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ORIGINAL RESEARCH

Association Between Changes in Smoking Habits and Incident Fracture After Acute Ischemic Stroke

Jeen Hwa Lee, MD*; Kyung-Do Han, PhD*; Dae Young Cheon, MD; Minwoo Lee, MD, PhD

BACKGROUND: Survivors of stroke, particularly the older population, are at an increased risk of falls and incident fractures. Smoking is a widely recognized risk factor for fractures. However, the association between changes in smoking habits before and after an index stroke and increased risk of fracture remains unelucidated.

METHODS AND RESULTS: Using the Korean National Health Insurance program, patients with ischemic stroke between 2010 and 2016 were enrolled. Individuals were classified by smoking habits: "never smoker," "former smoker," "smoking quitter," "new smoker," and "sustained smoker." The primary outcome was the composite outcome of the vertebral, hip, and any fractures. Multivariable Cox proportional hazards regression analysis was conducted, using the never-smoker group as the reference. Among 177 787 patients with health screening data within 2 years before and after ischemic stroke, 14 991 (8.43%) patients had any fractures. After multivariable adjustment, the sustained smokers had a significantly increased risk of composite primary outcomes of any, vertebral, and hip fractures (adjusted HR [aHR], 1.222 [95% CI, 1.124–1.329]; aHR, 1.27 [95% CI, 1.13–1.428]; aHR, 1.502 [95% CI, 1.218–1.853], respectively). Additionally, the new smoker group exhibited a similar or higher risk of any fractures and hip fractures (aHR, 1.218 [95% CI, 1.062–1.397]; aHR, 1.772 [95% CI, 1.291–2.431], respectively).

CONCLUSIONS: Sustained smokers had a significantly increased risk of vertebral and hip fractures after an ischemic stroke. The risk of any hip fractures was higher in new smokers after ischemic stroke. As poststroke fractures are detrimental to the rehabilitation process of patients with stroke, physicians should actively advise patients to stop smoking.

Key Words: bone fractures ■ hip fractures ■ ischemic stroke ■ smoking habits ■ vertebral fractures

In the 2019 Global Burden of Disease report, stroke was the third leading cause of mortality and disability,[1] which is additionally attributed to the 4-fold higher risk of experiencing fractures than the general population.[2] Over 70% of survivors of stroke with disabilities experience a fall during the first 6 months after the stroke, which may eventually lead to fractures.[3] A study evaluating the risk factors for hip fractures also identified a history of stroke as a significant risk factor.[4–6] The cumulative incidence of any fractures is reportedly 4.7%, 8%, and 13% at 1, 2, and 4 years, respectively, in Korean patients with stroke.[7,8]

Some trials have examined the association between smoking habits and the risk of fractures. In the general population, current smokers who did not have a history of stroke had a higher risk for all types of fractures, particularly hip and vertebral fractures.[9,10] Persistent smoking is a significant risk factor for stroke and fracture, and smoking cessation can effectively reduce the risk of fractures. Considering the importance of

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CLINICAL PERSPECTIVE

What Is New?

- Initiating or maintaining smoking habits after an acute stroke significantly increases the risk of fractures, including vertebral and hip fractures, underscoring smoking's detrimental impact on bone health in survivors of stroke.
- The association between changes in smoking habits after a stroke and increased fracture risk remains significant even after adjusting for sociodemographic factors and comorbidities.

What Are the Clinical Implications?

- Integrating smoking cessation programs into poststroke rehabilitation protocols may potentially reduce fracture risks among survivors, thereby enhancing their rehabilitation outcomes and quality of life.

Nonstandard Abbreviations and Acronyms

K-NHIS	Korean National Health Insurance Service

preventing fractures after a stroke to improve the quality of life, examining the relationship between changes in smoking status and the incidence of poststroke fractures is clinically valuable. However, our knowledge of the relationship between smoking habit change and fractures after stroke remains limited.

Thus, we aimed to assess the association of smoking habit changes and the risk of fracture in patients post stroke, using a national cohort from the Korean population.

METHODS

Trial Design and Patient Selection

The Korean National Health Insurance Service (K-NHIS) has a high enrollment rate, covering 97% of the Korean population. Data collected by the K-NHIS are comprehensive and include demographics, laboratory results, *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, hospitalization status, and medication prescription status. Thus, the use of claims based on medical data represents a real-world setting.[11] Therefore, we included data from patients ≥40 years of age who were first diagnosed with acute ischemic stroke between January 1, 2010, and December 31, 2016, based on the K-NHIS database. Patients with K-NHIS data within 2 years before and after acute ischemic stroke were enrolled in the study. Acute ischemic stroke was identified in individuals hospitalized for a minimum of 4 days, diagnosed with *ICD-10* codes I63 or I64, and who underwent brain computed tomography or magnetic resonance imaging scans during their hospital stay. Patients were excluded for the following reasons: having critical missing values, incomplete questionnaires on lifestyle behaviors, being <40 years of age, or having a history of any type of fractures.

This study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (#HDT 2023-01-010). Individuals who underwent national health examinations provided written informed consent for their data to be used in this study. The anonymized data set for this study is publicly available from the Korean National Health Insurance Sharing Service and can be accessed at https://nhiss.nhis.or.kr/.

Definition of Covariates

We collected demographic data, including age, sex, body weight, height, and history of hypertension, diabetes, and dyslipidemia. Body mass index was calculated by dividing the body weight in kilograms by height in meters squared (kg/m^2). Obesity was defined as having a body mass index ≥25 kg/m^2. Systolic and diastolic blood pressure and laboratory data, including renal function tests (estimated glomerular filtration rate, calculated using the Modification of Diet in Renal Disease equation), fasting glucose, and total cholesterol, were also collected. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2. We obtained data on lifestyle behaviors, including alcohol consumption, physical activity, and smoking habits, using self-reported questionnaires. Alcohol consumption was defined as alcohol consumption of >0 g/day. Regular exercise was defined as moderate to vigorous physical activity (extreme shortness of breath for >20 minutes per session, ≥3 days per week). Low-income status was defined as being covered by the Medical Aid program for the lowest-income population or being part of the lowest 20% of the people registered in the National Health Insurance based on monthly household income. We defined hypertension as having an antihypertensive prescription with *ICD-10* codes I10-13 and I15 or a screening test with systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Individuals with *ICD-10* codes E11-14 or screening tests and fasting glucose ≥126 mg/dL were defined as having diabetes. Dyslipidemia was defined using the *ICD-10* code E78 or having total cholesterol levels ≥240 mg/dL at screening.

Smoking Habit Assessment

Study participants were grouped based on changes in their smoking status before and after the diagnosis of ischemic stroke. A structured questionnaire was used to collect information in K-NHIS data, where participants chose one response from three options: "never smokers," "ex-smokers," and "current smokers." Cumulative pack-year smoking rates were recorded. These responses were collected within 2 years before and after the index ischemic stroke. These answers were used to categorize patients into "never smokers," "former smokers," "smoking quitters (who quit smoking after stroke)," "new smokers," and "sustained smokers" (who smoked before and after stroke) groups. Never-smokers were defined as individuals who never smoked, whereas former smokers referred to those who quit smoking before the first examination and remained nonsmokers at the subsequent examination. Smoking quitters were participants who were current smokers at the first health examination but quit smoking after being diagnosed with ischemic stroke during the subsequent questionnaire. New smokers were current smokers at the second examination but had never smoked during the first examination, whereas sustained smokers persistently smoked before and after diagnosis. We collected data of smoking habit change based on this questionnaire until December 31, 2019.

Outcome Variables

The primary composite outcome was the incidence of any fracture after ischemic stroke, defined as a composite of vertebral, hip, and any fractures. The vertebral fracture was defined as individuals with *ICD-10* codes S12.0, S12.1, S12.2, S22.0, S22.1, S32.0, M48.4, or M48.5 and visited the outpatient clinic at least twice.[8,12,13] Hip fractures were defined as patients diagnosed with *ICD-10* codes S72.0, S72.1, or 72.2 and hospitalized at least once.[13–16] Other fractures were defined as those with *ICD-10* codes S42.0, S42.2, S42.3, S52.5, S52.6, S82.3, S82.5, and S82.6 and visited the outpatient clinic at least twice.[8] The secondary outcomes included each occurrence of vertebral and hip fractures. The incidences of primary and secondary outcomes were calculated by dividing the number of events by 100 person-years.

Statistical Analysis

Continuous variables are presented as means±SD or medians with interquartile ranges, and categorical variables are reported as numbers and frequencies. For the comparison of baseline characteristics, one-way analysis of variance or the Kruskal–Wallis test was used for continuous variables, and chi-square tests or Fisher's exact tests were used for continuous variables, as appropriate. The incidence rate was calculated as the number of fracture events per 1000 person-years, derived from the total number of fractures and the person-years observed in each group, categorized by changes in smoking habits.

Multivariable Cox proportional hazard regression analyses were used to estimate adjusted hazard ratios (aHRs) and 95% CIs for the association between change in smoking habit and each outcome in patients with ischemic stroke, using the never-smoker group as the reference. Three models were used for multivariable-adjusted analysis: model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, alcohol consumption status, regular physical activity, low-income level, history of diabetes, hypertension, dyslipidemia, and chronic kidney disease; and model 3 was adjusted for all factors in model 2 and pack-years (multiplying the number of cigarettes smoked per day by the number of years smoked). Time-to-event variables were constructed based on all follow-up outcomes using Kaplan–Meier estimates and compared using the log-rank test. The proportional hazards assumption was assessed graphically using a log-minus-log plot and confirmed through Schoenfeld residuals for the Cox models. The parallel nature of the log-minus-log survival curves and the random distribution of Schoenfeld residuals indicated no significant deviations from the proportionality assumption. Additionally, the statistical test for the residuals was not significant.

Subgroup analysis was performed according to sex and age (<65 or ≥65 years). Using multivariable-adjusted analysis, we analyzed the association between each specified group and the incidence of any fracture depending on changes in smoking habits. Additionally, we evaluated the association between changes in smoking habits and other subgroups, including alcohol consumption, regular physical activity, low income, diabetes, hypertension, dyslipidemia, and chronic kidney disease. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA), and all tests were 2 sided with statistical significance at $P \leq 0.05$.

RESULTS

In this study, we initially included 1 005 879 individuals with the first incidence of acute ischemic stroke between January 2010 and December 2016. Among those who did not have 2 consecutive health data points within 2 years before and after the diagnosis of stroke (n=741 240), those who had missing values (n=6855), had a smoking questionnaire error (n=29 948), were <40 years old (n=4951), and had a history of previous fractures (n=39 754) were excluded. After a washout period of 1 year, 5344 individuals were

excluded. A total of 177 787 participants remained and were enrolled in the study. All patients were stratified into groups according to smoking habit changes: 115 380 never smokers; 24 798 former smokers; 12 240 smoking quitters; 3710 new smokers; and 21 659 sustained smokers. The median follow-up period was 4.14±2.03 years, and the maximum follow-up was 8.97 years (Figure 1).

Demographic characteristics according to smoking habits are presented in Table 1. Among the participants, 49.3% were male, and the mean age was 64.16±10.52 years. The majority of the groups exhibited a male-dominant distribution, with a proportion of >85%, except never smokers. Regarding comorbidities, 63.64% of the enrolled participants had hypertension, 24.75% had diabetes, 55.33% had dyslipidemia, and 12.06% had chronic kidney disease. Sustained smokers were the youngest and had a higher rate of alcohol consumption and reported less regular exercise.

Over the median follow-up period of 4.14 years, the overall incidence rates of any fracture, vertebral fracture, and hip fracture were 8.43%, 4.24%, and 1.16%, respectively. After adjusting for all covariates, both new smokers and sustained smokers exhibited a significantly increased risk of experiencing any fracture post stroke (aHR, 1.218 [95% CI, 1.062–1.397] and aHR, 1.222 [95% CI, 1.124–1.329], respectively) compared with never smokers. In the case of vertebral fractures, sustained smokers faced a significantly higher risk (aHR, 1.27 [95% CI, 1.13–1.428]) in contrast to never smokers, whereas new smokers did not show a significant association with vertebral fractures. Regarding hip fractures, new smokers, smoking quitters, and sustained smokers all demonstrated an increased risk of incident fractures (aHR, 1.772 [95% CI, 1.291–2.431]; aHR, 1.539 [95% CI, 1.194–1.984]; aHR, 1.502, [95% CI, 1.218–1.853], respectively) compared with never smokers, as presented in Table 2. The adjusted survival curves for both primary and secondary outcomes, which reflect the HRs after adjusting for all covariates, are shown in Figure 2.

To explore if the relationship between changes in smoking habits post stroke and the incidence of fractures varied across predefined subgroups, we categorized participants by sex and age into 2 groups: those aged 40 to 64 years and those aged ≥65 years. The subgroup analysis did not demonstrate any significant differences in the occurrence of fractures based on sex and age distinctions (Table 3). Subsequent analyses were performed to explore how other clinical factors might interact with the relationship between changes in smoking habits and the incidence of poststroke fractures. These exploratory analyses suggest a potential interaction effect, where the relationship appears to vary in subgroups delineated by alcohol consumption and hypertension status (P=0.0083 for alcohol consumption and P=0.0065 for hypertension, as detailed in Table S1).

DISCUSSION

In this study, we evaluated the association between changes in smoking habits and incident fractures after stroke. The principal findings of the study were as follows: (1) sustained smokers had a consistently higher risk of any fractures, hip fractures, and vertebral

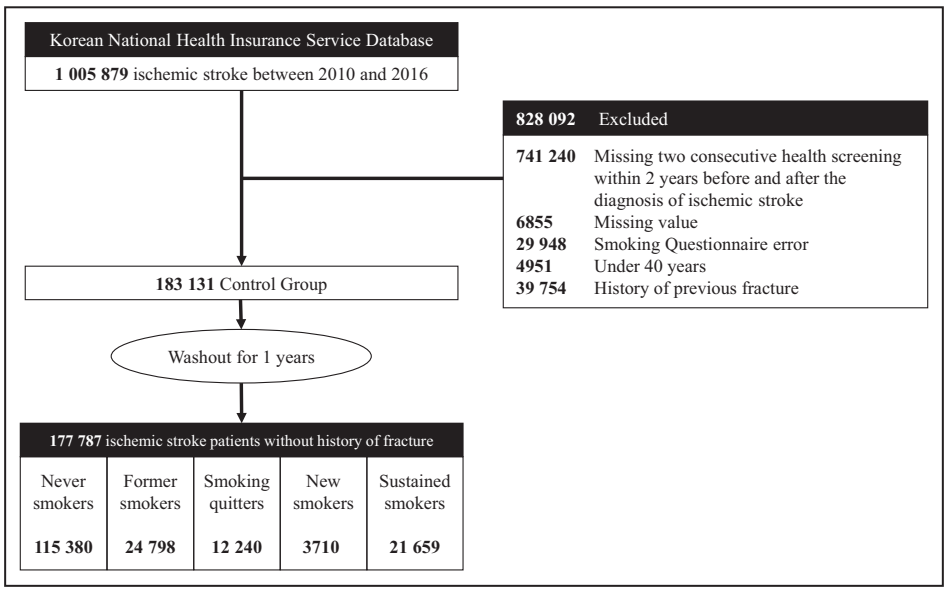

Figure 1. Flow chart of study population selection.

Table 1. Demographic and Clinical Characteristics of the Study Population According to Smoking Habit Changes

Characteristics	Total (n=177 787)	Never smokers (n=115 380)	Former smokers (n=24 798)	Smoking quitters (n=12 240)	New smokers (n=3710)	Sustained smokers (n=21 659)	*P* value
Baseline characteristics							
Male sex, n (%)	87 636 (49.29)	27 975 (24.25)	24 350 (98.19)	11 806 (96.45)	3213 (86.6)	20 292 (93.69)	<0.0001
Age of index stroke, y*	63.23±10.41	64.24±10.31	63.55±10.23	60.11±10.04	61.21±10.39	59.55±10.17	<0.0001
Age, y†	64.16±10.52	65.21±10.41	64.44±10.35	60.96±10.17	62.12±10.5	60.43±10.29	<0.0001
≥65 y, n (%)	87 668 (49.31)	61 677 (53.46)	12 679 (51.13)	4452 (36.37)	1511 (40.73)	7349 (33.93)	<0.0001
Smoking pack-y‡	8.41±15.69		21.27±17.94	28.91±20.12	19.88±16.57	24.93±16.63	<0.0001
Alcohol consumption, n (%)	45 541 (25.62)	15 467 (13.41)	11 412 (46.02)	4876 (39.84)	1910 (51.48)	11 876 (54.83)	<0.0001
Regular exercise, n (%)§	37 337 (21)	22 043 (19.1)	7398 (29.83)	3123 (25.51)	743 (20.03)	4030 (18.61)	<0.0001
Low income, n (%)	29 608 (17.08)	19 426 (17.29)	3345 (13.82)	1931 (16.18)	717 (19.83)	4189 (19.75)	<0.0001
BMI, kg/m^2	24.29±3.13	24.31±3.2	24.47±2.84	24.44±2.95	24.01±3.13	23.94±3.13	<0.0001
Obesity, BMI ≥25, n (%)	69 602 (39.15)	45 200 (39.17)	10 331 (41.66)	5056 (41.31)	1351 (36.42)	7664 (35.38)	<0.0001
Hypertension, n (%)	113 149 (63.64)	73 233 (63.47)	16 486 (66.48)	8127 (66.4)	2288 (61.67)	13 015 (60.09)	<0.0001
Diabetes, n (%)	43 995 (24.75)	26 347 (22.83)	6756 (27.24)	3521 (28.77)	1062 (28.63)	6309 (29.13)	<0.0001
Dyslipidemia, n (%)	98 372 (55.33)	62 537 (54.2)	13 955 (56.27)	8427 (68.85)	1883 (50.75)	11 570 (53.42)	<0.0001
Chronic kidney disease, n (%)	21 441 (12.06)	14 775 (12.81)	2969 (11.97)	1319 (10.78)	390 (10.51)	1988 (9.18)	<0.0001
Systolic BP, mm Hg	126.81±15.27	126.98±15.54	127.32±14.45	126.35±14.68	125.42±14.66	125.82±15.07	<0.0001
Diastolic BP, mm Hg	77.13±9.85	76.96±9.85	77.37±9.68	77.78±9.89	77.06±9.95	77.46±9.98	<0.0001
Glucose, mg/dL	105.32±28.76	103.97±27.23	106.7±27.58	108.33±31.77	108.29±34.76	108.78±34.12	<0.0001
Cholesterol, mg/dL	182.29±41.62	186±41.38	173.72±39.85	169.69±41.63	179.48±41.03	179.91±41.91	<0.0001
eGFR, mL/min per 1.73 m^2¶	84.45±43.31	83.65±35.37	84.26±56.87	85.96±55.68	86.12±49.42	87.83±53.32	<0.0001
Primary and secondary end points							
Any fracture	14 991 (8.43)	11 794 (10.22)	1177 (4.75)	581 (4.75)	238 (6.42)	1201 (5.55)	<0.0001
Vertebral fracture, n (%)	7543 (4.24)	5978 (5.18)	593 (2.39)	257 (2.1)	101 (2.72)	614 (2.83)	<0.0001
Hip fracture, n (%)	2054 (1.16)	1530 (1.33)	184 (0.74)	111 (0.91)	46 (1.24)	183 (0.84)	<0.0001

BMI indicates body mass index; BP, blood pressure; and eGFR, estimated glomerular filtration rate.
*The age when the index ischemic stroke was diagnosed.
†The age when enrolled to the study after the index stroke, the time when the individual had the health screening.
‡Smoking pack-years were calculated by multiplying the number of packs of cigarettes smoked per day and the number of years smoked.
§Regular exercise was defined as vigorous physical activity (extreme shortness of breath for >20 min per session, ≥3 days per week).
¶eGFR (mL/min per 1.73 m^2)=175×(S_{cr})$^{-1.154}$×(Age)$^{-0.203}$×(0.742 if female)×(1.212 if Black).

fractures; (2) new smokers also had a higher risk of any fractures and hip fractures after ischemic stroke, which was similar or even higher than that of sustained smokers; and (3) in the prespecified subgroup analysis, we observed interaction effects involving the status of alcohol consumption and hypertension.

Incidence of stroke was associated with an increased risk of fractures (relative risk, 2.11 [95% CI, 1.62–2.75]) in a meta-analysis of 11 relevant trials.[6] In Western countries, the occurrence of any fractures within 2 years after having a stroke was estimated to be 6.1% and 4.7% in 2 American veteran cohort studies.[17] Also, any low-trauma fractures after stroke were reported as 5.7% in the Ontario Stroke Registry.[18] The incidence of fractures 2 years after stroke between January 2011 and November 2013, based on K-NHIS data, was 8.09% for any fracture, 3.28% for vertebral fractures, and 1.86% for hip fractures.[8] Similarly, the incidence of fractures in our study was 8.43% in any fracture, 4.24% in vertebral fractures, and 1.16% in hip fractures.

One study, which included both observational studies and clinical trials, suggested that poststroke hip fractures in women can lead to 23.3% of deaths in approximately 3 years. In this study, smoking habit was not a significant predictor of poststroke fractures.[19] However, we divided the population according to more detailed changes in smoking habits. After adjusting for various sociodemographic factors and comorbidities, both sustained and new smokers were found to have a significantly higher risk of fractures. This trend was consistent for hip fractures; however, only sustained smokers showed an increased risk of vertebral fractures, a finding for which we currently lack a clinically relevant explanation. Interestingly, individuals who quit smoking showed a fracture risk similar to that of never smokers, which was notably lower than the risk observed in sustained smokers. This underscores the

Table 2. Adjusted Multivariable Analysis About the Association Between Smoking Habit Change and Fractures After Ischemic Stroke

Smoking habits	Total number	Fracture	Duration (PY)	Rate	HR (95% CI)			IR per 1000 PY (95% CI)		
					Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Any fracture										
Never smoker	115380	11794	479205.97	24.61	1 (Ref.)	1 (Ref.)	1 (Ref.)	16.11 (15.68–16.55)	16.02 (15.58–16.46)	16.28 (15.78–16.79)
Former smoker	24798	1177	100736.29	11.68	0.962 (0.895–1.035)	0.98 (0.911–1.054)	0.939 (0.865–1.020)	15.46 (14.53–16.45)	15.66 (14.72–16.67)	15.23 (14.25–16.29)
Smoking quitter	12240	581	50850.26	11.43	1.098 (1.002–1.204)	1.098 (1.001–1.204)	1.036 (0.931–1.153)	17.65 (16.23–19.2)	17.56 (16.14–19.1)	16.81 (15.32–18.44)
New smoker	3710	238	15537.22	15.32	1.252 (1.097–1.429)	1.264 (1.107–1.443)	1.218 (1.062–1.397)	20.16 (17.74–22.91)	20.25 (17.82–23.01)	19.80 (17.39–22.54)
Sustained smoker	21659	1201	89852.01	13.37	1.274 (1.188–1.366)	1.283 (1.196–1.377)	1.222 (1.124–1.329)	20.49 (19.31–21.75)	20.53 (19.34–21.8)	19.84 (18.55–21.22)
Vertebral fracture										
Never smoker	115380	5978	494468.91	12.09	1 (Ref.)	1 (Ref.)	1 (Ref.)	6.93 (6.66–7.22)	6.85 (6.57–7.13)	7.11 (6.8–7.44)
Former smoker	24798	593	102157.75	5.80	0.982 (0.887–1.087)	1.013 (0.914–1.122)	0.911 (0.810–1.024)	6.79 (6.22–7.41)	6.92 (6.33–7.55)	6.45 (5.86–7.1)
Smoking quitter	12240	257	51611.17	4.98	1.042 (0.909–1.194)	1.047 (0.914–1.201)	0.908 (0.776–1.062)	7.21 (6.36–8.18)	7.16 (6.32–8.13)	6.44 (5.6–7.39)
New smoker	3710	101	15854.7	6.37	1.108 (0.906–1.356)	1.131 (0.924–1.384)	1.032 (0.838–1.271)	7.68 (6.31–9.35)	7.74 (6.36–9.42)	7.33 (6.01–8.94)
Sustained smoker	21659	614	91323.38	6.72	1.405 (1.275–1.549)	1.43 (1.296–1.578)	1.27 (1.130–1.428)	9.73 (8.95–10.57)	9.78 (8.99–10.64)	9.01 (8.19–9.9)
Hip fracture										
Never smoker	115380	1530	506621.16	3.02	1 (Ref.)	1 (Ref.)	1 (Ref.)	1.34 (1.23–1.45)	1.25 (1.15–1.36)	1.29 (1.18–1.42)
Former smoker	24798	184	103115.79	1.78	1.027 (0.857–1.232)	1.071 (0.892–1.286)	0.972 (0.790–1.198)	1.36 (1.15–1.6)	1.33 (1.13–1.56)	1.24 (1.04–1.48)
Smoking quitter	12240	111	51996.24	2.13	1.705 (1.375–2.114)	1.754 (1.413–2.176)	1.539 (1.194–1.984)	2.26 (1.86–2.76)	2.19 (1.8–2.66)	1.98 (1.58–2.46)
New smoker	3710	46	16027.11	2.87	1.839 (1.357–2.491)	1.924 (1.419–2.609)	1.772 (1.291–2.431)	2.46 (1.83–3.31)	2.41 (1.8–3.24)	2.29 (1.7–3.09)
Sustained smoker	21659	183	92384.96	1.98	1.608 (1.347–1.921)	1.671 (1.397–1.999)	1.502 (1.218–1.853)	2.14 (1.83–2.5)	2.08 (1.78–2.44)	1.93 (1.62–2.3)

Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, alcohol consumption status, regular physical activity, low-income level, duration of diabetes and hypertension, history of dyslipidemia, chronic kidney disease; model 3 was adjusted for all factors in model 2 and pack-years (multiplying the number of packs of cigarettes smoked per day and the number of years smoked). HR indicates hazard ratio; IR, incidence rate; and PY, person-years.

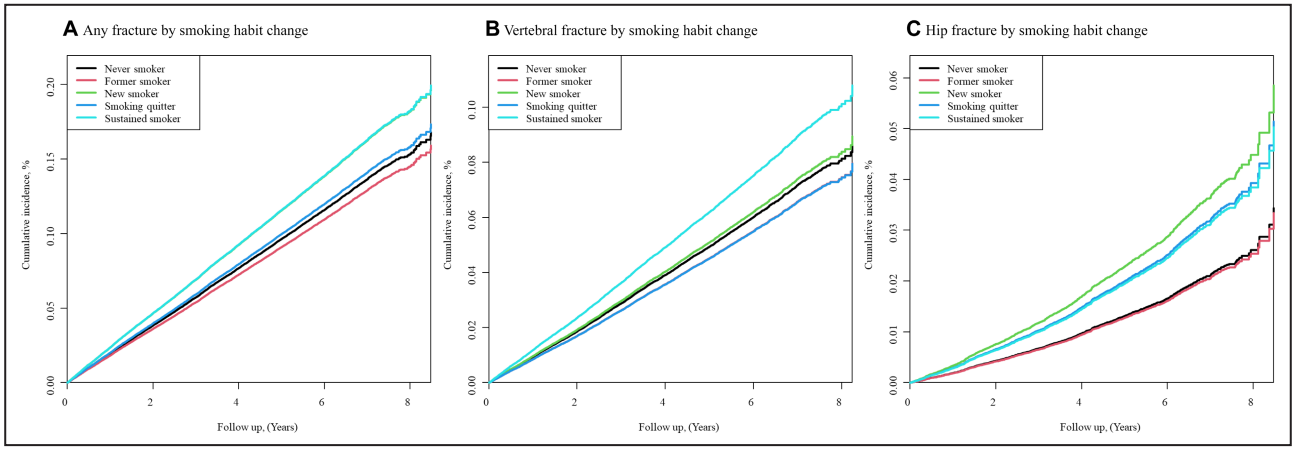

Figure 2. The adjusted survival curves for the cumulative incidence probability of fractures after ischemic stroke according to smoking habit change.
Adjusted survival curves for the primary and secondary outcomes. **A**, The cumulative incidence of any fractures after ischemic stroke according to smoking habit change. **B**, The cumulative incidence vertebral fractures after ischemic stroke according to smoking habit change. **C**, The cumulative incidence of hip fractures after ischemic stroke according to smoking habit change.

importance of smoking cessation education for poststroke survivors. Such educational efforts could significantly reduce fracture risk and potentially improve the quality of life in this vulnerable population.

Interestingly, although the incidence rate of vertebral fractures was higher than that of hip fractures, the impact of smoking—whether continued, newly initiated, or ceased—on the risk of hip fractures was significantly more pronounced. The observed differences in the effect size of smoking habits on the risk of hip and vertebral fracture underline the intricate interaction between smoking habits and bone health. Our findings suggest a detrimental impact of smoking on bone strength and integrity, particularly in areas of the skeleton that bear more weight and undergo greater mechanical stress. The differences in the risk levels for hip and vertebral fractures suggest that vertebral bones might be less susceptible to smoking's negative effects, potentially due to factors unique to each anatomical site, such as variations in bone density.,[20] mechanical loading patterns, and fall patterns among those who have had strokes.[21]

The American Heart Association/American Stroke Association guidelines highlight the importance of smoking cessation in patients with stroke to reduce the risk of future stroke and adverse cardiovascular outcomes.[22] After the first cerebrovascular event, smoking cessation reduces mortality and other adverse outcomes, but approximately two thirds persist.[23,24] In our study, the sustained smokers had significantly higher risk ratios for the incidence of any fractures, vertebral fractures, and hip fractures. In addition, new smokers had a significantly higher risk of hip fracture after stroke. These results may be clinically valuable for planning a national smoking cessation program.

Some studies have analyzed clinical risk factors for fractures after ischemic stroke. The findings from the Scottish National Hospital-based cohort study suggested that female sex and older age were significant clinical risk factors for fractures after stroke.[5] A Korean multicenter, stroke registry-based, prospective trial showed that any fractures after acute ischemic stroke were higher for older participants (age by 10-year increments; HR, 1.23 [95% CI, 1.17–1.30]), women (HR, 1.74 [95% CI, 1.54–1.97]), and those with a previous fracture (HR, 1.72 [95% CI, 1.54–1.92]).[8] In our study, those with poststroke fractures did not have significantly different risks by sex after adjusting for multiple covariates. However, the rate of fractures was higher among women who were new smokers and men who were sustained smokers. In addition, no fractures after ischemic stroke were significantly different by age group after adjustment.

In the specified subgroup analysis, the relationship between poststroke fractures and change of smoking habits was significantly different according to the presence of hypertension and alcohol consumption. In the research of the Council of the Korean Stroke Society, the population-attributable risk for stroke differed by age group; smoking was the most significant risk factor among young and middle-aged men, whereas hypertension was the most important risk factor among women.[7] However, studies evaluating poststroke fractures based on the relationship between changes in smoking habits and alcohol consumption or the presence of hypertension are limited. More specific risk factors for poststroke fractures in the Korean population require further evaluation.

This study has some limitations. First, although the K-NHIS data accurately represent the general Korean

Table 3. Adjusted Multivariable Analysis of the Association Between Smoking Habit Change and Any Fracture After Ischemic Stroke According to Sex and Age

Subgroup		Smoking habits	No.	Fractures	Duration (PY)	Rate	HR (95% CI)		
							Model 1	Model 2	Model 3
Sex	Male	Never smoker	27 975	1579	115 259.62	13.70	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Former smoker	24 350	1153	98 878.2	11.66	0.98 (0.908–1.057)	0.998 (0.925–1.078)	0.953 (0.872–1.041)
		Smoking quitter	11 806	539	49 161.98	10.96	1.104 (1.001–1.218)	1.104 (1–100.218)	1.036 (0.923–1.163)
		New smoker	3213	173	13 546.52	12.77	1.182 (1.010–1.383)	1.197 (1.022–1.401)	1.144 (0.971–1.346)
		Sustained smoker	20 292	1044	84 346.15	12.38	1.283 (1.186–1.388)	1.294 (1.195–1.401)	1.225 (1.113–1.347)
	Female	Never smoker	87 405	10 215	363 946.35	28.07	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Former smoker	448	24	1858.09	12.92	0.587 (0.394–0.877)	0.597 (0.400–0.892)	0.586 (0.392–0.875)
		Smoking quitter	434	42	1688.28	24.88	1.089 (0.804–1.475)	1.092 (0.807–1.479)	1.063 (0.784–1.442)
		New smoker	497	65	1990.7	32.65	1.505 (1.179–1.921)	1.511 (1.184–1.929)	1.481 (1.159–1.892)
		Sustained smoker	1367	157	5505.86	28.52	1.253 (1.07–1.467)	1.257 (1.073–1.472)	1.223 (1.043–1.436)
	P for interaction						0.0616	0.0645	0.0683
Age	40–64 y	Never smoker	53 703	3260	235 234.85	13.86	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Former smoker	12 119	321	52 129.59	6.16	0.898 (0.795–1.014)	0.914 (0.808–1.033)	0.884 (0.779–1.003)
		Smoking quitter	7788	251	33 298.39	7.54	1.123 (0.981–1.284)	1.119 (0.978–1.281)	1.065 (0.923–1.228)
		New smoker	2199	108	9600.79	11.25	1.466 (1.207–1.780)	1.477 (1.215–1.794)	1.430 (1.175–1.742)
		Sustained smoker	14 310	536	60 970.89	8.79	1.287 (1.166–1.420)	1.292 (1.170–1.428)	1.238 (1.112–1.379)
	≥65 y	Never smoker	61 677	8534	243 971.12	34.98	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Former smoker	12 679	856	48 606.69	17.61	0.989 (0.912–1.072)	1.007 (0.929–1.093)	0.963 (0.879–1.056)
		Smoking quitter	4452	330	17 551.87	18.80	1.083 (0.964–1.217)	1.085 (0.965–1.219)	1.020 (0.896–1.162)
		New smoker	1511	130	5936.43	21.90	1.120 (0.939–1.335)	1.132 (0.949–1.350)	1.089 (0.909–1.303)
		Sustained smoker	7349	665	28 881.12	23.03	1.268 (1.163–1.383)	1.279 (1.173–1.395)	1.216 (1.101–1.343)
	P for interaction						0.1537	0.1615	0.1668

Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, alcohol consumption status, regular physical activity, low-income level, duration of diabetes and hypertension, history of dyslipidemia, chronic kidney disease; model 3 was adjusted for all factors in model 2 and pack-years (multiplying the number of packs of cigarettes smoked per day and the number of years smoked). HR indicates hazard ratio; and PY, person-years.

population, they primarily consist of East Asian participants, especially Korean participants. Therefore, research conducted with multinational populations might produce different outcomes. Second, given that the K-NHIS database consists of claim data, discrepancies may arise between the diagnoses recorded and the actual conditions of the patients, potentially introducing bias.[25] To address potential biases arising from such discrepancies, we employed strategies such as validating key diagnoses against medical records where possible and using multivariable-adjusted analysis to control for known confounders, thereby enhancing the robustness of our findings. Third, a history of prior fractures is recognized as a significant risk factor for subsequent fractures. However, our exclusion of patients with a history of fractures means that our results may not fully represent the characteristics of a broader population of individuals with ischemic stroke. Fourth, the relatively short follow-up period of our study (4.14 years) limits our ability to fully ascertain the long-term impact of smoking status on poststroke fractures. Consequently, collecting data over a more extended period is essential to comprehensively understand this relationship.

CONCLUSIONS

We examined the association between changes in smoking habits and poststroke fractures based on K-NHIS data and demonstrated that sustained smoking has a considerable impact on increasing the risk of all types of fractures, including vertebral and hip fractures. Our findings suggested that initiating smoking after ischemic stroke was associated with a similar or even higher risk of incidence of any fractures and hip fractures. As poststroke fracture is detrimental to rehabilitation after stroke, physicians should actively advise patients to quit smoking.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

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