

Differential Effect of the Metabolic Syndrome on the Incidence of Retinal Vein Occlusion in the Korean Population: A Nationwide Cohort Study

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Purpose: To investigate the impact of the metabolic syndrome (METS) on the incidence of retinal vein occlusion (RVO).

Methods: This is a retrospective cohort study using Korean National Health Insurance System data. 23,153,600 subjects without previous history of RVO underwent a National Health Screening Program examination between 2009 and 2012. They were monitored for RVO development (registration of diagnostic code for RVO) until 2015. Presence of METS was defined using the data from the National Health Screening Program examination according to the revised criteria of the National Cholesterol Education Program Adult Treatment Panel III. A multivariate adjusted Cox regression analysis was used to reveal hazard ratios and 95% confidence interval for RVO development in the presence of METS.

Results: The age of the subjects was 47.64 ± 13.51 years. In this cohort, 11,747,439 (50.7%) were male, 11,406,161 (49.3%) were female, and 6,398,071 subjects (27.6%) were diagnosed with METS. The overall incidence of RVO was 0.947 per 1000 person-years. The adjusted hazard ratio of RVO in the presence of METS was 1.458 (95% confidence interval, 1.440–1.475; $P < 0.001$) after adjusting for age, sex, smoking status, alcohol consumption, physical activity, and income. Among all of the criteria for METS diagnosis, elevated blood pressure was the greatest risk for RVO development (adjusted hazard ratio, 1.610; 95% confidence interval, 1.589–1.631; $P < 0.001$).

Conclusions: METS and each of diagnostic criteria was associated with an increased risk of RVO development. Elevated blood pressure seems to be especially important factors for RVO development.

Translational Relevance: Our results provide information about the link between METS and RVO.

Introduction

Retinal vein occlusion (RVO) is one of the most prevalent retinal vascular disease worldwide.^{1–4} RVO is regarded to be an arterial disease; retinal arterial stiffening causes compression of the retinal vein, provides hemodynamic changes, and leads to obstruction

of venous return of the retinal circulation.^{2–5} Systemic vascular diseases including arterial hypertension,^{6–8} diabetes mellitus,^{7–9} atherosclerosis, cardiovascular disease,^{10,11} and thrombophilia¹² are considered to be major risk factors for RVO occurrence.

The metabolic syndrome (METS) is a set of diseases including high blood pressure (BP), hyperglycemia, dyslipidemia, and central obesity. These metabolic

abnormalities frequently coexist, and the prevalence of METS has been continuously increasing in recent decades. METS is thought to be a distinct entity that affects a large proportion of the adult population^{13,14} and is well-known to be strongly related to the development of cerebrocardiovascular diseases.^{15,16}

Although the vascular compromises complicating METS are well-established in the literature, there are only limited reports regarding the link between METS and RVO, the main vision threatening vascular diseases in the ophthalmology.¹⁷ Furthermore, there has not been any longitudinal study of the association between METS and the development of RVO yet. Given the high prevalence of METS in developed countries, elucidating the association of METS and the risk of RVO would promote the understanding of the burden of METS on the ophthalmic field.

Therefore, we investigated the association between METS and the risk of RVO development through a nationwide, large-scale retrospective cohort study based on the Korean National Health Insurance Database from 2002 to 2015.

Methods

Study Setting

The data analyzed in this study were derived from the database of the Korean National Health Insurance Service (NHIS). The Korean NHIS is an obligatory public health insurance system that provides universal health coverage to all Koreans except for Medicaid beneficiaries in the lowest income bracket (approximately 3% of the population). Hence, the NHIS comprises a complete set of health information that covers about 51 million people in the Korean population.

The Korean NHIS offers a biennial National Health Screening Program (NHSP) to all members older than 30 years of age. The Korean NHIS collects all necessary information for the reimbursement of each medical service provided, including basic patient information, identifier for the clinic or hospital, disease code, and costs incurred.¹⁸ Patient information includes age, sex, average monthly insurance premium, and residential area (categorized as city area, metropolitan area, and rural area), as well as a completed questionnaire (past medical history, health behavior), anthropometric exam (body mass index [BMI], BP), and laboratory tests (blood sugar, cholesterol, and others).¹⁹ The Korean NHIS database has, therefore, been widely used in various epidemiological studies.²⁰ Moreover, diagnostic codes based on the Korean Standard Classi-

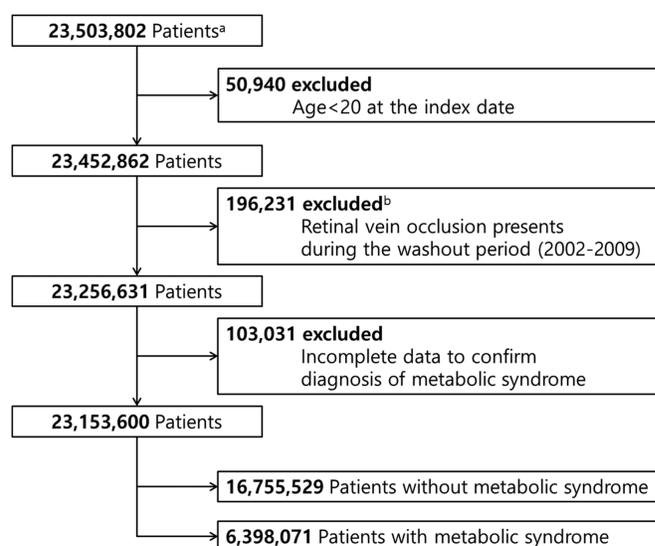


Figure 1. Flow diagram for identifying the study population for incident RVO cohort. ^aPatients who participated in the NHSP at least once in the years between 2009 and 2012. ^bPatients diagnosed with RVO (Korean Standard Classification of Diseases code H34.8 corresponding to *International Classification of Diseases-9-clinical modification* [CM] code 362.35, central RVO, or 362.36, venous tributary [branch] occlusion) during the washout period (2002–2008) were excluded.

fication of Diseases have been used in South Korea, and these are comparable to the *International Classification of Diseases*. The details of the Korean NHIS are described in previous reports.^{21,22}

Study Population

A total of 23,503,802 subjects who participated in the NHSP at least once between 2009 and 2012 were initially enrolled. Among these, 50,940 subjects who were less than 20 years old, 196,231 subjects with a diagnostic code of RVO (Korean Standard Classification of Diseases code: H34.8) during the washout period (2002–2008) and 103,031 subjects with incomplete sets of data for the assessment of METS were excluded. Hence, this study included 23,153,600 subjects who were more than 20 years old without previous history of RVO who underwent a health examination at least one time between January 1, 2009, and December 31, 2012. All subjects were monitored for development of RVO until December 31, 2015. If patients were diagnosed with RVO more than once during the monitoring period, the first visit was considered to be the RVO incident date. This date was used for statistical analyses. Eligibility criteria are summarized in [Figure 1](#).

The study adhered to the Declaration of Helsinki, and the study protocol was reviewed and approved by

the Institutional Review Board of Samsung Medical Center (SMC 2018-05-190). The board waived the requirement for informed consent as the NHIS anonymized all participants according to strict confidentiality guidelines.

Measurements and Definition of the METS and Other Risk Factors

For those who underwent health screening more than once between 2009 and 2012, the first health screening measures were used for the analysis.

BP was measured while the subject was in a seated position after 5 minutes of rest during the daytime using automated sphygmomanometer. Blood samples were collected after overnight fasting. The serum levels of glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol were measured using the enzymatic method.²³

METS was defined based on the revised criteria of the National Cholesterol Education Program Adult Treatment Panel III.²⁴ According to the guideline, three or more of the following five components constitute a diagnosis of METS: (i) elevated waist circumference (WC) (≥ 90 cm for men and ≥ 85 cm for women, according to the Korean Society for the Study of Obesity's cut-off points for central or abdominal obesity)²⁵; (ii) elevated TG level (≥ 150 mg/dL) or taking medications for hypertriglyceridemia; (iii) reduced HDL cholesterol (< 40 mg/dL in men and < 50 mg/dL in women); (iv) elevated BP (systolic BP of ≥ 130 mm Hg or diastolic BP of ≥ 85 mm Hg) or receiving antihypertensive treatment; and (v) elevated fasting glucose (≥ 100 mg/dL) or taking medications for increased glucose.²⁶

If the systolic BP was 140 mm Hg or higher or the diastolic BP was 90 mm Hg or higher, the fasting blood glucose level was 126 mg/dL or higher, or total cholesterol was 240 mg/dL or higher, subjects were considered to have hypertension, diabetes mellitus, and dyslipidemia, respectively. Additionally, if subjects were prescribed with antihypertensive, glucose-lowering, or lipid-lowering medication (correspond with ATC code C02 [antihypertensive], A10 [glucose lowering], and C10 [lipid lowering], respectively) in the year of NHSP with corresponding a diagnostic code (hypertension, I15; diabetes, E11–E14; dyslipidemia, E78), they were considered to have hypertension, diabetes mellitus, and dyslipidemia, respectively. Stroke was defined according to diagnostic codes (I63 and I64) for diagnoses made during hospitalization together with brain computed tomography or magnetic resonance imaging. Heart disease included myocardial infar-

tion (diagnostic codes I21 and I22) and heart failure (diagnostic code I50) diagnosed during hospitalization.²⁷ The presence of chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m² from serum creatinine measured by kinetic Jaffe method or end point Jaffe method.

Lifestyle variables were recorded using the NHSP questionnaire. The definition of lifestyle variables was as follows.²⁸ Smoking status was categorized into three groups: nonsmokers, current smokers who had smoked 100 cigarettes or more in their lifetime, and former smokers, who had smoked in the past but had since quit at least 1 month prior. Alcohol consumption status was categorized into three groups: nondrinker, those who drank less than 30 g/d on average and those who drank more than 30 g/d. Regular exercise was defined as strenuous physical activity that was performed for at least 30 minutes at least five times in a week. This factor was ascertained through subject questionnaires.²³ BMI was defined as the weight in kilograms divided by the square of height in meters. Subjects with income of less than the lower 20 percentile were defined to have a low income. Hospitals wherein these health examinations were performed were certified by the NHIS and subjected to regular quality control.

Statistical Analysis

Data are summarized as numbers with percentages for categorical variables, and mean values with standard deviations are used for continuous variables. Multivariate adjusted Cox regression analysis was conducted to examine RVO development hazard ratios (HR) and associated 95% confidence intervals (CIs) for risk factors of interest after adjusting for age, sex, smoking, alcohol consumption, and income level. These risk factors included the presence of METS, hypertension, diabetes, dyslipidemia, and each of the five components constituting a diagnosis of METS. Further, the HR for the number of METS components was also evaluated. A *P* value of less than 0.05 was considered statistically significant. Statistical Analysis System software version 9.4 (SAS Inc, Cary, NC) was used for all analyses.

Results

Baseline characteristics of the study population are presented in Table 1. The average age of the study subjects was 47.64 ± 13.51 years; 11,747,439 (50.7%) were male and 11,406,161 (49.3%) were female.

Table 1. Descriptive Analytics of Subjects With and Without the METS ($N = 23,153,600$)

	METS		Standardized Mean Difference
	Absent ($n = 16,755,529$)	Present ($n = 6,398,071$)	
Age (years)	44.59 ± 13.68	55.63 ± 13.04	0.82637
Age ≥65 years	1,505,273 (8.98)	1,698,718 (26.55)	0.47221
Sex (male)	8,466,519 (50.53)	3,280,920 (51.28)	0.01501
Current smoker ^a	4,202,227 (25.08)	1,493,084 (23.34)	0.04070
Alcohol consumption ^b	15,731,657 (93.89)	5,889,392 (92.05)	0.07201
Regular exercise ^c	8,502,852 (50.75)	2,982,749 (46.62)	0.08264
Low income ^d	4,532,725 (27.05)	1,652,799 (25.83)	0.02765
BMI	22.87 ± 2.92	25.82 ± 3.2	0.96586
Five diagnostic components of METS			
WC ¹	1,528,453 (9.12)	3,127,072 (48.88)	0.97457
BP ²	4,775,697 (28.5)	5,253,026 (82.1)	1.27999
Glucose ³	3,127,605 (18.67)	4,187,843 (65.45)	1.07634
TGs ⁴	2,268,748 (13.54)	4,343,588 (67.89)	1.69230
High-density lipoprotein ⁵	2,817,436 (16.81)	5,207,948 (81.4)	1.32782
HTN	2,314,216 (13.81)	3,752,103 (58.64)	1.05442
DM	527,560 (3.15)	1,610,862 (25.18)	0.66589
Dyslipidemia	1,536,237 (9.17)	2,911,475 (45.51)	0.89285
Stroke	101,008 (0.99)	128,431 (2.77)	0.13158
Heart disease	166,644 (1.63)	309,898 (6.66)	0.25468
CKD	642,171 (3.83)	634,029 (9.91)	0.24199
RVO development during study period	59,515 (0.36)	58,177 (0.91)	0.06995

Numerical continuous parameters are described as mean ± standard deviation, and categorical parameter are described as total number (percentage).

HTN, hypertension; DM, diabetes mellitus.

^aCurrent smokers are counted.

^bSubjects who regularly consume alcohol are counted.

^cRegular exercise was defined as strenuous physical activity performed for at least 30 minutes at least five times in a week.

^dSubjects with income of less than the lower 20 percentile are defined as having a low income.

¹Elevated WC (≥90 cm for men and ≥85 cm for women, according to the Korean Society for the Study of Obesity's cut-off points for central or abdominal obesity).

²Elevated BP (systolic BP ≥130 mm Hg, diastolic BP ≥85 mm Hg, or receiving antihypertensive treatment).

³Elevated fasting glucose (≥100 mg/dL) or taking medications for increased glucose.

⁴Elevated TGs level (≥150 mg/dL) or taking medications for hypertriglyceridemia.

⁵Reduced high-density lipoprotein (<40 mg/dL in men and <50 mg/dL in women).

The total number of subjects without METS was 16,755,529 and with METS was 6,398,071. Among subjects without METS, 59,515 subjects (0.36%) were diagnosed with RVO within the study period, and 58,177 subjects (0.91%) with METS developed RVO. Compared with participants without METS, those with METS were more likely to be male; over 65 years old; and have higher systolic BP and diastolic BP, blood glucose, total cholesterol, low-density lipoprotein cholesterol, and TG, and lower HDL cholesterol. Diabetes mellitus, hypertension, dyslipidemia, stroke,

heart disease, and CKD were all more prevalent in participants with METS ($P < 0.001$).

Table 2 shows the independent associations between specific components of METS and RVO. Each model includes the five syndrome components as independent variables. Multivariable Cox regression analyses adjusted for confounders were performed, and HR on RVO development and its 95% CI by METS and five syndrome components were obtained. The confounders adjusted for in each model are as follows: model 1, age and sex; model 2, age, sex, smoking

Table 2. Cox Regression Analysis on RVO Development by METS and Its Components

	HR (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
METS			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.455* (1.438–1.473)	1.458* (1.440–1.475)	1.363* (1.345–1.381)
Components of METS			
WC ¹			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.214* (1.199–1.230)	1.212* (1.197–1.227)	1.011† (0.995–1.027)
BP ²			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.612* (1.591–1.634)	1.610* (1.589–1.631)	1.532* (1.511–1.553)
Glucose ³			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.289* (1.274–1.304)	1.288* (1.273–1.303)	1.239* (1.224–1.254)
TGs ⁴			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.245* (1.230–1.259)	1.253* (1.238–1.267)	1.182* (1.168–1.197)
High-density lipoprotein ⁵			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.267* (1.252–1.282)	1.270* (1.255–1.286)	1.214* (1.199–1.229)

HRs (95% CI) were calculated using a Cox proportional hazards model.

^aAdjusted for age and sex.

^bAdjusted for age, sex, smoking status, alcohol consumption, physical activity, and income level.

^cAdjusted for age, sex, smoking status, alcohol consumption, physical activity, income level, and BMI.

¹Elevated WC (≥ 90 cm for men and ≥ 85 cm for women, according to the Korean Society for the Study of Obesity's cut-off points for central or abdominal obesity).

²Elevated BP (systolic BP ≥ 130 mm Hg, diastolic BP ≥ 85 mm Hg, or receiving antihypertensive treatment).

³Elevated fasting glucose (≥ 100 mg/dL) or taking medications for increased glucose.

⁴Elevated TGs level (≥ 150 mg/dL) or taking medications for hypertriglyceridemia.

⁵Reduced high-density lipoprotein (< 40 mg/dL in men and < 50 mg/dL in women).

* $P < 0.001$.

† $P = 0.177$.

status, alcohol consumption, physical activity, and income; and model 3, age, sex, smoking status, alcohol consumption, physical activity, income, and BMI. HRs and 95% CIs for RVO according to the presence of METS and each of the five METS criteria were calculated. All of the METS criteria were associated with a significantly increased the risk of RVO. The adjusted HRs of RVO by presence of METS were 1.455 (95% CI, 1.438–1.473; $P < 0.001$) in model 1, 1.458 (95% CI, 1.440–1.475; $P < 0.001$) in model 2, and 1.363 (95% CI, 1.345–1.381; $P < 0.001$) in model 3. For those with the WC criterion of METS fulfilled, the adjusted RVO HRs were 1.214 (95% CI, 1.199–1.230; $P < 0.001$) in model 1, 1.212 (95% CI, 1.197–1.227; $P < 0.001$) in model 2, and 1.011 (95% CI, 0.995–1.027; $P = 0.177$) in model 3. For those satisfying the BP criterion of

METS, the adjusted RVO HRs were 1.612 (95% CI, 1.591–1.634; $P < 0.001$) in model 1, 1.610 (95% CI, 1.589–1.631; $P < 0.001$) in model 2, and 1.532 (95% CI, 1.511–1.553; $P < 0.001$) in model 3. For the elevated glucose component of METS diagnosis, the adjusted RVO HRs were 1.289 (95% CI, 1.274–1.304; $P < 0.001$) in model 1, 1.288 (95% CI, 1.273–1.303; $P < 0.001$) in model 2, and 1.239 (95% CI, 1.224–1.254; $P < 0.001$) in model 3. The TG and HDL cholesterol components of METS showed similar HR increases, and these results are listed in Table 2.

The RVO incidence rate showed a dose-dependent pattern as the number of METS components satisfied increased (Table 3). The overall incidence of RVO was 0.947 per 1000 person-years. Those with no METS criteria satisfied showed an RVO incidence of

Table 3. Incidence Rate and HR of RVO According to the Number of METS Components Individuals Have

No. of METS Components	Event	Person-Years	Incidence Rate ^a	HR (95% CI)		
				Model 1 ^b	Model 2 ^c	Model 3 ^d
0	10,802	32,466,658.41	0.33	1 (Ref.)	1 (Ref.)	1 (Ref.)
1	21,852	31,927,227.21	0.68	1.450* (1.417–1.485)	1.454* (1.42–1.488)	1.429* (1.396–1.463)
2	26,861	25,530,204.28	1.05	1.755* (1.715–1.795)	1.761* (1.721–1.802)	1.704* (1.664–1.744)
3	25,850	18,153,925.23	1.42	2.001* (1.955–2.048)	2.010* (1.964–2.058)	1.922* (1.875–1.969)
4	21,350	11,324,723.38	1.89	2.248* (2.194–2.303)	2.257* (2.203–2.312)	2.136* (2.082–2.192)
5	10,977	4,751,745.48	2.31	2.375* (2.31–2.441)	2.385* (2.32–2.452)	2.221* (2.156–2.289)

^aRVO incidence per 1000 person-years.

^bHRs (95% CI) with a Cox proportional hazards model adjusted for age and sex.

^cAdjusted for age, sex, smoking status, alcohol consumption, physical activity, and income level.

^dAdjusted for age, sex, smoking status, alcohol consumption, physical activity, income level, and BMI.

* $P < 0.001$.

0.33 per 1000 person-years, whereas those who met all five criteria showed a RVO incidence rate of 2.31 per 1000 person-years. Figure 2 demonstrates the HRs of RVO occurrence by every combination of METS diagnostic criteria after adjusting confounders using model 3. The combination of BP and WC criteria fulfillment increased the risk of RVO; the HR was 2.005 (95% CI, 1.933–2.080; $P < 0.001$). BP and HDL cholesterol criteria fulfillment also increased the risk of RVO; the HR was 2.015 (95% CI, 1.938–2.094; $P < 0.001$). Other details are presented in Figure 2.

Additional subgroup HR analyses for RVO development and METS were performed and are presented in Figure 3 (model 3). Subjects were grouped by age, sex, smoking, alcohol consumption, amount of physical activity, income level, and history of CKD, stroke, and heart diseases. For subjects below the age of 65, the presence of METS increased the risk of RVO occurrence significantly compared with those over the age of 65 (HR, 1.443 for age <65 years, 1.161 for age ≥65 years; P for interaction < 0.0001). METS increased the risk of RVO development greater in the smoking subgroup than in the nonsmoking subgroup (HR, 1.500 for current smoker, 1.344 for nonsmoker and past smoker, P for interaction < 0.0001) and in the CKD subgroup than the non-CKD subgroup (HR, 1.468 for CKD patients, 1.344 for non-CKD patients, P for interaction < 0.0001). Other variables did not show significant differences.

To evaluate the effect of METS itself, excluding hypertension and diabetes, the associations between METS components and RVO were analyzed after excluding those who have hypertension or diabetes at the baseline (Table 4). Even after excluding subjects with hypertension or diabetes, METS did increase the risk of RVO occurrence.

Discussion

This nationwide population-based study demonstrates that METS and each of its diagnostic criteria increase the risk of RVO occurrence. Our team previously reported that lower HDL cholesterol level is associated with a greater risk of RVO using the claims data from NHIS.²⁷ The previous study focused only on HDL cholesterol and measured RVO risk adjusting all other variables including HTN, DM, and dyslipidemia. In addition to the previous findings, the present study further focused on METS and each five components and revealed the association with RVO development. Previous reports in the literature regarding the association of METS and RVO defined METS as a combination of hypertension, diabetes, and dyslipidemia, which is a lot different from the widely accepted METS definition.^{17,29} In this point, our study is the first report to show an association between METS and RVO with a proper METS definition. We also analyzed the risk of RVO development associated with the number of METS diagnostic components satisfied and found that the BP criterion was the most important for RVO development. In addition, we investigated the impact of METS on various subgroups and compared the outcomes. Therefore, the current study may provide information in establishing effective and tailored treatment strategies.

The National Cholesterol Education Program's Adult Treatment Panel III report defined METS as a specific entity that requires more clinical attention.³⁰ Previous clinical studies showed that microvascular diseases, including RVO, may be an integral component of METS.^{31–33} These studies said the change of the microcirculation in the aspect of structure and function

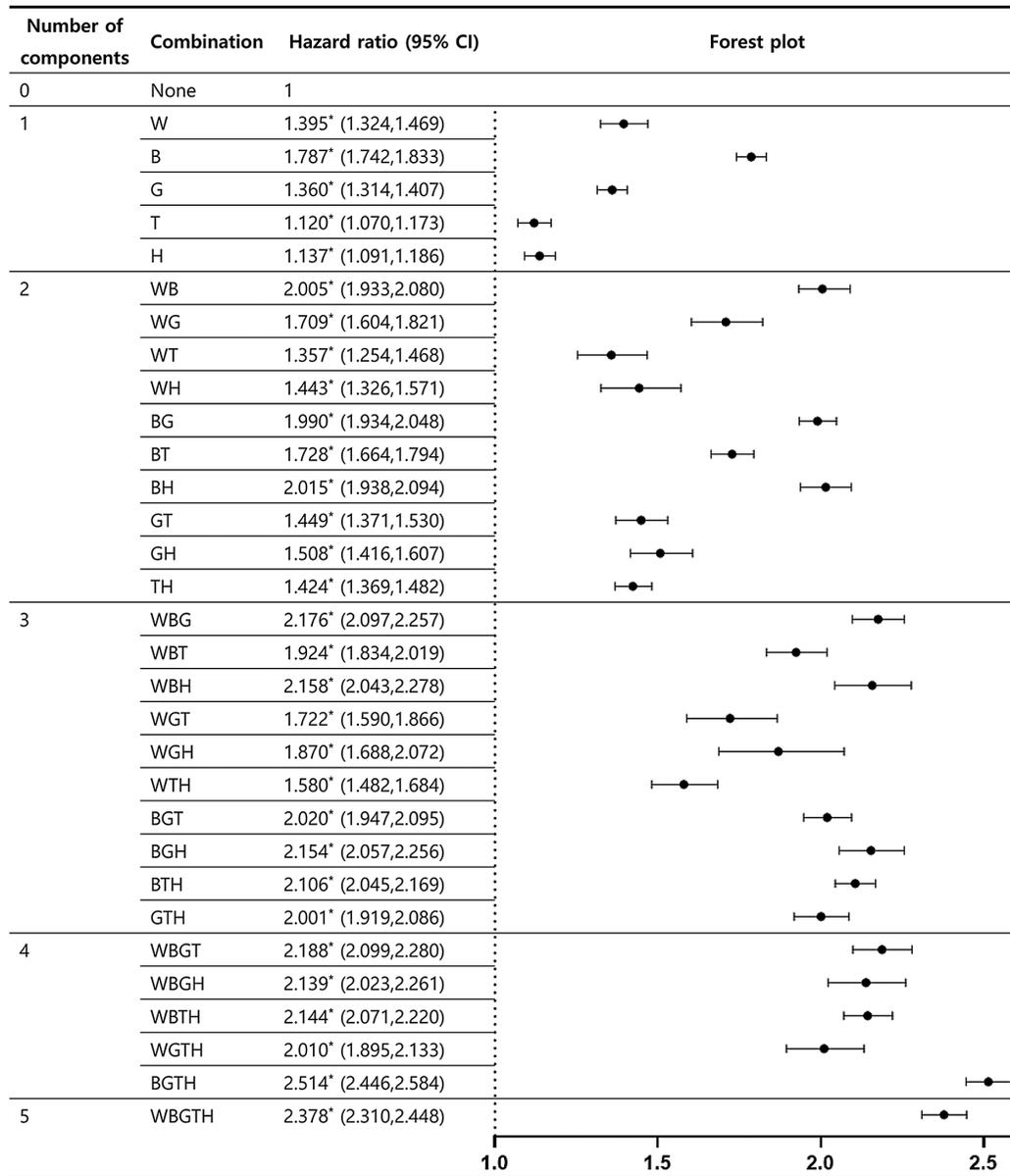


Figure 2. HR for RVO occurrence by combinations of METS diagnostic criteria. HRs with 95% CI were calculated using a Cox proportional hazards model adjusting age, sex, smoking status, alcohol consumption, physical activity, income, and BMI. * $P < 0.0001$. W, elevated WC (≥ 90 cm for men and ≥ 85 cm for women, according to the Korean Society for the Study of Obesity’s cut-off points for central or abdominal obesity); B, elevated BP (systolic BP of ≥ 130 mm Hg, diastolic BP of ≥ 85 mm Hg, or receiving antihypertensive treatment); G, Elevated fasting glucose (≥ 100 mg/dL) or taking medications for increased glucose; T, elevated TG level (≥ 150 mg/dL) or taking medications for hypertriglyceridemia; H, reduced high-density lipoprotein (< 40 mg/dL in men and < 50 mg/dL in women).

in the skin and skeletal muscles in METS patients^{31–33} or with specific components of METS, such as abdominal obesity,³⁴ diabetes mellitus,³⁵ dyslipidemia, and hypertension.^{33,36,37} These findings support our results that the presence of METS increases the risk of RVO and that the presence of each of the five METS diagnostic components is independently associated with an increased risk of RVO. This finding suggests

the importance of the impact of each component on microvascular diseases, including RVO.

Interestingly, among the five diagnostic components, the impact of the BP criterion on RVO occurrence was particularly significant. A possible explanation for the greater impact of high BP on RVO occurrence in our study is that high BP directly induces shear-related injury to the vasculature and promotes

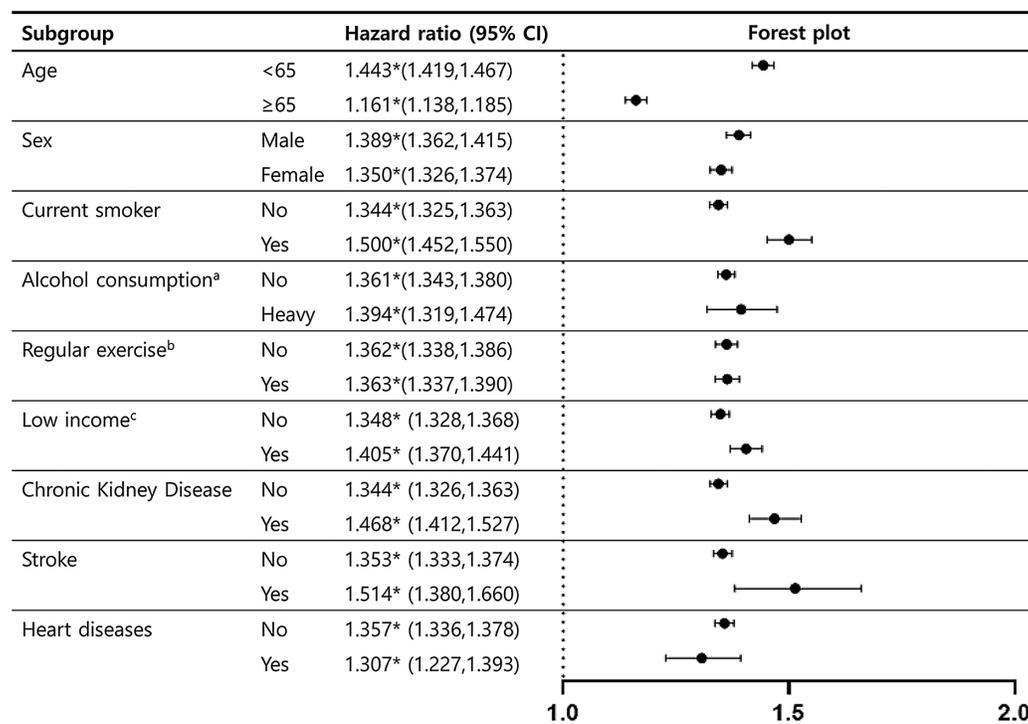


Figure 3. HR of RVO occurrence by presence of METS in various subgroups. HRs with 95% CI were calculated using a Cox proportional hazards model adjusting age, sex, smoking status, alcohol consumption, physical activity, income, and BMI. * $P < 0.0001$. ^aHeavy drinkers were defined as those who drank more than 30 g/d. ^bRegular exercise was defined as strenuous physical activity that was performed for at least 30 minutes for at least five times in a week. ^cSubjects with an income of less than the lower 20th percentile were defined to have a low income.

vascular cell proliferation,³⁸ whereas the other factors only indirectly damage arteries by modifying insulin sensitivity, lipid metabolism, and molecular susceptibility to lipid accumulation.^{39,40} Controlling BP is particularly important for prevention of RVO. Moreover, as shown in Figure 2, the HRs for the combination of BP and WC criteria and the combination of BP and HDL cholesterol criteria were more than 2.000. Because three criteria need to be fulfilled, these combinations are not sufficient for a METS diagnosis. However, the impact of these combinations on RVO development is comparable with that of METS. Hence, controlling those combinations of factors is of clinical importance.

The subgroup analysis for the impact of METS on RVO occurrence (Fig. 3) has revealed that METS has greater impact on younger subjects (age <65 years) and on subjects who smoke. Similar to the results of our study, there are many studies that demonstrate the lesser impact of METS on older patients.^{41–43} They reported that a lesser degree of risk of cardiovascular diseases in older participants with METS and suggested that METS in young participants may be different from that in older participants with different

prognostic and treatment implications, although the exact mechanism is unclear and requires further investigation.⁴² Also, many studies reported that the combination of smoking and METS markedly increases risk of cardiovascular disease beyond that of either condition that concord with our study.⁴⁴ Our results suggest that clinicians should pay extra attention to those who are young and smoking and thoroughly control METS components to decrease the risk of RVO.

A large proportion of the subjects with METS were diabetic and hypertensive in the current study. Because the risk of RVO occurrence should be high enough if the risk is defined by those who have diabetes or hypertension, the investigators wanted to evaluate the relationship between METS itself (which has not been advanced to hypertension or diabetes yet) and RVO. Table 4 demonstrates that, even after excluding hypertension and diabetes, METS was associated with increased the risk of RVO occurrence. In addition, the increased BP and glucose level were associated with increased risk of RVO, meaning that the prehypertension and the impaired fasting glucose increases the risk of RVO.

Table 4. Cox Regression Analysis on RVO Development by METS and Its Components for Those Without Hypertension or Diabetes Mellitus

	HR (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
METS			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.258* (1.231–1.285)	1.261* (1.234–1.289)	1.137* (1.111–1.163)
Components of METS			
WC ¹			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.210* (1.184–1.238)	1.209* (1.182–1.236)	0.984 [†] (0.958–1.011)
BP ²			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.299* (1.274–1.325)	1.298* (1.273–1.323)	1.247* (1.223–1.272)
Glucose ³			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.076* (1.054–1.098)	1.075* (1.053–1.097)	1.040* (1.019–1.062)
TGs ⁴			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.135* (1.114–1.157)	1.144* (1.122–1.166)	1.074* (1.053–1.095)
High-density lipoprotein ⁵			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.134* (1.112–1.157)	1.139* (1.117–1.162)	1.090* (1.068–1.112)

HRs (95% CI) were calculated using a Cox proportional hazards model.

^aAdjusted for age and sex.

^bAdjusted for age, sex, smoking status, alcohol consumption, physical activity, and income level.

^cAdjusted for age, sex, smoking status, alcohol consumption, physical activity, income level, and BMI.

¹Elevated WC (≥ 90 cm for men and ≥ 85 cm for women, according to the Korean Society for the Study of Obesity's cut-off points for central or abdominal obesity).

²Elevated BP (systolic BP ≥ 130 mm Hg, diastolic BP ≥ 85 mm Hg, or receiving antihypertensive treatment).

³Elevated fasting glucose (≥ 100 mg/dL) or taking medications for increased glucose.

⁴Elevated TGs level (≥ 150 mg/dL) or taking medications for hypertriglyceridemia.

⁵Reduced high-density lipoprotein (< 40 mg/dL in men and < 50 mg/dL in women).

* $P < 0.001$.

[†] $P = 0.253$.

The strengths of the present study include the long study period, large samples, and availability of sufficient clinical information to enable standardized identification of METS. The current study was representative of the entire Korean population; our data included 23,153,600 subjects, approximately one-half of that population. Also, the data included information between 2002 and 2015, and this scope enabled the current study to establish a washout period of 7 years to exclude patients who were previously diagnosed with RVO. The long washout period decreased the innate limitation of claims data-based epidemiologic studies by maximizing the identification of only true incident cases. In addition, our data included not only diagnostic codes, but also detailed clinical, information includ-

ing income, health behavior, BP, WC, BMI, and laboratory tests that enabled reliable METS verification.

Our study had several limitations. First, RVO patients were identified by claims data from health care use, and this factor means we might have missed patients with asymptomatic RVO or those who were unable to access the health care system. Therefore, the RVO cases in our study should be regarded as clinically diagnosed RVO cases. Second, we were not able to confirm the RVO and METS diagnosis by reviewing the medical records. RVO diagnoses based on Korean Standard Classification of Diseases codes might be less accurate than the diagnoses confirmed from a medical record with fundus descriptions and images. Therefore, there is a chance that subjects without actual RVO

development are regarded as RVO cases in the present study. Nevertheless, registration of the diagnostic codes is made by expert ophthalmologists, and the ability to diagnose RVO has improved by technological advances in ocular imaging. In addition, in the cases of METS, the diagnosis was made accurately based on the examination data, and additionally medication code, thereby decreasing the concern about inaccuracy. Therefore, we believe that the current study provides a reliable diagnosis of RVO and METS. Third, we could not evaluate the type, severity, or extent of RVO. There is currently no specific code separating central RVO and branched RVO or representing the extent and severity of the disease. Further studies investigating these facets of RVO are required. Last, we were unable to address more detailed socioeconomic markers, such as residential area or inflammatory markers like C-reactive protein or white blood cell counts. Providing this information would have resulted in better study, and future research elucidating this point should be warranted.

In conclusion, we herein report a nationwide, population-based cohort study in South Korea highlighting the impact of METS on RVO development. We demonstrated that the components of METS contribute additively to the risk of RVO, and elevated BP significantly affects development of RVO. We also suggest that METS control should be more strongly emphasized for the younger population and for smokers to prevent RVO. This study would offer a better understanding on pathophysiology of RVO and offer insight into establishing effective clinical management of METS and RVO.

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Tae-Young Chung designed the study. Dong Hui Lim, Kyoung Yoon Shin, and Kyungdo Han analyzed and interpreted the clinical data. Dong Hui Lim and Kyoung Yoon Shin wrote the final paper. Se Woong Kang, Don-Il Ham, Sang Jin Kim, Tae-Young Chung, and Yong Gyu Park reviewed the design, the results, and the final paper. Dong Hui Lim and Kyoung

Yoon Shin equally contributed to the manuscript as the first author. Tae-Young Chung contributed to the manuscript as the corresponding author. All authors read and approved the final manuscript.

Data Availability: The data used in the present study are prohibited from being shared. The raw data used in this study can be accessed at the request of qualified investigator through the Korea National Health Insurance system.

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