

ORIGINAL RESEARCH

Metabolic Syndrome and Risk of Moyamoya Vasculopathy and Subsequent Stroke in Young Adults

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BACKGROUND: Moyamoya vasculopathy (MMV) is a rare cerebrovascular disease of unclear cause. In this study, we aimed to determine whether metabolic syndrome (MetS) is associated with the development of MMV and subsequent stroke risk in young adults.

METHODS: Using a nationwide database, we retrospectively analyzed the data of 6 891 400 Korean adults aged 20 to 40 years who underwent health screening between 2009 and 2012. Participants were monitored until December 31, 2021, to identify patients newly diagnosed with MMV. We further examined the risk of ischemic and hemorrhagic stroke in patients newly diagnosed with MMV without prior stroke. Hazard ratios (HR) were calculated using multivariable Cox regression models adjusted for relevant confounders.

RESULTS: Over a median follow-up of 9.65 years, 1754 individuals developed MMV. These participants exhibited significantly poorer baseline metabolic profiles, including a higher body mass index and a higher prevalence of diabetes, hypertension, and dyslipidemia (all $P < 0.0001$). Metabolic syndrome was associated with a significantly increased risk of MMV development (adjusted HR, 2.94 [95% CI, 2.60–3.33]). The association between metabolic derangements and MMV risk was stronger in women. Among newly diagnosed patients with MMV, metabolic syndrome was associated with an increased risk of subsequent stroke (adjusted HR, 2.05 [95% CI, 1.25–3.37]), primarily ischemic stroke.

CONCLUSIONS: Metabolic syndrome could substantially increase the risk of MMV development and subsequent stroke events in young adults. These findings emphasize the importance of managing metabolic health to prevent MMV and related neurological outcomes.

Key Words: metabolic syndrome ■ moyamoya vasculopathy ■ stroke

Moyamoya vasculopathy (MMV) is a rare, progressive cerebrovascular disease characterized by chronic intracranial arterial stenosis and compensatory collateral vessel formation, resulting in a “puff of smoke” appearance on angiographic imaging.^{1–3} MMV is associated with serious

neurological complications, including ischemic and hemorrhagic stroke, transient ischemic attacks (TIA), and seizures.^{4–6} Epidemiological data indicate a higher prevalence of MMV in East Asian populations, particularly among female subjects, with peak incidence observed during childhood and young adulthood

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CLINICAL PERSPECTIVE

What is New?

- Metabolic syndrome is significantly associated with an increased risk of Moyamoya vasculopathy development in young adults, particularly in women.
- Among newly diagnosed young adults with Moyamoya vasculopathy, the presence of metabolic syndrome was associated with an increased risk of stroke.

What Are the Clinical Implications?

- Early screening for metabolic syndrome, a modifiable risk factor, in young adults could help identify those at risk of developing or already affected by Moyamoya vasculopathy, offering opportunities for timely intervention and prevention strategies.

Nonstandard Abbreviations and Acronyms

MetS	metabolic syndrome
MMD	Moyamoya disease
MMS	Moyamoya syndrome
MMV	Moyamoya vasculopathy
NHIS	National Health Insurance Service

(around 10 and 30 to 40 years of age, respectively), suggesting the presence of distinct pathophysiological mechanisms in these age groups.^{4,7–10} Although genetic factors, such as single-nucleotide polymorphisms in RNF213 (ring finger protein 213), have been implicated in MMV susceptibility, the precise cause remains unclear.¹¹ RNF213 is involved in lipid metabolism, fat storage, and adipogenesis pathways, suggesting a potential role for metabolic dysfunction in MMV pathogenesis.^{12–15} Metabolic syndrome (MetS), defined by central obesity, elevated blood pressure, dyslipidemia, and impaired glucose metabolism, is increasingly prevalent among young adults in East Asia. MetS is a known risk factor for endothelial dysfunction and cerebrovascular disease; however, its association with MMV is yet to be clearly defined. Given the concurrent increase in the prevalence of MMV and MetS, we hypothesized that metabolic impairment contributes to the development of MMV and influences its clinical outcomes.¹⁶ Therefore, in this study, we aimed to examine whether MetS is associated with an increased risk of MMV development and subsequent stroke in young adults.

METHODS

Data Source

This retrospective observational study used data from the Korean National Health Insurance Corporation. The National Health Insurance Service (NHIS) is a single public health insurance program in Korea. All Korean individuals aged >19 years are required to participate in the biennial health surveillance. The National Health Insurance Sharing Service can provide data to researchers upon request after the review board and data provision committee have approved their research proposals.¹⁷

The data used in this research were obtained from the National Health Insurance Data Integration Service website of the Health Insurance Corporation (<http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do>). To gain access to NHIS data, petitioners must submit completed application forms, research proposals, and institutional review board–approved documentation for review by the NHIS Research Grant Review Board.

Study Population

The institutional review board of the Catholic University of Korea approved the study (No. KC23ZISI0012). The claimed data were provided to the researchers from the Korean National Health Insurance Corporation after de-identification; hence, the institutional review board waived the informed consent requirement.

To focus on adult-onset MMV, we enrolled 6 891 400 participants aged 20 to 39 years who were engaged in national health surveillance between 2009 and 2012. Those with a history of MMV, missing data, or who could not be followed up for more than a year were excluded. All enrolled participants were followed up until December 31, 2020, to monitor the incidence of MMV and stroke events. To assess the risk of stroke in young adults with MMV, patients with a history of ischemic stroke, hemorrhagic stroke, and TIA were excluded. Patients who had experienced a stroke event at baseline were also excluded. The final cohort of 923 patients was followed up until December 31, 2020, and stroke events were examined.

Definition and Measurements

A diagnosis of MMV was established when participants fulfilled the criteria of the *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* code I67.5, and the registration application for exempted calculation of health insurance for rare, incurable diseases with code V128. To register for code V128, patients must provide radiological confirmation of cerebrovascular malformations with characteristics consistent with MMV, as detected via cerebral angiography, magnetic resonance imaging (MRI), or magnetic

resonance angiography. These characteristics include (1) stenosis or blockage in the terminal portion of the internal carotid artery or the proximal sections of the anterior or middle cerebral arteries and (2) abnormal vascular networks adjacent to the affected areas during the arterial phase.¹⁸ The term MMV includes both moyamoya disease (MMD) and moyamoya syndrome (MMS). MMS is defined by the presence of identifiable secondary causes such as autoimmune disorders, meningitis, atherosclerosis, brain tumors, Down syndrome, neurofibromatosis type 1, or cerebrovascular damage following cranial irradiation.^{3,7,19} As for defining MMD, we excluded patients with a history of conditions known to cause moyamoya-like vascular changes based on *ICD-10* codes, as used in previous study.¹⁸ MetS was defined in accordance with the National Cholesterol Education Program Adult Treatment Panel III guidelines using an adjusted waist circumference cutoff value for Koreans.^{20,21} The diagnosis of MetS was required to meet ≥ 2 of the following criteria:

- Waist circumference: male ≥ 90 cm, female ≥ 85 cm
- Blood pressure: systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or prescribed antihypertensive medications
- Glucose: fasting plasma glucose ≥ 100 mg/dL or prescribed antidiabetic drugs
- High-density lipoprotein cholesterol levels: male < 40 mg/dL, female < 50 mg/dL, or prescribed antidyslipidemia medications
- Triglyceride: < 150 mg/dL or prescribed antidyslipidemia medications

Stroke events included ischemic stroke, hemorrhagic stroke, and TIA. Ischemic stroke was defined as meeting *ICD-10* codes I63 or I64 during hospitalization, confirmed by brain imaging using computed tomography or MRI. Hemorrhagic stroke was defined as meeting *ICD-10* codes I60 through I62 during hospitalization, which was confirmed by brain computed tomography or MRI imaging. An event of TIA was defined when the patient met *ICD-10* codes (G45.8 or G45.9). Questionnaires were used to collect information regarding alcohol consumption, smoking history, exercise, and economic status. Regular exercise was defined as engaging in ≥ 3 sessions of vigorous activity for at least 20 minutes or ≥ 5 sessions of moderate activity for at least 30 minutes. Lower income was defined as an income of less than 25% of the overall population. Hypertension was defined as systolic/diastolic blood pressure $\geq 140/90$ mm Hg or at least 1 claim annually under *ICD-10* codes I10–I13 and/or I15, or at least 1 claim annually for a prescription of antihypertensive medications. A previous history of diabetes was established when participants had met relevant *ICD-10* codes (E10–E14), their fasting blood glucose level

was > 125 mg/dL, or they had a previous history of anti-diabetic drug prescription. Following an overnight fast, blood tests were performed in hospitals certified by the NHIS.

Statistical Analysis

Baseline characteristics of participants are described as numbers and frequencies (percentages). A 2-sided Student's *t* test or chi-square test (for categorical variables) was used to compare the baseline features of the group who developed MMV and the nondeveloped group. Multivariable Cox proportional hazard regression analysis was used to adjust for covariates, including age, sex, income, smoking, drinking, and regular exercise, and their interactions were analyzed. A *P*-value of < 0.05 was deemed statistically significant. To evaluate the risk of MMV with respect to MetS, multivariate-adjusted Cox proportional hazard ratios (HRs) were estimated for each MetS component. HRs were further described according to the presence or number of MetS components, and the multivariate-adjusted Cox proportional HR was estimated. For each condition, the risk of MMV was subanalyzed according to sex. To assess the risk of stroke in relation to MetS, the multivariate-adjusted Cox proportional HR was estimated in patients with newly diagnosed MMV and no history of stroke. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

Of the 6 891 400 participants, 547 with a history of MMV, 523 535 with missing values, and 2560 who could not be followed up for more than a year were excluded. Finally, 6364 758 participants were analyzed (Figure S1). The median follow-up period was 9.65 years, with an interquartile range of 8.55 to 10.24 years.

During the follow-up period, 1754 of 6364 758 participants (incidence rate of 2.94 per 100 000 person-years) were diagnosed with MMV. Participants who developed MMV were more frequently female and had a significantly higher baseline body mass index, along with higher prevalence rates of diabetes, hypertension, dyslipidemia, chronic kidney disease, and current smoking ($P < 0.0001$; Table 1).

MetS Is Associated With an Increased Risk of MMV

MetS significantly increased the risk of developing MMV, with an adjusted HR of 2.94 (95% CI, 2.60–3.33). Each MetS component (waist circumference, blood pressure, fasting glucose, triglycerides, and high-density

Table 1. Baseline Characteristics of Enrolled Population (N=6364758)

	MMV (–)	MMV (+)	P value
Number	6363004	1754	
Age, y	30.85±5	31.04±5.05	0.109
Age, y			0.0938
<30	2686916 (42.23)	706 (40.25)	
≥30	3676088 (57.77)	1048 (59.75)	
Sex, n (%)			<0.0001
Male	3778653 (59.38)	795 (45.32)	
Female	2584351 (40.62)	959 (54.68)	
Body mass index, kg/m ²	23±3.61	24.18±4.3	<0.0001
Waist circumference, cm	77.51±10.01	79.41±11.21	<0.0001
Systolic blood pressure, mmHg	117.72±13.19	125.27±15.29	<0.0001
Diastolic blood pressure, mmHg	73.77±9.46	78.14±11.1	<0.0001
Smoking, n (%)			<0.0001
Non	3487142 (54.8)	1099 (62.66)	
Ex	656737 (10.32)	169 (9.64)	
Current	2219125 (34.88)	486 (27.71)	
Drinking, n (%)			0.7395
Non	2404056 (37.78)	676 (38.54)	
Mild	3397756 (53.4)	930 (53.02)	
Heavy	561192 (8.82)	148 (8.44)	
Regular exercise, n (%)	816524 (12.83)	226 (12.88)	0.9476
Income, lowest Q1	1375613 (21.62)	390 (22.23)	0.5309
Diabetes, n (%)	123484 (1.94)	85 (4.85)	<0.0001
Hypertension, n (%)	470064 (7.39)	358 (20.41)	<0.0001
Dyslipidemia, n (%)	438473 (6.89)	196 (11.17)	<0.0001
Chronic kidney disease, n (%)	172645 (2.71)	61 (3.48)	0.0488
Estimated glomerular filtration rate, mLmin ^{−1} 1.73m ^{−2}	96.1±49.72	97.73±71.36	0.1695
Fasting glucose, mg/dL	90.88±16.65	94.26±26.61	<0.0001
Total cholesterol, mg/dL	184.54±33.82	188.21±36.56	<0.0001
Triglyceride, mg/dL	96.73 (96.69–96.78)	103.88 (100.94–106.9)	<0.0001
High-density lipoprotein cholesterol, mg/dL	57.33±21.96	56.59±20.35	0.158
Low-density lipoprotein cholesterol, mg/dL	104.65±34.42	107.51±42.87	0.0005

All data were expressed as mean±SD, median (interquartile range), median (95% CI), or n (%). Student's *t* test (continuous variables) and χ^2 test (categorical variables) were used for statistical analysis, and *P* values <0.05 was regarded as statistical significance. The baseline characteristics between patients with developed and nondeveloped MMV were compared.

MMV indicates moyamoya vasculopathy.

lipoprotein cholesterol-C) independently increased the risk of MMV (Figure 1A, Table 2, and Table S1), with elevated blood pressure exhibiting the strongest association with the MMV risk (adjusted HR, 3.59 [95% CI, 3.24–3.98]). Importantly, the risk of MMV increased significantly with an increase in the number of MetS components, particularly among women (Figure 1B).

MetS Increases the Risk of Stroke in Patients With MMV

To investigate the association between MetS and stroke risk in young adults with MMV, we analyzed the incidence and risk of stroke (including ischemic and hemorrhagic

stroke) in patients newly diagnosed with MMV. Among the 1754 individuals newly diagnosed with MMV, 923 had no prior stroke and were followed up for a median of 3.54 years. During the follow-up period, 87 stroke events occurred (incidence rate: 24.51 per 1000 person-years), including 50 ischemic and 47 hemorrhagic strokes. The presence of MetS significantly elevated the risk of stroke overall (adjusted HR, 2.05 [95% CI, 1.25–3.37]), predominantly driven by ischemic stroke events (Table 3, Figure 2). However, the relationship with hemorrhagic stroke was statistically nonsignificant.

To strengthen the validity of our findings and preclude secondary causes of MMV, we excluded patients with a history of conditions known to cause

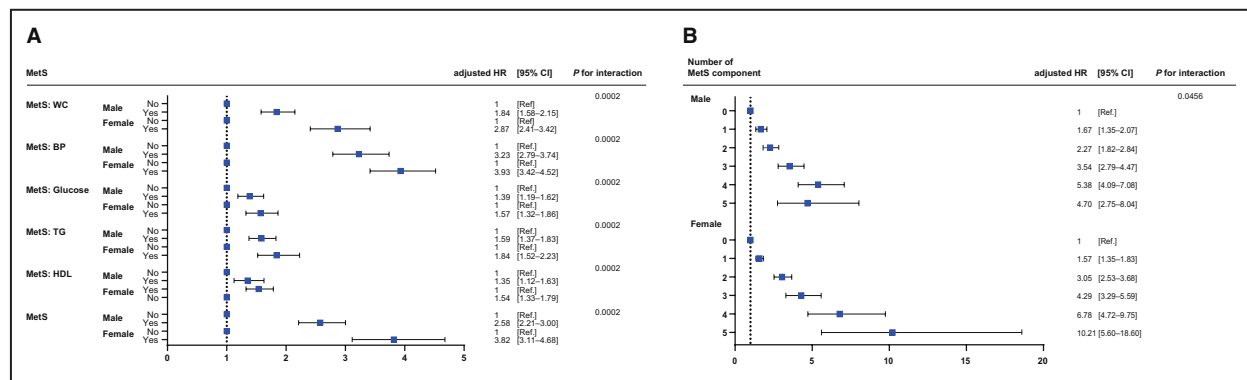


Figure 1. MetS is associated with an increased risk of MMV.

The risk of MMV development with respect to MetS and its components were calculated after adjusting for variables (age, sex, income, smoking, drinking, and regular exercise) using multivariable Cox proportional hazard regression analysis. **A**, The adjusted HR of MMV in the presence of MetS was estimated. The risk was further estimated according to each component (waist circumference, blood pressure, triglyceride, HDL) of MetS. Subgroup analysis was performed according to sex. **B**, The adjusted HRs of MMV, according to the number of MetS components, were estimated. Subgroup analysis was performed according to sex. BP indicates blood pressure; HR, hazard ratio; MetS, metabolic syndrome; MMV, moyamoya vasculopathy; TG, triglyceride; and WC, waist circumference.

moyamoya-like vascular changes. Even after applying the operational definition of MMD from previous studies, the association between MetS and MMD development remained significant (HR, 2.77 [95% CI, 2.38–3.24]; [Tables S2](#)). Likewise, the risk of stroke in patients with newly diagnosed MMD was elevated in the presence of MetS (HR, 2.41 [95% CI, 1.29–4.50], [Table S3](#)).

DISCUSSION

The objective of this study was to explore the relationship between MetS and MMV risk, focusing on the subsequent risk of stroke in patients with MMV. Our findings indicate that MetS could be an independent risk factor for MMV and, importantly, it could markedly elevate the risk of ischemic stroke in patients with newly diagnosed MMV. The risk of MMV gradually increased as the number of MetS components increased, and the presence of MetS correlated with a greater risk of both MMV and ischemic stroke. This suggests that metabolic derangements not only contribute to the development of MMV but also play a critical role in its neurological consequences, particularly ischemic stroke. To the best of our knowledge, this is the first study to clarify the relationship between MetS as a risk factor for both the development of MMV and the increased risk of stroke among patients with MMV.

In the current study, the incidence rate of MMV was 2.94 per 100,000 person-years, which is comparable to that reported in a previous epidemiological study conducted in Korea but higher than those reported in Japan, China, Taiwan, and the United States.^{9,22–25} This disparity could be attributed to differences in the

study period, genetic background, study design, or representativeness of the study population. Our study relied on data from the Korean NHIS, a single public insurance organization that mandates the registration of all Korean citizens.¹⁷ Given that all Korean citizens >19 years of age undergo biennial health screenings, we believe that our data set adequately represents the general Korean population.

The prevalence of MMV in East Asia has been steadily increasing, and this trend was similarly observed for MetS among young East Asian adults.²⁶ Given that the age of secondary peak MMV incidence correlates with the incidence of MetS, our findings suggest that the increasing prevalence of MetS may have contributed to the rising incidence of MMV.

Previous epidemiological studies have consistently reported a higher prevalence of MMV among women.^{22,27} However, the underlying factors contributing to this sex predominance have not been sufficiently clarified. Our data indicate that the detrimental effect of MetS on the risk of MMV was consistently higher among women. Therefore, our study partially explains the female predominance of MMV.

In this study, blood pressure had the highest HR (3.59 [95% CI, 3.24–3.98]) among MetS risk factors for MMV development. Blood pressure has been identified as a crucial risk factor for cerebrovascular diseases.^{28,29} In the Framingham study, hypertension was associated with a 57% increased risk of developing cerebral infarction in patients with diabetes.²⁸ The contribution of blood pressure to cerebrovascular disease has been considered especially prominent among Asians.^{30,31} We speculate that these organs and regional specificities may have contributed to the high

Table 2. Association Between MetS and MMV (N=6364758)

	No.	Event (n)	Duration (person-years)	IR (per 1000 person-years)	HR (95% CI)	Adjusted HR (95% CI)
MetS: waist circumference						
No	5531905	1373	51826611.71	0.026492	1 (Ref.)	1 (Ref.)
Yes	832853	381	7778605.38	0.048981	1.851 (1.652–2.073)	2.218 (1.972–2.496)
MetS: blood pressure						
No	4746773	951	44379430.02	0.021429	1 (Ref.)	1 (Ref.)
Yes	1617985	803	15225787.07	0.052739	2.455 (2.235–2.697)	3.591 (3.239–3.980)
MetS: glucose						
No	5257557	1369	49191019.66	0.02783	1 (Ref.)	1 (Ref.)
Yes	1107201	385	10414197.44	0.036969	1.325 (1.184–1.484)	1.468 (1.307–1.648)
MetS: triglyceride						
No	4902115	1268	45758951.18	0.02771	1 (Ref.)	1 (Ref.)
Yes	1462643	486	13846265.92	0.0351	1.260 (1.134–1.398)	1.674 (1.492–1.880)
MetS: high-density lipoprotein						
No	5425831	1385	50759077.88	0.027286	1 (Ref.)	1 (Ref.)
Yes	938927	369	8846139.22	0.041713	1.524 (1.359–1.710)	1.466 (1.305–1.646)
MetS						
No	5707469	1392	53412271.64	0.026061	1 (Ref.)	1 (Ref.)
Yes	657289	362	6192945.46	0.058454	2.236 (1.992–2.510)	2.939 (2.596–3.329)
Number of MetS components						
0	2912012	566	27117082.65	0.020872	1 (Ref.)	1 (Ref.)
1	1840046	485	17283746.76	0.028061	1.340 (1.187–1.512)	1.648 (1.457–1.864)
2	955411	341	9011442.22	0.037841	1.804 (1.577–2.063)	2.670 (2.317–3.075)
3	454638	217	4288198.03	0.050604	2.411 (2.062–2.820)	3.936 (3.330–4.653)
4	168428	119	1583967.42	0.075128	3.583 (2.940–4.366)	6.036 (4.903–7.432)
5	34223	26	320780.01	0.081052	3.870 (2.612–5.733)	6.425 (4.313–9.569)

HRs of MMV development with respect to metabolic syndrome and its components are expressed. Adjusted HR was estimated after adjusting for variables (age, sex, income, smoking, drinking, regular exercise) using multivariable Cox proportional hazard regression analysis. HR indicates hazard ratio; IR, incidence rate; MetS, metabolic syndrome; MMV, moyamoya vasculopathy.

HR of blood pressure to MMV. Likewise, a previous small retrospective study reported that hypertension was associated with unfavorable outcomes in MMV.³² Therefore, optimal management of blood pressure may be essential for patients with MMV.

Several studies have investigated the underlying causes of MMV, exploring factors such as vascular endothelial growth factor, hepatocyte growth factor, transforming growth factor β 1, basic fibroblast growth factor, mitochondrial dysfunction, and endothelial progenitor cells.^{33–38} A recent study involving 276 Chinese participants suggested an association between low high-density lipoprotein cholesterol and high body mass index with MMV development.³⁹ Additionally, a retrospective study conducted in the United States, involving 156 subjects from various ethnicities, suggested that patients with MMV presented with a high number of comorbidities, including type 2 diabetes and hypertension.⁴⁰ Our study strengthens the findings of previous studies by using a larger sample size and further delineates the risk of MMV in relation to MetS.

In the current study, we further expanded this finding by demonstrating that MetS could increase the risk of stroke.

Our results suggest the need for early detection and aggressive management of MetS components to mitigate stroke risk in this vulnerable population. MetS is composed of modifiable risk factors that can be adjusted through lifestyle modifications and pharmacological or surgical interventions.⁴¹ Therefore, future studies should explore whether improving MetS factors can prevent the development and progression of MMV.

Considering the rarity of MMV, previous research has frequently been constrained by limited sample sizes. However, our study leveraged the comprehensive health care system of Korea, enabling us to analyze a cohort of 6364758 participants with a median study period of 9.65 (interquartile range, 8.55–10.24) years. During the follow-up period, 1754 participants developed MMV. Among those newly diagnosed with MMV without a prior history of stroke ($n=923$), 87 stroke events were

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	Stroke (ischemic or hemorrhagic)				Ischemic stroke				Hemorrhagic stroke							
	No.	Event (n)	Duration (person-y)	IR (per 1000 person-y)	HR (95% CI)	Adjusted HR (95% CI)	Event (n)	Duration (person-y)	IR (per 1000 person-y)	HR (95% CI)	Adjusted HR (95% CI)	Event (n)	Duration (person-y)	IR (per 1000 person-y)	HR (95% CI)	Adjusted HR (95% CI)
MetS: waist circumference																
No	730	61	2842.69	21.4585	1 (Ref.)	1 (Ref.)	34	2930.92	11.6004	1 (Ref.)	1 (Ref.)	33	2937.21	11.2351	1 (Ref.)	1 (Ref.)
Yes	193	26	706.61	36.7952	1.663 (1.051–2.632)	1.721 (1.072–2.764)	16	733.83	21.8035	1.838 (1.015–3.331)	1.925 (1.043–3.554)	14	748.64	18.7006	1.611 (0.862–3.010)	1.715 (0.900–3.269)
MetS: blood pressure																
No	520	47	2006.21	23.4273	1 (Ref.)	1 (Ref.)	23	2074.41	11.0875	1 (Ref.)	1 (Ref.)	29	2062.6	14.0599	1 (Ref.)	1 (Ref.)
Yes	403	40	1543.1	25.9219	1.108 (0.727–1.689)	1.177 (0.748–1.852)	27	1590.34	16.9775	1.515 (0.869–2.643)	1.715 (0.945–3.113)	18	1623.25	11.0888	0.802 (0.446–1.445)	0.839 (0.447–1.575)
MetS: glucose																
No	742	64	2917.56	21.9361	1 (Ref.)	1 (Ref.)	34	3010.51	11.2938	1 (Ref.)	1 (Ref.)	36	3021.67	11.914	1 (Ref.)	1 (Ref.)
Yes	181	23	631.75	36.4071	1.577 (0.979–2.541)	1.652 (1.007–2.710)	16	654.24	24.4559	2.054 (1.133–3.725)	2.217 (1.196–4.109)	11	664.19	16.5616	1.337 (0.680–2.628)	1.355 (0.671–2.738)
MetS: triglyceride																
No	692	61	2680.82	22.7542	1 (Ref.)	1 (Ref.)	33	2772.02	11.9047	1 (Ref.)	1 (Ref.)	34	2778.84	12.2353	1 (Ref.)	1 (Ref.)
Yes	231	26	868.48	29.9374	1.293 (0.817–2.046)	1.478 (0.888–2.460)	17	892.73	19.0426	1.563 (0.871–2.806)	1.864 (0.971–3.578)	13	907.01	14.3328	1.158 (0.611–2.194)	1.380 (0.683–2.789)
MetS: high-density lipoprotein																
No	736	72	2819.94	25.5325	1 (Ref.)	1 (Ref.)	40	2926.36	13.6689	1 (Ref.)	1 (Ref.)	41	2936.7	13.9612	1 (Ref.)	1 (Ref.)
Yes	187	15	729.36	20.5659	0.811 (0.465–1.414)	0.797 (0.454–1.400)	10	738.39	13.5429	0.988 (0.494–1.975)	0.925 (0.458–1.866)	6	749.15	8.0091	0.577 (0.245–1.359)	0.565 (0.238–1.344)
MetS																
No	742	61	2875.68	21.2124	1 (Ref.)	1 (Ref.)	32	2967.96	10.7818	1 (Ref.)	1 (Ref.)	35	2973.72	11.7698	1 (Ref.)	1 (Ref.)
Yes	181	26	673.62	39.5973	1.813 (1.145–2.869)	2.048 (1.245–3.369)	18	696.79	25.8329	2.381 (1.336–4.243)	2.865 (1.527–5.373)	12	712.14	16.8507	1.428 (0.741–2.751)	1.598 (0.789–3.236)

The risk of stroke with respect MetS in patients with newly diagnosed MMV. The adjusted HRs were calculated after adjusting for variables (age, sex, income, smoking, drinking, regular exercise) using multivariable Cox proportional hazard regression analysis. HR indicates hazard ratio; IR, incidence rate (per 1000); MetS, metabolic syndrome; and MMV, moyamoya vasculopathy.

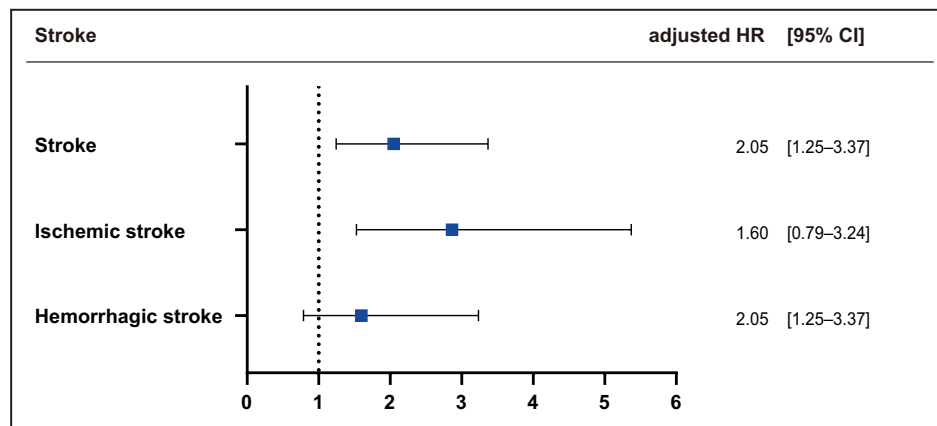


Figure 2. The risk of stroke with respect to MetS in patients with newly diagnosed MMV. The risk of stroke with respect to MetS was calculated after adjusting for variables (age, sex, income, smoking, drinking, and regular exercise) using multivariable Cox proportional hazard regression analysis. HR indicates hazard ratio; MetS, metabolic syndrome; and MMV, moyamoya vasculopathy.

analyzed over a median follow-up of 3.54 years (interquartile range, 1.12–5.52 years), facilitating a robust analysis of MMV cause and stroke outcomes. With the largest sample size of any MMV cause study conducted to date, our investigation represents a substantial advancement in understanding this rare disease and identifying its novel risk factors. The large sample size is a strength of our investigation, increasing the statistical power of our analyses and enabling us to explore potential confounding factors in greater detail.

The presence of MetS was not only associated with the development of MMV but also with an increased risk of ischemic stroke among patients newly diagnosed with MMV. Ischemic stroke is a major complication of MMV infection. Considering the cause of ischemic stroke and MMV, we speculated that the presence of MetS contributes to the progression of MMV and, consequently, to the development of ischemic stroke.^{1–3} In our data, the correlation between MetS and hemorrhagic stroke failed to reach statistical significance. This finding may have been influenced by the limited number of stroke events during the follow-up period. The study design may have affected the results. We analyzed stroke events among patients newly diagnosed with MMV, excluding those with a previous stroke event at baseline. Therefore, it is possible that severe cases, including hemorrhagic MMV at initial presentation, were excluded, and that prior surgical or medical interventions may have influenced our findings. Previously, Hirano et al. demonstrated that hypertension and dyslipidemia are associated with an increased risk of hemorrhagic stroke in patients with MMV.⁴² They further showed that the risk factors for developing ischemic and hemorrhagic stroke in patients with MMV do not significantly differ. The ICD-10 codes for TIA (G45.8 or G45.9) are frequently misused

or overapplied, particularly when ordering MRI scans. To ensure a conservative estimate of stroke events, individuals who met the operational definition of TIA at baseline were excluded. Consequently, this approach may have contributed to the underestimation of stroke events in our study. Further studies are required to clarify the relationship between MMV and hemorrhagic stroke.

Among 1754 patients with newly diagnosed MMV, we analyzed 923 patients for further evaluation of stroke after excluding 831 patients with a prior history of stroke. The relatively high number of asymptomatic MMV cases in our cohort may reflect the accessibility and affordability of MRI and magnetic resonance angiography in the Korean health care system. With this advantage, our study provides novel insights into the relationship between MMV and stroke risk in newly diagnosed asymptomatic patients.

A limited number of studies have examined the relationship between stroke risk and MMV development. Kuroda et al. reported that Grade 2 choroidal anastomosis is associated with the risk of future stroke in patients with asymptomatic MMV.⁴³ The authors enrolled 103 patients with a 5-year follow-up, during which there were 7 stroke events (1 ischemic, 6 hemorrhagic). A meta-analysis by Wei et al. suggested that previous ischemia, posterior cerebral artery involvement, and diabetes were associated with the risk of postoperative stroke.⁴⁴ The meta-analysis analyzed 8 studies encompassing 1649 patients with MMV who underwent surgery, with 177 cases of ischemic stroke and 22 cases of hemorrhagic stroke. Upon analyzing 923 patients with a median follow-up period of 3.54 years and 97 stroke events, we identified a novel modifiable risk factor associated with the development of ischemic stroke in patients newly diagnosed with MMV.

Herein, we detected a strong correlation between MetS and MMV development; however, these metabolic derangements may fail to comprehensively clarify the pathogenesis of MMV. Although MetS is more prevalent in Western countries, MMV is more prevalent among East Asians. Therefore, East Asians may have a distinctive underlying susceptibility to MMV or metabolic stress-induced MMV development. A previous genome-wide association study suggested a strong association between MMV and a single-nucleotide polymorphism in *RNF213* in East Asians; however, this genetic variance explains only a small proportion of MMV cases, and most carriers of the *RNF213* variant do not develop MMV.^{45,46} Investigating whether *RNF213* carriers are more susceptible to developing MMV under metabolic stress would be an interesting subject for further exploration.

Owing to the retrospective nature of the study design, we cannot exclude the possibility that metabolic derangements are a manifestation of genetic predisposition rather than a causative factor for MMV development. For instance, it remains unclear whether carriers of the *RNF213* p.R4810K variant are more prone to developing MetS. Nevertheless, *Rnf213* expression was induced by inflammatory cytokines, including interferon- β and tumor necrosis factor- α , in vitro.⁴⁷ Additionally, *RNF213* R4757K (an ortholog to human p.R4810K) variant knock-in transgenic mice reportedly developed cranioarteriopathy under hypoxic conditions, which was not observed under normal conditions.⁴⁸ These findings suggest that inflammatory signals combined with hypoxic conditions may trigger the development of MMV in genetically susceptible hosts. Individuals with MetS are commonly associated with increased systemic inflammation.⁴⁹ Furthermore, the presence of MetS increases the risk of ischemic stroke in patients with newly developed MMV. Therefore, we speculate that metabolic impairments are more likely to be drivers rather than manifestations of the genetic background of MMV development. However, further prospective clinical studies describing the metabolic phenotype of *RNF213* p.R4810K variant carriers and investigating whether strict metabolic control can prevent or delay MMV progression would clarify this hypothesis.

In this study, we established a diagnosis of MMV based on electronic medical record disease codes (*ICD-10* I675), radiological findings, and MMV-related symptoms. The term MMV encompasses the concepts of MMD and MMS. By definition, MMS can be diagnosed with specific secondary causes, such as autoimmune disease, meningitis, atherosclerosis, brain tumors, Down syndrome, neurofibromatosis 1, or cerebrovascular lesions after head irradiation.^{7,19} However, as we could not exclude these causal factors in our study, our definition does not distinguish between

patients with MMD and those with MMS. Therefore, we used the term MMV instead of distinguishing between MMD and MMS. In our additional analysis using the operational definition of MMD adopted in previous study, the association between MetS and stroke among patients with newly diagnosed MMV remained consistent across both subgroups: MMD (HR, 2.41 [95% CI, 1.29–4.50]) and MMS (HR, 2.20 [95% CI, 0.96–5.01]).¹⁸ However, given that MMD is often defined as a condition of unknown cause, we conservatively chose to include all patients under the broader category of MMV in our analysis.

CONCLUSIONS

In conclusion, our findings demonstrate that MetS could be an important risk factor for both the development of MMV and stroke outcomes in young adults. Specifically, MetS markedly increased the risk of ischemic stroke in patients with MMV. Further investigations are necessary to determine the potential clinical implications of our findings and explore the effectiveness of metabolic control in preventing the development and progression of MMV.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

Figure S1

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