine, rivastigmine, donepezil, or memantine | Admission or outpatient department ≥ 1 |
| Vascular Dementia | F01 and prescription of medication for dementia, including galantamine, rivastigmine, donepezil, or memantine | Admission or outpatient department ≥ 1 |

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.

eTable 2. Hazard Ratios of Dementia: Unadjusted and Models 1 and 2

| Smoking status | Number | Events | IR | Unadjusted HR (95% CI) | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|-----------------------|--------|--------|------|------------------------|---------------------|---------------------|
| Dementia | | | | P=<0.001 | P=<0.001 | P=<0.001 |
| Never smoker | 65579 | 3773 | 18.4 | 1.898 (1.734,2.078) | 0.673 (0.607,0.746) | 1 (reference) |
| Ex-smoker | 34670 | 1308 | 12.3 | 1.277 (1.155,1.412) | 0.689 (0.622,0.762) | 1.019 (0.940,1.106) |
| Quitter | 8919 | 310 | 10.9 | 1.128 (0.980,1.297) | 0.866 (0.753,0.996) | 1.163 (1.026,1.317) |
| Current smoker | 17084 | 534 | 9.7 | 1 (reference) | 1 (reference) | 1.406 (1.267,1.560) |
| A-Dementia | | | | P=<0.001 | P=<0.001 | P=<0.001 |
| Never smoker | 65579 | 2871 | 14 | 2.097 (1.881,2.337) | 0.707 (0.626,0.799) | 1 (reference) |
| Ex-smoker | 34670 | 942 | 8.9 | 1.336 (1.184,1.507) | 0.700 (0.620,0.790) | 0.986 (0.896,1.084) |
| Quitter | 8919 | 214 | 7.5 | 1.130 (0.955,1.338) | 0.855 (0.722,1.012) | 1.089 (0.939,1.263) |
| Current smoker | 17084 | 368 | 6.7 | 1 (reference) | 1 (reference) | 1.336 (1.181,1.512) |
| V-Dementia | | | | P=<0.001 | P=<0.001 | P=<0.001 |
| Never smoker | 65579 | 553 | 2.7 | 1.258 (1.032,1.535) | 0.512 (0.405,0.649) | 1 (reference) |
| Ex-smoker | 34670 | 229 | 2.2 | 1.011 (0.809,1.262) | 0.603 (0.482,0.755) | 1.177 (0.961,1.442) |
| Quitter | 8919 | 51 | 1.8 | 0.840 (0.605,1.166) | 0.674 (0.485,0.936) | 1.193 (0.874,1.629) |
| Current smoker | 17084 | 118 | 2.1 | 1 (reference) | 1 (reference) | 1.908 (1.503,2.423) |

Model 1: age and sex-adjusted

Model 2: age, sex, body mass index, heavy drinker, regular physical activity, low income, diabetes, hypertension, dyslipidemia, previous myocardial infarction, previous stroke, previous congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA2DS2-VASc score, warfarin, non-vitamin K antagonist oral anticoagulants, aspirin, clopidogrel, statin.

Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

eTable 3. Hazard Ratios of Dementia in Each Group Stratifying by the Smoking Amount

| Smoking status | Smoking amount | Number | Events | IR | Unadjusted | Model 1 | Model 2 |
|-----------------------|------------------------|--------|--------|------|---------------------|---------------------|---------------------|
| | (pack-years) | | | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Dementia | | | | | <0.001 | <0.001 | <0.001 |
| Never smoker | 0 | 65579 | 3773 | 18.4 | 1 (reference) | 1 (reference) | 1 (reference) |
| Ex-smoker | >0 to <10 | 10178 | 307 | 9.8 | 0.532 (0.474,0.598) | 0.958 (0.845,1.087) | 0.978 (0.862,1.109) |
| | ≥10 to <20 | 8870 | 293 | 10.7 | 0.586 (0.520,0.660) | 1.026 (0.901,1.169) | 1.032 (0.907,1.175) |
| | ≥20 to <30 | 6404 | 250 | 12.7 | 0.694 (0.611,0.789) | 1.06 (0.923,1.218) | 1.064 (0.927,1.223) |
| | ≥30 | 9218 | 458 | 16.5 | 0.904 (0.820,0.996) | 1.061 (0.949,1.185) | 1.024 (0.916,1.145) |
| Quitter | >0 to <10 | 1795 | 55 | 9.4 | 0.509 (0.39,0.664) | 1.252 (0.958,1.636) | 1.165 (0.891,1.522) |
| | ≥10 to <20 | 2038 | 56 | 8.6 | 0.469 (0.361,0.611) | 1.288 (0.986,1.683) | 1.148 (0.879,1.501) |
| | ≥20 to <30 | 1689 | 47 | 8.7 | 0.476 (0.357,0.634) | 1.083 (0.810,1.450) | 0.988 (0.738,1.322) |
| | ≥30 | 3397 | 152 | 14.2 | 0.777 (0.661,0.914) | 1.389 (1.171,1.648) | 1.242 (1.046,1.474) |
| Current smoker | >0 to <10 | 3577 | 94 | 8.1 | 0.439 (0.357,0.538) | 1.434 (1.164,1.766) | 1.338 (1.086,1.648) |
| | ≥10 to <20 | 4647 | 116 | 7.8 | 0.425 (0.353,0.511) | 1.365 (1.128,1.652) | 1.307 (1.079,1.583) |
| | ≥20 to <30 | 3645 | 135 | 11.5 | 0.628 (0.529,0.745) | 1.736 (1.451,2.077) | 1.633 (1.364,1.954) |
| | ≥30 | 5215 | 189 | 11.2 | 0.607 (0.524,0.702) | 1.454 (1.244,1.699) | 1.379 (1.178,1.614) |

IR, per 1000 person-years

Model 1: age and sex-adjusted

Model 2: age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior MI, PAD, CKD, COPD, cancer, BMI, heavy drinker, regular exercise, low income, use of OAC, use of antiplatelet agent, use of statin, and CHA₂DS₂-VASc score.

Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Table 4. Sensitivity Analysis With 1-Year Landmark Analysis: Hazard Ratios of Dementia at Landmark Time: Unadjusted and Models 1 and 2

| Smoking status | Unadjusted HR (95% CI) | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|--------------------------|------------------------|---------------------|---------------------|
| Dementia | | | |
| Never smoker | 1.872 (1.687,2.078) | 0.666 (0.591,0.750) | 0.697 (0.618,0.785) |
| Ex-smoker | 1.297 (1.156,1.456) | 0.700 (0.623,0.787) | 0.733 (0.652,0.824) |
| Quit-smokers | 1.105 (0.940,1.299) | 0.843 (0.717,0.991) | 0.805 (0.684,0.947) |
| Current smoker | 1 (reference) | 1 (reference) | 1 (reference) |
| Alzheimer disease | | | |
| Never smoker | 2.082 (1.837,2.359) | 0.715 (0.621,0.824) | 0.752 (0.652,0.866) |
| Ex-smoker | 1.388 (1.209,1.594) | 0.728 (0.634,0.837) | 0.765 (0.665,0.880) |
| Quit-smokers | 1.140 (0.939,1.383) | 0.857 (0.706,1.040) | 0.814 (0.670,0.988) |
| Current smoker | 1 (reference) | 1 (reference) | 1 (reference) |
| Vascular dementia | | | |
| Never smoker | 1.274 (1.014,1.602) | 0.492 (0.374,0.647) | 0.492 (0.373,0.648) |
| Ex-smoker | 1.033 (0.800,1.334) | 0.614 (0.475,0.795) | 0.618 (0.476,0.802) |
| Quit-smokers | 0.746 (0.502,1.108) | 0.593 (0.399,0.881) | 0.552 (0.371,0.821) |
| Current smoker | 1 (reference) | 1 (reference) | 1 (reference) |

Model 1: age and sex-adjusted

Model 2: age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior MI, PAD, CKD, COPD, cancer, BMI, heavy drinker, regular exercise, low income, use of OAC, use of antiplatelet agent, use of statin, and CHA₂DS₂-VASc score.

Abbreviation: CI, confidence interval; HR, hazard ratio

All, p for trends < 0.001

eTable 5. Baseline Characteristics of Quit and Current Smoker Groups Before and After Propensity Score Matching

| | Before PS matching | | | After PS matching | | |
|---|--------------------|----------------|-------|-------------------|----------------|--------|
| | Quit-smoker | Current smoker | ASD | Quit-smoker | Current smoker | ASD |
| Number | 8918 | 17084 | | 8573 | 8573 | |
| Age (years) | 59.1 (11.9) | 56.2 (12.5) | 0.234 | 58.8 (11.9) | 58.9 (12.1) | 0.009 |
| <65 years | 5753 (64.5) | 12,411 (72.7) | | 5606 (65.4) | 5560 (64.9) | |
| 65 to <75 years | 2371 (26.6) | 3553 (20.8) | | 2226 (26.0) | 2215 (25.8) | |
| ≥75 years | 795 (8.9) | 1120 (6.6) | | 741 (8.6) | 798 (9.3) | |
| Sex (Male) | 8354 (93.7) | 16,134 (94.4) | 0.032 | 8029 (93.7) | 8031 (93.7) | 0.001 |
| CHA₂DS₂-VASc | 2.4 (1.6) | 1.7 (1.5) | 0.284 | 2.4 (1.6) | 2.4 (1.6) | 0.003 |
| 0 | 846 (9.5) | 2405 (14.1) | | 834 (9.7) | 851 (9.9) | |
| 1 | 2084 (23.4) | 5339 (31.3) | | 2050 (23.9) | 2150 (25.1) | |
| ≥2 | 5989 (67.2) | 9340 (54.7) | | 5689 (66.4) | 5572 (65.0) | |
| Hypertension | 6106 (68.5) | 10,939 (64.0) | 0.093 | 5834 (68.1) | 5843 (68.2) | 0.002 |
| Diabetes mellitus | 2266 (25.4) | 4096 (24.0) | 0.033 | 2165 (25.3) | 2111 (24.6) | 0.014 |
| Dyslipidemia | 984 (11.0) | 2060 (12.1) | 0.032 | 958 (11.2) | 959 (11.2) | <0.001 |
| Heart failure | 2456 (27.5) | 3679 (21.5) | 0.139 | 2320 (27.1) | 2367 (27.6) | 0.012 |
| Prior MI | 766 (8.6) | 850 (5.0) | 0.144 | 686 (8.0) | 698 (8.1) | 0.005 |
| PAD | 1761 (19.7) | 3195 (18.7) | 0.026 | 1695 (19.8) | 1681 (19.6) | 0.004 |

| | | | | | | |
|-----------------------------------|-------------|-------------|-------|-------------|-------------|--------|
| CKD | 1186 (13.3) | 1543 (9.0) | 0.135 | 1092 (12.7) | 1111 (13.0) | 0.006 |
| COPD | 2059 (23.1) | 2990 (17.5) | 0.139 | 1902 (22.2) | 1857 (21.7) | 0.012 |
| Cancer | 729 (8.2) | 513 (3.0) | 0.226 | 587 (6.9) | 505 (5.9) | 0.039 |
| OAC | 3000 (33.6) | 3771 (22.1) | 0.260 | 2791 (32.6) | 2823 (32.9) | 0.008 |
| Warfarin | 2422 (27.2) | 2988 (17.5) | 0.233 | 2251 (26.3) | 2295 (26.8) | 0.011 |
| DOAC | 822 (9.2) | 1027 (6.0) | 0.121 | 753 (8.8) | 753 (8.8) | <0.001 |
| Aspirin | 1889 (21.2) | 3513 (20.6) | 0.015 | 1823 (21.3) | 1838 (21.4) | 0.004 |
| P2Y₁₂ inhibitor | 838 (9.4) | 1079 (6.3) | 0.114 | 780 (9.1) | 800 (9.3) | 0.008 |
| Statin | 1789 (20.1) | 2690 (15.8) | 0.112 | 1686 (19.7) | 1684 (19.6) | <0.001 |
| BMI (kg/m²) | 24.6 (3.4) | 24.4 (3.4) | 0.067 | 24.6 (3.4) | 24.6 (3.5) | 0.001 |
| Heavy drinker | 722 (8.1) | 2665 (15.6) | 0.233 | 720 (8.4) | 674 (7.9) | 0.019 |
| Regular exercise | 2056 (23.1) | 3376 (19.8) | 0.080 | 1941 (22.6) | 1979 (23.1) | 0.010 |
| Low income | 1500 (16.8) | 3057 (17.9) | 0.028 | 1452 (16.9) | 1420 (16.6) | 0.0100 |

Continuous variables are presented as mean \pm standard deviation and categorical variables are presented as numbers (percentage).

Abbreviation: ASD, absolute standardized difference; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; MI, myocardial infarction; OAC, oral anticoagulant; PAD, peripheral artery disease; PS, propensity score.

eTable 6. Event Number, Incidence Rate, and Hazard Ratio of Dementia After Propensity Score Matching

| | Number | Events | IR | HR (95% CI) | p-value |
|--------------------------|---------------|---------------|-----------|---------------------|----------------|
| Total dementia | | | | | 0.037 |
| Current smoker | 8573 | 344 | 12.8 | 1 (reference) | |
| Quit-smoker | 8573 | 298 | 10.9 | 0.848 (0.726-0.991) | |
| Alzheimer disease | | | | | 0.059 |
| Current smoker | 8573 | 240 | 8.9 | 1 (reference) | |
| Quit-smoker | 8573 | 205 | 7.5 | 0.836 (0.694-1.007) | |
| Vascular dementia | | | | | 0.012 |
| Current smoker | 8573 | 77 | 2.9 | 1 (reference) | |
| Quit-smoker | 8573 | 50 | 1.8 | 0.636 (0.446-0.908) | |

IR, per 1000 person-years

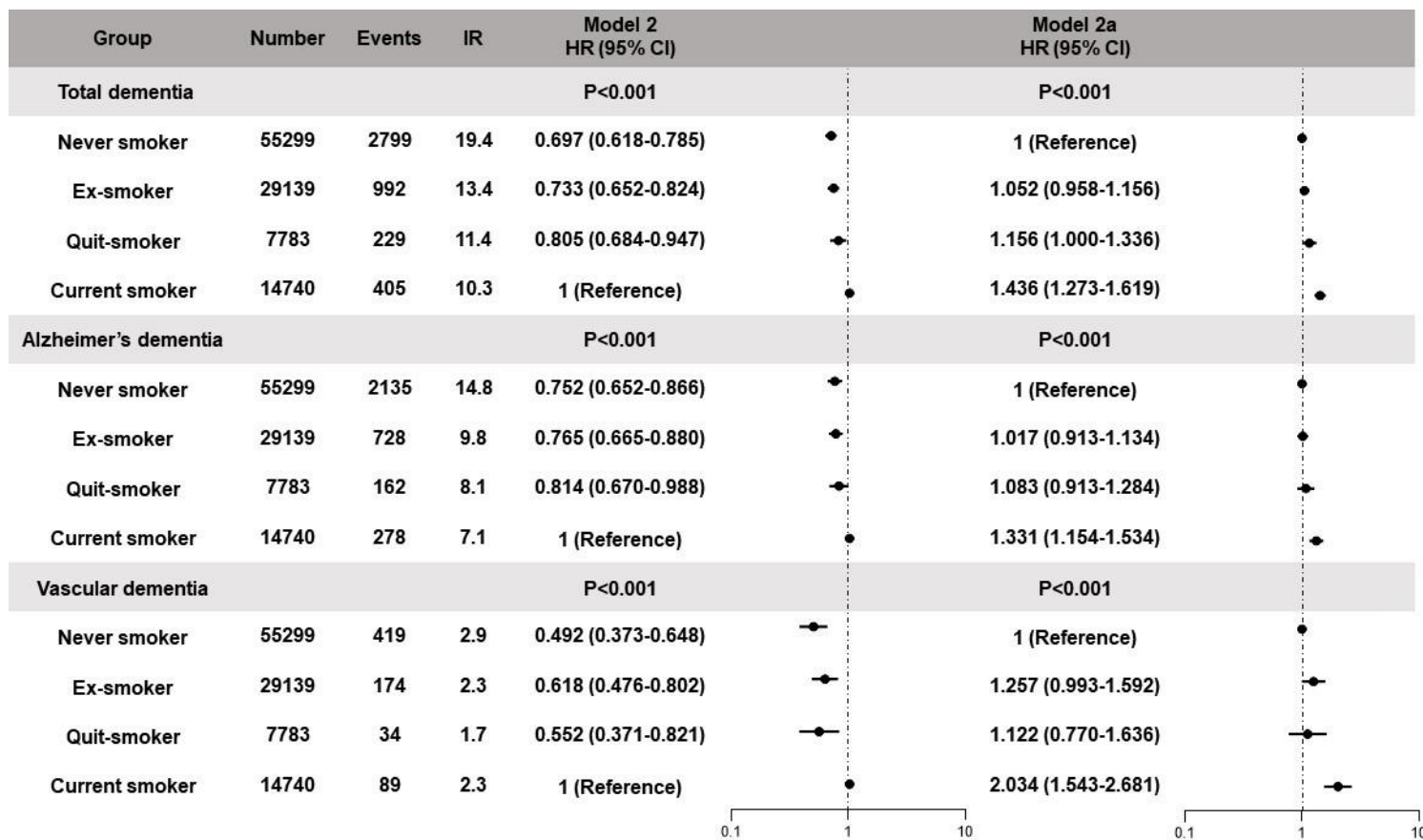
Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

eTable 7. Competing Risk Analysis

| | Model 2 HR (95% CI) | p-value | Model 2a HR (95% CI) | p-value |
|-------------------|------------------------|---------|-------------------------|---------|
| Total dementia | | <0.001 | | <0.001 |
| Never smoker | 0.736 (0.663-0.819) | | 1 (reference) | |
| Ex-smoker | 0.746 (0.673-0.827) | | 1.013 (0.933-1.100) | |
| Quit-smoker | 0.839 (0.727-0.968) | | 1.139 (1.003-1.294) | |
| Current smoker | 1 (reference) | | 1.358 (1.222-1.509) | |
| Alzheimer disease | | <0.001 | | <0.001 |
| Never smoker | 0.777 (0.685-0.881) | | 1 (reference) | |
| Ex-smoker | 0.761 (0.673-0.861) | | 0.980 (0.890-1.078) | |
| Quit-smoker | 0.829 (0.698-0.984) | | 1.067 (0.916-1.242) | |
| Current smoker | 1 (reference) | | 1.287 (1.135-1.459) | |
| Vascular dementia | | <0.001 | | <0.001 |
| Never smoker | 0.539 (0.425-0.682) | | 1 (reference) | |
| Ex-smoker | 0.631 (0.504-0.791) | | 1.171 (0.955-1.436) | |
| Quit-smoker | 0.631 (0.452-0.88) | | 1.171 (0.862-1.59) | |
| Current smoker | 1 (reference) | | 1.856 (1.466-2.351) | |

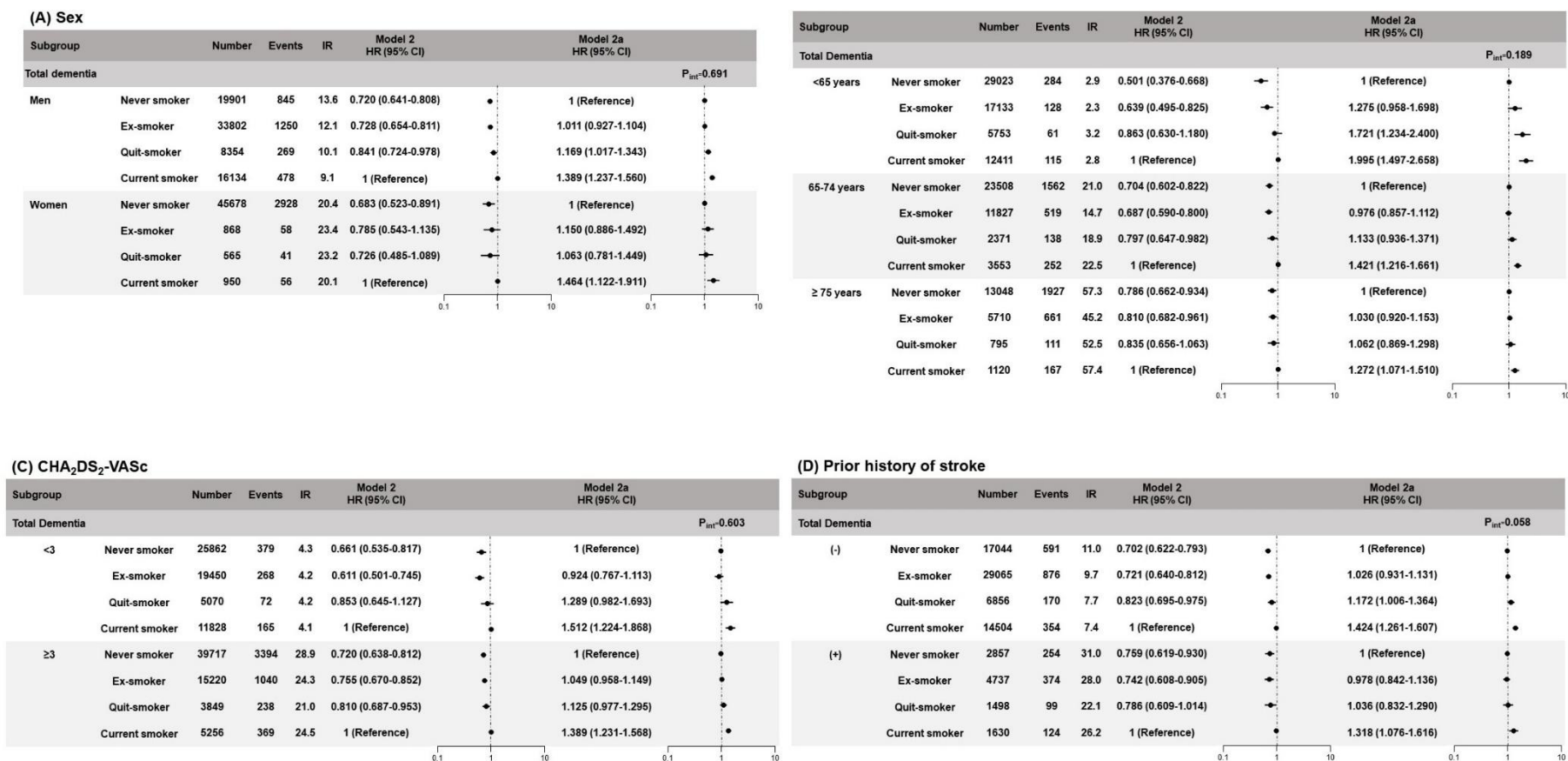
Model 2a showed hazard ratio of each group compared to never smoker as a reference group.
Abbreviation: CI, confidence interval; HR, hazard ratio.

eFigure 1. Sensitivity Analysis With 1-Year Landmark Analysis: Hazard Ratios of Smoking Status on the Risk of Total Dementia, Alzheimer Disease, and Vascular Dementia



For model 2a, never smokers acted as the reference group. IR, per 1000 person-years. Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

eFigure 2. Subgroup Analyses by Sex, Age, CHA₂DS₂-VAsC Score, and Previous Stroke (Total Dementia)



For model 2a, never smokers acted as the reference group.

IR, per 1000 person-years

Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate; Pint, p for interaction.

eFigure 3. Subgroup Analyses by Sex, Age, CHA₂DS₂-VAsC Score, and Previous Stroke (Alzheimer Disease)

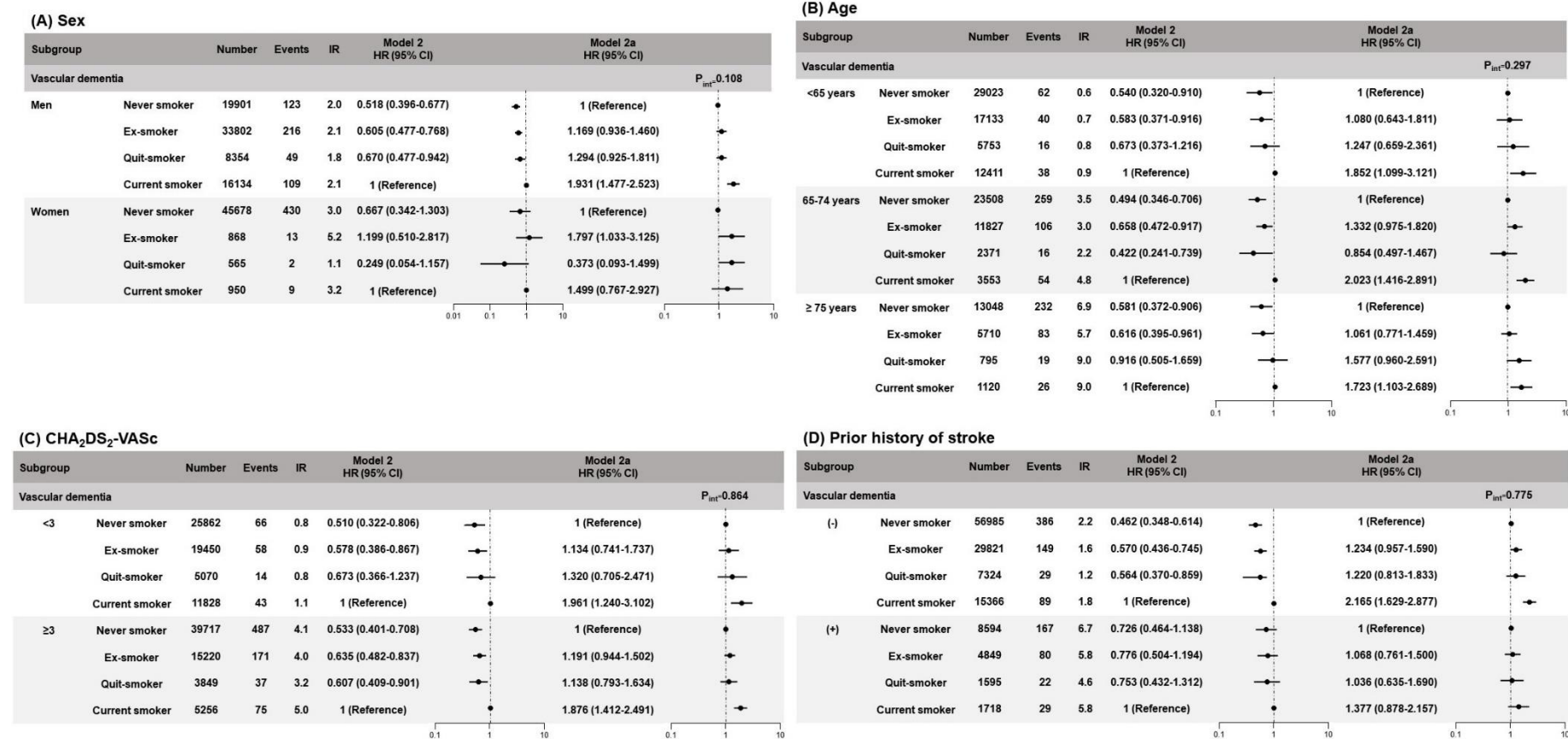


For model 2a, never smokers acted as the reference group.

IR, per 1000 person-years

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

eFigure 4. Subgroup Analyses by Sex, Age, CHA₂DS₂-VASc Score, and Previous Stroke (Vascular Dementia)



For model 2a, never smokers acted as the reference group.

IR, per 1000 person-years

Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate; Pint, p for interaction.

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