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Original Article

Relationship between Metabolic Syndrome and the Incidence of Stroke

Im Seok Koh [a], Jae Wook Choi [b **], Hyeongsu Kim [c *], Hai Won Yoo [c]

[a] *Department of Neurology, National Medical Center, Seoul, Korea,* [b] *Department of Preventive Medicine, College of Medicine, Korea University, Seoul, Korea,* [c] *Department of Preventive Medicine, College of Medicine, Konkuk University, Chungcheongbuk-do, Korea*

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SUMMARY

Purpose: This study aims to find out the effect of metabolic syndrome on the incidence of stroke, encompassing both cerebral hemorrhage and cerebral infarction.
Methods: The data of National Health Insurance Service in Korea were used. The study subjects (N = 6,972,909) were classified into three stages of metabolic syndrome: Normal group (having 0 metabolic syndrome factors), Pre-metabolic syndrome (Pre-MS) group (having 1–2 metabolic syndrome factors), and metabolic syndrome (MS) group (having 3–5 metabolic syndrome factors), based on their 2009 health examination results. Employing a longitudinal design, the incidence of stroke was monitored based on the claim data for health insurance from the initial screening date in 2009 until December 31, 2017. The risk of stroke by the metabolic syndrome was analyzed with Cox proportional hazard regression, adjusting for confounding factors such as age, health behaviors, family history, and laboratory values.
Results: The risk of cerebral hemorrhage in the Pre-MS and MS groups was elevated by 1.29-fold (95% CI 1.25–1.33) and 1.46-fold (95% CI 1.40–1.52), respectively, in comparison to the normal group. And the risk of cerebral infarction was amplified by 1.4-fold (95% CI 1.37–1.42) and 1.86-fold (95% CI 1.81–1.90) in the Pre-MS and MS groups, respectively, in comparison to the normal group.
Conclusions: This study establishes metabolic syndrome as a significant risk factor for both cerebral infarction and cerebral hemorrhage. Consequently, the continual implementation of preventive strategies and management of metabolic syndrome such as weight regulation, dietary adjustments, exercise modifications etc. might mitigate stroke risk.

1. Introduction

Stroke is the second leading cause of death globally and the third most significant contributor to disability. The annual economic costs imposed by stroke exceed US $721 billion, which equates to 0.66% of global GDP.[1,2] From 1990 to 2019, the incidence of stroke increased by 70.0%, accompanied by a 43.0% increase in stroke-related deaths.[2] In Korea, the prevalence of stroke among adults aged ≥ 19 years was 1.71% (690,000) in 2014 (1.9% [n = 380,000] in men and 1.52% [n = 310,000] in women).[3] A comparison of the general population to stroke patients revealed that high alcohol intake, hypertension, diabetes, and atrial fibrillation were more common in stroke patients. Hypertension accounted for 31%, and diabetes for 19%, of the stroke risk of those aged 55–74 years.[3]

Conventional stroke risk factors include hypertension, heart disease, smoking, and diabetes; but recent studies have emphasized that these factors are interconnected rather than independent. Metabolic syndrome (MS), a combination of high blood pressure, high blood glucose, and obesity, is a major risk factor for cerebrovascular diseases.[4] A recent meta-analysis found that MS patients had a 1.23-fold greater risk of all-cause mortality and a 1.24-fold higher risk of stroke than the general population.[5] However, the findings of Korean longitudinal studies of MS have been inconsistent. One cohort study performed in a general hospital found no association between MS status and stroke in men, whereas in women stroke risk was 3.96-fold higher.[6] Other smaller studies have reported varying results; further work is required to conclusively determine if there is a correlation between MS and cerebrovascular disease. In this large-scale study, we performed long-term follow-up using national health examination data and health insurance claims. We established relationships between MS and the incidences of cerebral hemorrhage and infarction, and we provide objective evidence that could shape future policies aimed preventing and managing MS.

2. Materials and methods

2.1. Study design and population

We retrospectively followed up individuals aged ≥ 30 years using "big data" of the National Health Insurance Service of Korea, i.e., general health assessments and health insurance claims. MS risk factors were identified using data from general health assessments conducted in 2009. The incidences of stroke (cerebral infarction and

* Corresponding author. Department of Preventive Medicine, College of Medicine, Konkuk University, 268 Chungwon-daero, Chungju-si, Chungcheongbuk-do, 27478, Korea.
E-mail address: mubul@kku.ac.kr (H. Kim)
** Corresponding author. Department of Preventive Medicine, College of Medicine, Korea University, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea.
E-mail address: shine@korea.ac.kr (J. W. Choi)

hemorrhage) were extracted from health insurance claims. In 2009, 15,036,607 individuals were eligible for general health checkups, and 9,927,538 were screened; these served as our primary population. The final population included individuals who met the following criteria:

(1) **Aged ≥ 30 years:** A total of 1,329,007 individuals aged < 30 years were excluded.
(2) **No missing data:** A total of 1,625,622 subjects for whom the fasting blood glucose level, systolic and diastolic blood pressure, triglyceride and/or high-density lipoprotein level(s), and/or waist circumference data were missing were excluded, along with those diagnosed with cerebrovascular disease (cerebral infarction or hemorrhage) and/or cardiovascular disease within the past 5 years.

The final study population included 6,972,909 participants, who were divided into three groups according to the number of MS risk factors. A total of 2,318,888 individuals were classified as normal (no risk factors), 3,539,111 were classified as pre-MS (1–2 risk factors), and 1,114,910 were classified as MS (3–5 risk factors) (Figure 1).

2.2. Measurements

2.2.1. Dependent variable: Stroke

Relevant events were defined as follows:

(1) **Cerebral hemorrhage:** KCD-7 diagnostic code I60, I61, or I62 entered by any medical institution during follow-up.
(2) **Cerebral infarction:** KCD-7 diagnostic code I63.

2.2.2. Observation period

The incidences of stroke and death revealed by the claims data were monitored from the initial 2009 screenings to 31 December 2017.

2.2.3. Independent variable: MS

The five MS components of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria were evaluated during the general health examinations. The diagnostic criteria are:

(1) **Waist circumference:** ≥ 90 cm in men and ≥ 85 cm in women.
(2) **Blood pressure:** systolic blood pressure ≥ 130 mmHg or diastolic pressure ≥ 85 mmHg, or use of blood pressure-lowering medications.
(3) **Triglycerides:** triglyceride level ≥ 150 mg/dL or use of drug lowering triglyceride level.
(4) **High-density lipoprotein cholesterol (HDL) cholesterol:** HDL cholesterol ≤ 40 mg/dL in men and ≤ 50 mg/dL in women.
(5) **Fasting blood glucose:** fasting blood glucose level ≥ 100 mg/dL or the use of diabetes medication or insulin injections.

Subjects who did not meet any of these criteria were categorized as normal. Those who met one or two of the criteria constituted the pre-MS group and all other subjects were assigned to the MS group.

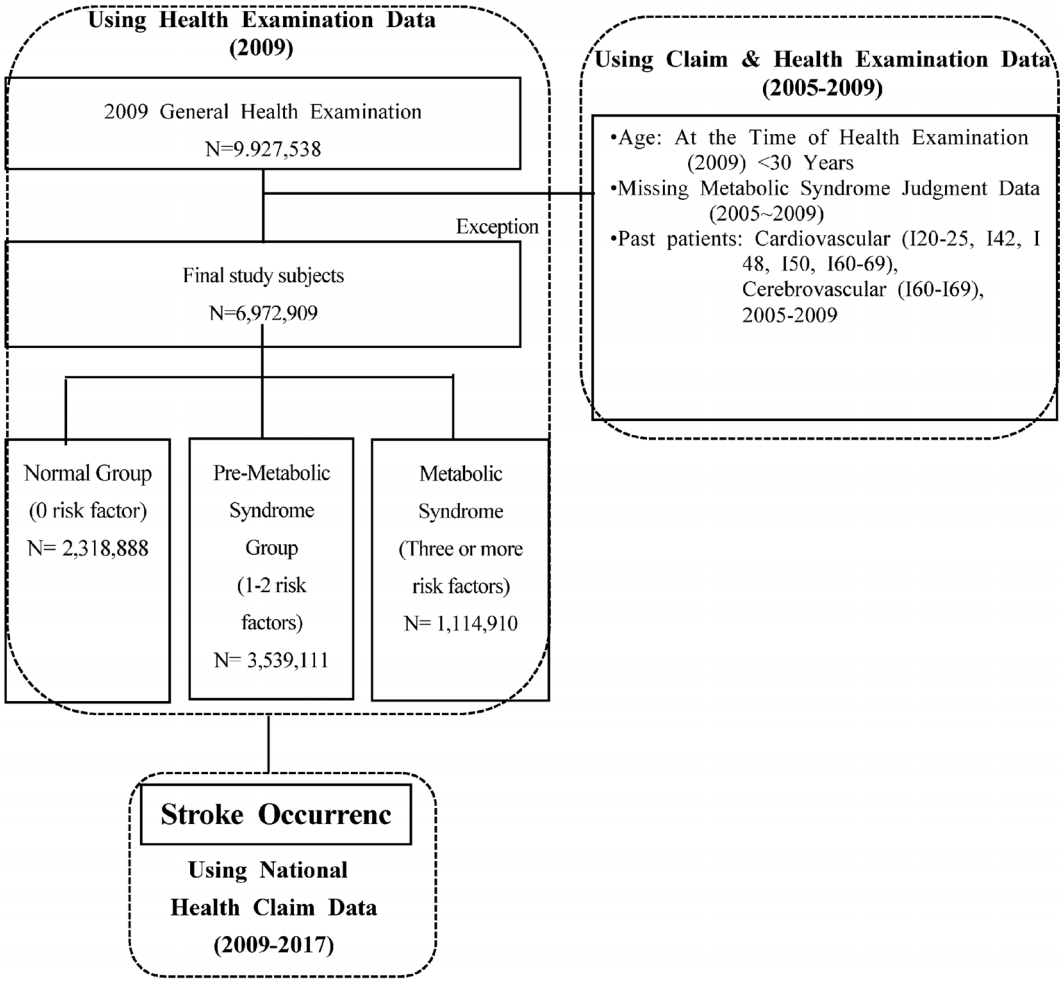

Figure 1. Study design & process of selecting population.

2.2.4. Adjusted variables: Sex, age, health behaviors, relevant family history, and laboratory data

The adjusted variables included sex, age, health behaviors, relevant family history, and laboratory data. Health behaviors included smoking, alcohol consumption, and physical activity status. Smoking status was classified as “never-smoker,” “former smoker,” or “current smoker.” Alcohol consumption was classified as “never drank,” “consume 2–3 times a month,” “consume 1–4 times a week,” or “consume > 5 times a week.” Physical activity was classified as “none,” “1–4 times a week,” or “≥ 5 times a week." Relevant family history was classified as “yes” or “no” for hypertension, diabetes, stroke, ischemic heart disease, and/or cancer. The laboratory findings included the body mass index and the hemoglobin, serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, and alanine aminotransferase (ALT) levels.

2.3. Statistical analysis

Cox proportional hazard regression was performed to calculate hazard ratios (HRs) for cerebrovascular diseases associated with MS. Three proportional hazard models were built to compare the unadjusted and adjusted risks of disease incidence.

(1) **Unadjusted:** Not adjusted for confounding variables.
(2) **Model 1:** Adjusted for gender, age, and smoking and physical activity status.
(3) **Model 2:** Adjusted for Model 1 variables plus any relevant family history.
(4) **Model 3:** Adjusted for Model 2 variables plus BMI and hemoglobin level.

The results are presented as HRs with 95% confidence intervals (CIs). p-values < 0.05 were considered statistically significant. SAS software (version 9.1; SAS Institute Inc., Cary, NC, USA) was used for all analyses.

2.4. Ethical considerations

Claims data were obtained with the approval of the National Health Insurance Service National Health Information Data Provision Review Committee (approval no. NHIS-2019-1-403). Ethical approval was granted by the Institutional Review Board of Konkuk University (approval no: 7001355-201906-E-095).

3. Results

3.1. General characteristics

The normal, pre-MS, and MS subjects accounted for 33.3%, 50.8% and 16.0% of the total (N = 6,972,909) study population, respectively (Table 1). The sex, age, health behaviors, relevant family history, and laboratory data are listed in Table 1.

Table 1
General characteristics.

Category	Normal, N (%)	Pre-MS, N (%)	MS, N (%)
Total	2,318,888 (33.3)	3,539,111 (50.8)	1,114,910 (16.0)
Age at baseline, years			
30–39	730,398 (52.3)	581,284 (41.6)	86,072 (6.2)
40–49	682,985 (35.0)	987,185 (50.6)	279,709 (14.3)
50–59	617,707 (29.0)	1,136,910 (53.4)	373,778 (17.6)
≥ 60	287,798 (19.2)	833,732 (55.7)	375,351 (25.1)
Sex			
Male	1,036,971 (25.7)	2,191,716 (54.3)	807,438 (20.1)
Female	1,281,917 (43.7)	1,347,395 (45.8)	307,472 (10.5)
Smoking status			
Non-smoker	1,518,198 (39.3)	1,866,994 (48.3)	481,649 (12.5)
Ex-smoker	234,002 (24.7)	513,530 (54.2)	200,382 (21.1)
Smoker	550,901 (26.1)	1,137,724 (53.8)	426,293 (20.2)
Alcohol consumption			
No drink	1,107,146 (36.1)	1,527,463 (43.7)	432,818 (14.1)
2–3/per month	972,427 (33.8)	1,454,847 (50.6)	450,174 (15.6)
1–4/per week	164,597 (23.0)	390,778 (54.4)	162,596 (22.7)
≥ 5/per week	41,414 (18.7)	122,993 (55.5)	57,130 (25.8)
Physical exercise, per week			
No exercise	1,080,936 (33.9)	1,605,920 (50.3)	506,633 (15.9)
1–4	481,314 (34.0)	711,353 (50.3)	222,874 (15.7)
≥ 5/per week	736,478 (31.9)	1,193,533 (51.7)	376,796 (16.3)
Family history of hypertension			
Yes	231,065 (28.0)	425,838 (51.5)	169,292 (20.5)
No	1,533,367 (34.1)	2,271,217 (50.5)	691,741 (15.4)
Family history of diabetes			
Yes	205,369 (29.1)	356,485 (50.5)	143,803 (20.4)
No	1,558,117 (33.8)	2,338,977 (50.7)	716,821 (15.5)
Family history of stroke			
Yes	114,892 (27.4)	222,867 (53.1)	82,297 (19.6)
No	1,558,117 (33.8)	2,338,977 (50.7)	716,821 (15.5)
Family history of heart disease			
Yes	79,899 (31.4)	130,462 (51.3)	44,120 (17.3)
No	1,682,016 (33.2)	2,562,410 (50.6)	815,214 (16.1)
Family history of cancer			
Yes	259,808 (36.4)	363,696 (50.9)	91,024 (12.7)
No	1,504,466 (36.9)	2,050,168 (50.3)	518,503 (12.7)

MS, metabolic syndrome; Pre-MS, pre-metabolic syndrome.

3.2. Risk of stroke with MS progression

The cerebral hemorrhage risk with MS progression from normal to pre-MS and MS is shown in Table 2. Before adjustment, the cerebral hemorrhage HRs in the pre-MS and MS groups (compared to the normal group) were 1.55 (95% CI 1.50–1.59) and 2.03 (95% CI 1.96–2.10), respectively. In Model 3, the respective HRs were 1.29 (95% CI 1.25–1.33) and 1.46 (95% CI 1.40–1.52). Table 3 details the cerebral infarction risk of the three groups. Before adjustment, the HRs of the pre-MS and MS groups (compared to the normal group) were 2.04 (95% CI 2.00–2.07) and 3.53 (95% CI 3.46–3.60), respectively. In Model 3, the HRs were 1.40 (95% CI 1.37–1.42) and 1.86 (95% CI 1.81–1.90) in the pre-MS and MS groups, respectively, compared to the normal group.

4. Discussion

We explored the effects of MS stages on the incidences of cerebral hemorrhage and infarction. Using a large dataset from the National Health Insurance Service, our retrospective analysis spanned approximately 8 years. Our findings clearly show that there is a significant association between MS progression and the risk of cerebral hemorrhage. Even after adjustment for age, health behaviors, relevant family history, and laboratory data, the pre-MS and MS cohorts exhibited 1.29-fold (95% CI 1.25–1.33) and 1.46-fold (95% CI 1.40–1.52) higher HRs than the normal group, respectively. Similarly, the risk of cerebral infarction increased as MS advanced. The pre-MS and MS groups exhibited 1.4-fold (95% CI 1.37–1.42) and 1.86-fold (95% CI 1.81–1.90) higher HRs, respectively, than the normal group.

A comprehensive review of the literature revealed that MS is a major risk factor for cardiovascular disease and ischemic stroke. Central obesity and insulin resistance are the primary causes of atherosclerotic changes in blood vessels; such alterations are key components of the above diseases.[7] Diabetes and insulin-resistance are often associated with hypertension and lipid abnormalities, further increasing susceptibility to stroke. Remarkably, hypertension alone accounts for approximately 50% of all strokes.[8] A Japanese study emphasized the preeminent role played by hypertension (an MS component) in the development of carotid atherosclerosis.[9] Although hypertension is the "least metabolic" component, it would act more powerful risk factor for stroke than other MS components. Up to 50% of hypertensive patients experience insulin resistance or hyperinsulinemia,[10] both of which induce endothelial dysfunction that culminates in vasoconstriction.[11] The endothelium, a vital regulatory barrier, protects the vasculature from damaging agents. Recent research has revealed intricate interplay between MS and various cerebral pathologies, attributable mainly to dysregulated cytokine production and chronic inflammation in adipose tissues of MS-afflicted individuals. Several inflammatory cytokines and mediators, including interleukin-6 and tumor necrosis factor-α, are well-documented drivers of vascular inflammation.[12] Given such pathological connections between MS and cerebrovascular diseases, our findings are in

Table 2
Hazardous ratio (HR) incidence rates of cerebral hemorrhage according to the progression of metabolic syndrome.

Covariates	Levels	Cerebral hemorrhage			
		HR (95% CI)			
		Non-adjusted	Model 1	Model 2	Model 3
MS stage	Normal	1	1	1	1
	Pre-MS	1.55 (1.5–1.59)	1.29 (1.25–1.33)	1.29 (1.25–1.32)	1.29 (1.25–1.33)
	MS	2.03 (1.96–2.10)	1.5 (1.45–1.56)	1.49 (1.44–1.54)	1.46 (1.40–1.52)
Sex	Female		1	1	1
	Male		0.92 (0.89–0.95)	0.93 (0.9–0.96)	0.97 (0.93–1.01)
Age	30–39		1	1	1
	40–49		1.48 (1.41–1.55)	1.47 (1.4–1.54)	1.46 (1.40–1.53)
	50–59		2.5 (2.4–2.62)	2.47 (2.36–2.58)	2.47 (2.36–2.58)
	≥ 60		3.66 (3.53–3.82)	3.6 (3.44–3.76)	3.62 (3.46–3.79)
Smoke	Non-smoker		1	1	1
	Ex-smoker		0.97 (0.93–1.01)	0.96 (0.92–1.00)	0.96 (0.92–1.00)
	Smoker		1.25 (1.21–1.29)	1.25 (1.21–1.29)	1.24 (1.20–1.29)
Exercise	No exercise		1	1	1
	1–4/per week		0.94 (0.91–0.97)	0.94 (0.91–0.97)	0.94 (0.91–0.97)
	≥ 5/per week		0.94 (0.92–0.97)	0.94 (0.91–0.96)	0.95 (0.92–0.97)
F/H of hypertension	No			1	1
	Yes			1.14 (1.11–1.18)	1.14 (1.10–1.17)
F/H of stroke	No			1	1
	Yes			1.18 (1.13–1.23)	1.18 (1.13–1.23)
F/H of heart disease	No			1	1
	Yes			0.98 (0.93–1.03)	0.98 (0.93–1.04)
F/H of diabetes	No			1	1
	Yes			0.94 (0.91–0.98)	0.94 (0.90–0.97)
BMI					1 (1.00–1.00)
Hemoglobin					0.98 (0.97–0.99)
Serum creatinine					0.97 (0.96–0.98)
Total cholesterol					1 (1.00–1.00)
LDL cholesterol					1 (1.00–1.00)
ALT (SGPT)					1 (1.00–1.00)

Values are presented as β (95% confidence interval).
ALT, alanine aminotransferase; FH, family history; MS, metabolic syndrome; Pre-MS, pre-metabolic syndrome.
Model 1 adjusted: sex, age; Model 2 adjusted: sex, age smoke, alcohol consumption, and exercise; Model 3 adjusted: sex, age smoke, alcohol consumption, exercise, FH of HP, FH of DM, FH of Stroke, FH of heart disease, and FH of CA; Model 4 adjusted: sex, age smoke, alcohol consumption, exercise, FH of HP, FH of DM, FH of Stroke, FH of Heart Disease, FH of CA, hemoglobin, serum creatinine, total cholesterol, LDL cholesterol, and ALT.

Table 3
Hazardous ratio (HR) incidence rates of cerebral infarction according to the progression of metabolic syndrome.

Covariates	Levels	Cerebral infarction			
		HR (95% CI)			
		Non-adjusted	Model 1	Model 2	Model 3
MS stage	Normal	1	1	1	1
	Pre-MS	2.04 (2.00–2.07)	1.46 (1.43–1.49)	1.45 (1.42–1.48)	1.4 (1.37–1.42)
	MS	3.53 (3.46–3.60)	2.07 (2.02–2.11)	2.03 (1.99–2.07)	1.86 (1.81–1.90)
Sex	Female		1	1	1
	Male		0.9 (0.89–0.92)	0.92 (0.90–0.94)	0.91 (0.89–0.93)
Age	30–39		1	1	1
	40–49		2.41 (2.30–2.52)	2.37 (2.27–2.48)	2.31 (2.21–2.42)
	50–59		6.86 (6.58–7.15)	6.7 (6.42–6.99)	6.55 (6.27–6.83)
	≥ 60		15.97 (15.32–16.65)	15.6 (14.97–16.27)	15.21 (14.59–15.86)
Smoke	Non-smoker		1	1	1
	Ex-smoker		0.98 (0.96–1.01)	0.97 (0.95–0.99)	0.97 (0.94–0.99)
	Smoker		1.21 (1.19–1.24)	1.21 (1.18–1.23)	1.21 (1.19–1.24)
Exercise	No exercise		1	1	1
	1–4/per week		0.92 (0.90–0.93)	0.91 (0.89–0.93)	0.91 (0.89–0.93)
	≥ 5/per week		0.9 (0.89–0.91)	0.89 (0.88–0.91)	0.89 (0.88–0.91)
F/H of hypertension	No			1	1
	Yes			1.18 (1.16–1.21)	1.18 (1.16–1.20)
F/H of stroke	No			1	1
	Yes			1.28 (1.25–1.3)	1.28 (1.25–1.30)
F/H of heart disease	No			1	1
	Yes			0.95 (0.92–0.98)	0.95 (0.92–0.98)
F/H of diabetes	No			1	1
	Yes			1.01 (0.99–1.03)	1 (0.98–1.02)
BMI					1.02 (1.02–1.02)
Hemoglobin					1.01 (1.00–1.01)
Serum creatinine					0.97 (0.97–0.98)
Total cholesterol					1 (1.00–1.00)
LDL cholesterol					1 (1.00–1.00)
ALT (SGPT)					1 (1.00–1.00)

Values are presented as β (95% confidence interval).
ALT, alanine aminotransferase; FH, family history; MS, metabolic syndrome; Pre-MS, pre-metabolic syndrome.
Model 1 adjusted: sex, age; Model 2 adjusted: sex, age smoke, alcohol consumption, and exercise; Model 3 adjusted: sex, age smoke, alcohol consumption, exercise, FH of HP, FH of DM, FH of stroke, FH of heart disease, and FH of CA; Model 4 adjusted: sex, age smoke, alcohol consumption, exercise, FH of HP, FH of DM, FH of stroke, FH of heart disease, FH of CA, hemoglobin, serum creatinine, total cholesterol, LDL cholesterol, and ALT.

line with those of previous works.

Although it is clear that the MS is the risk factor for hemorrhagic or ischemic stroke, the effect of MS on the incidence is different by sex. In this study, the incidence of cerebral hemorrhage and cerebral infarction is significantly higher in female than in male after adjustment of MS regardless of reverse prevalence of MS/preMS. The similar results were revealed in some studies. Using the US National Health and Nutrition Examination Survey, women with MS had a 2.0-fold higher risk of ischemic stroke (95% CI 1.3–3.1) while men had a 1.1-fold higher risk (95% CI 0.6–1.9).[10] The MS-stable group had the highest risk of cardiovascular disease (CVD) and coronary heart disease (CHD), compared with the MS-free group, but the associations were stronger in women than men: the HR (95% CI) were (2.76, 2.00–3.82) and (3.08, 2.15–4.40) for CVD and CHD, respectively, in women, and (1.60, 1.23–2.09) and (1.74, 1.30–2.31) for men.[13] Based on the meta-analysis, the relative risk for stroke of MS compared to MS-free in females and males was 1.83 (95% CI: 1.31–2.56) and 1.47 (95% CI: 1.22–1.78), respectively.[14] Apart from PreMS/MS, we need to pay attention female-specific risk factors for stroke such as oral contraceptive, menopausal hormone therapy, lifetime of estrogen exposure, parity, breast feeding, etc.[15]

We used data from the National Health Insurance Service to form a large cohort of cerebral infarction and hemorrhage patients. This facilitated comprehensive long-term follow-up. We derived the incidences of cerebral infarction and hemorrhage as MS progressed. Thus, we were able to derive accurate RRs; these will greatly aid future investigations on the interplay between MS and cerebrovascular diseases.

In contrast to many prior studies that ignored potential confounding variables, we meticulously adjusted for sociodemographic characteristics, relevant family history, and laboratory results; the associations between MS and the risks of both cerebral hemorrhage and infarction remained significant after adjustment.

This study had certain limitations, including the accuracy of the diagnostic codes of insurance claims used to identify cerebral hemorrhage and infarction patients. Also, we lacked clinical follow-up data; all risk factors for MS were assessed at a single timepoint. In addition, we did not use some well-known risk factors for stroke such as chronic kidney disease, atrial fibrillation, etc. Future research should incorporate longitudinal follow-up of MS risk factors and well-known risk factors to achieve a more comprehensive understanding of this complex topic.

5. Conclusion

MS was a significant predictor of cerebrovascular diseases, i.e., cerebral infarction and hemorrhage. As the burden of cerebrovascular diseases increases, particularly in the elderly, proactive intervention and meticulous management of MS components, including weight and diet, and the introduction of structured exercise rou-

tines, will play a central role in preventing cerebrovascular diseases and improving health.

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Statement of ethics

Ethics approval was obtained from the Institutional Review Board of Konkuk University.

Disclosure statement

The authors have no conflicts of interest to declare.

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