

Traditional and Novel Cardiovascular Risk Factors for Retinal Vein Occlusion: The Multiethnic Study of Atherosclerosis

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PURPOSE. To describe the prevalence of retinal vein occlusion (RVO) and its association with cardiovascular, inflammatory, and hematologic risk factors in a multiethnic cohort.

METHODS. This was a population-based, cross-sectional study of 6147 participants (whites, blacks, Hispanics, Chinese) from six U.S. communities. RVO was defined from retinal photographs taken from both eyes according to a standardized protocol. Risk factors were assessed from interviews, examinations, and laboratory and radiologic investigations.

RESULTS. The prevalence of RVO was 1.1% (0.9% for branch RVO and 0.2% for central RVO) and was similar across different ethnic groups: 0.9% in whites, 1.2% in blacks, 1.2% in Hispanics, and 1.1% in Chinese ($P = 0.76$). Independent risk factors associated with RVO were hypertension (odds ratio [OR], 2.06; 95% confidence interval [CI], 1.18–3.59), older age (OR, 1.34; 95% CI, 1.00–1.81, per decade increase), less education (OR, 4.08; 95% CI, 2.20–7.54), hypertriglyceridemia (OR, 1.98; 95% CI, 1.10–3.56), renal dysfunction (OR, 1.85; 95% CI, 1.01–3.39), and the presence of retinal arteriovenous nicking (OR, 4.01; 95% CI, 2.06–7.81) and focal arteriolar narrowing (OR, 4.38; 95% CI, 1.44–13.34). RVO was not significantly associated with direct measures of subclinical atherosclerosis (e.g., carotid intima media thickness and coronary artery calcium scores) or markers of inflammation (e.g., C reactive protein, interleukin-6) and endothelial dysfunction (e.g., soluble intercellular adhesion molecule-1) or coagulation (e.g., D-dimer).

CONCLUSIONS. The prevalence of RVO is similar across different racial/ethnic groups. In the general population, RVO is associated with hypertension, dyslipidemia, and renal dysfunction,

but not with atherosclerotic disease, systemic inflammation, and hematologic abnormalities. (*Invest Ophthalmol Vis Sci* 2008;49:4297–4302) DOI:10.1167/iovs.08-1826

Retinal vein occlusion (RVO), including central and branch RVO, is a sight-threatening condition that most commonly affects middle-aged to older people. There are limited population-based studies on the epidemiology of RVO, with reported prevalence rates ranging from 0.3% to 1.6%.^{1–4} The variability in prevalence rates may be due in part to racial/ethnic differences in study populations. Indeed, racial/ethnic variations in the prevalence of other major retinal diseases, such as age-related macular degeneration and diabetic retinopathy, are well recognized,^{5,6} but ethnicity-specific prevalence data on RVO are lacking.

Although RVO has been associated with a variety of cardiovascular risk factors, its pathogenesis remains incompletely understood. Previous studies indicate that hypertension and related hypertensive retinal arteriolar changes (e.g., arteriovenous nicking) are the strongest and most consistent risk factors for RVO.^{1–3,7} Studies have found less consistent relationships with other cardiovascular risk factors, such as smoking, diabetes, obesity, hyperhomocysteinemia, and dyslipidemia.^{1,2,8} Furthermore, few studies have examined whether novel cardiovascular risk factors, such as biomarkers of inflammation (e.g., C-reactive protein), endothelial dysfunction (e.g., soluble intercellular adhesion molecule-1), and direct measures of subclinical systemic atherosclerosis (e.g., carotid artery disease), are also major risk factors for RVO in the general population.

The purposes of this study were to describe the prevalence of RVO in a multiethnic population-based cohort of whites, blacks, Hispanics, and Chinese and to examine the associations of RVO with a range of traditional (e.g., blood pressure, diabetes, lipids, cigarette smoking) and novel (e.g., inflammation, hematologic, endothelial dysfunction, and subclinical atherosclerosis) cardiovascular risk factors.

METHODS

Study Population

The Multiethnic Study of Atherosclerosis (MESA) is a prospective cohort study of men and women aged 45 to 84 years without a history of clinical cardiovascular disease, sampled from six U.S. communities.⁹ In brief, there were 6814 participants at the first examination (July 2000–August 2002). Of these, 6176 returned for the second examination and had retinal photographs taken (August 2002–January 2004).^{5,10,11} There were 29 participants with ungradable photographs of both eyes, mostly due to media opacities from cataract. These participants were excluded, leaving 6147 for analysis.

The tenets of the Declaration of Helsinki were observed, and institutional review board approval was granted at each study site. Written informed consent was obtained from each participant. All procedures followed were in accordance with institutional guidelines.

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Retinal Photography

Fundus photography was performed at each site using a standardized protocol.^{5,10-12} Participants were seated in a darkened room, and both eyes were photographed with a 45° digital nonmydriatic camera. Two photographic fields (optic disc and macula centered) were taken in both eyes. All images were evaluated by trained graders masked to participants' characteristics at the Fundus Photograph Reading Center at the University of Wisconsin, Madison. The presence or absence of either central or branch RVO was defined according to a standardized protocol from the Beaver Dam Eye Study.^{1,2} Recent central RVO was characterized by retinal edema, optic disc hyperemia or edema, scattered superficial and deep retinal hemorrhages, and venous dilation. Old central RVOs were characterized by occluded and sheathed retinal veins or vascular anastomosis at the optic disc. Branch RVOs involved a more localized area of the retina in the sector of the obstructed venule and were characterized by scattered superficial and deep retinal hemorrhages, venous dilation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. All cases of RVOs were adjudicated by a retinal specialist (RK). The presence of any RVO was defined as the presence of branch or central RVO in either eye.

Retinal arteriovenous nicking and focal arteriolar narrowing were also graded from retinal photographs, according to a standardized protocol.¹³ Retinal vascular caliber was measured by using a computer-based program based on a detailed protocol described elsewhere.¹⁰⁻¹⁵ Reproducibility of retinal measurements has been reported, with intra- and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99.¹⁰⁻¹⁵ Retinal vascular caliber was measured in one eye. Other qualitative retinal signs (e.g., arteriovenous nicking and focal arteriolar narrowing) were graded in both eyes.

Assessments and Definitions of Cardiovascular Risk Factors

Participants underwent a detailed and comprehensive interview, clinical examination, and laboratory investigation for the assessment of cardiovascular risk factors, as described in detail in previous publications.^{9-11,14} Variables for this analysis were based on data collected at the second examination, unless not available, in which case, data from the baseline examination were used. Resting blood pressure was measured by using a standardized protocol, and hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/L (126 mg/dL) or use of insulin or oral hypoglycemic medication. Body mass index was categorized as normal or overweight (grade 1, 2, or 3) according to the World Health Organization definitions. A detailed questionnaire was used to obtain information about education levels, medical history (e.g., hypertension, diabetes), cigarette smoking, alcohol consumption, and medication use (e.g., oral steroids, aspirin).

Fasting (>8 hours) blood samples were drawn from participants and analyzed for all the blood factors examined in this study by use of standardized protocols.^{14,16} Hypertriglyceridemia was defined as a triglyceride level of ≥ 200 mg/dL. Hypercholesterolemia was defined as total cholesterol > 240 mg/dL. Hyperhomocysteinemia was defined as a plasma homocysteine level of > 12 mmol/L.¹⁷ Estimated glomerular filtration rate (eGFR; mL/min per 1.73 m²) was calculated from serum creatinine by using the refined Modification of Diet in Renal Disease equation.¹⁸ Renal dysfunction was defined as absent (eGFR ≥ 90) or present (eGFR < 90). When renal dysfunction was present, it was further categorized into mild ($60 \leq$ eGFR < 90) and moderate-severe (eGFR < 60).¹⁹ Biomarkers of inflammation (e.g., C-reactive protein, interleukin-6), endothelial dysfunction (e.g., soluble intercellular adhesion molecule-1), and coagulation (e.g., D-dimer, factor VIII, fibrinogen) and other hematologic abnormalities (e.g., sphingomyelin, plasmin- α_2 -antiplasmin complex) were also measured as detailed elsewhere.^{14,20}

Detailed assessment of subclinical atherosclerosis was performed as one of the primary objectives of the MESA.^{16,21} Carotid ultrasonog-

raphy was used to determine carotid atherosclerosis and was defined as present if there was $\geq 25\%$ stenosis.²¹ Chest computed tomography was used to quantify coronary atherosclerosis, which was defined as present if there was an Agatston calcium score ≥ 200 .²¹ The ankle-brachial index was used to assess peripheral arterial atherosclerosis and was defined as present if < 0.9 .²¹

Statistical Analysis

RVO was analyzed as a binary outcome variable (present versus absent). Cardiovascular risk factors were analyzed as present versus absent for binary traits (e.g., hypertension, renal disease, carotid artery disease) and categorized into quartiles or SD difference for continuous traits (e.g., blood pressure, C-reactive protein, interleukin-6). More severe grading of the qualitative retinal signs (e.g., focal arteriolar narrowing, arteriovenous nicking) was used in the person-specific analyses. Analysis of variance (ANOVA) or χ^2 tests were used to compare the prevalence rates of central, branch, and any RVO by age, sex, and ethnicity. We used logistic regression models to estimate odds ratios (ORs) for any RVO for each risk factor, adjusting for age, sex, ethnicity, and study center. In multivariate analysis, we selected variables for simultaneous inclusion in the regression model if candidate variables were independently significant at $P < 0.05$ in the model, adjusting for age, sex, ethnicity, and study center. As central and branch RVO may have differences in pathogenesis, we repeated the multivariate analysis after excluding central RVO in supplementary analysis. We also examined interactions with race by inclusion of cross-product terms of race and each risk factor in the models. All analyses were performed in commercial statistical software (SPSS ver. 12.0.1; SPSS Inc., Chicago, IL).

RESULTS

Participants' characteristics in the MESA have been published.^{5,14} In our study population, there were 66 cases of RVO (57 branch RVO and 9 central RVO) identified (65 participants). One participant had bilateral RVO (central RVO in the left eye and branch RVO in the right). This participant did not have any retinal microvascular characteristics. Table 1 shows that the prevalence of RVO increased with age ($P \leq 0.01$), but did not vary by sex. Figure 1 shows that the prevalence rates of RVO and its subtypes were largely similar across different ethnic groups, ranging from 0.9% in whites to 1.2% in blacks and Hispanics.

Table 2 shows the associations of RVO with various traditional cardiovascular risk factors. After adjustment for age, sex, ethnicity, and study center, each decade increase in age, lower education level, hypertension, higher blood pressure, and hy-

TABLE 1. Prevalence of RVO in the MESA by Age and Sex

	N	Branch RVO		Central RVO		Any RVO	
		n (%)	P*	n (%)	P*	n (%)	P*
Overall	6147	57 (0.9)		9 (0.2)		65 (1.1)	
Age, y							
45-54	1437	4 (0.3)	0.01	0 (0.0)	0.01	4 (0.3)	0.002
55-64	1805	19 (1.1)		0 (0.0)		19 (1.1)	
65-74	1896	22 (1.2)		7 (0.4)		29 (1.5)	
≥ 75	1009	12 (1.2)		2 (0.2)		13 (1.3)	
Sex							
Male	2931	31 (1.1)	0.31	4 (0.1)	0.85	35 (1.2)	0.31
Female	3216	26 (0.8)		5 (0.2)		30 (0.9)	

N, number at risk; n, number with event; %, prevalence.

* P for trend for age groups or based on χ^2 test comparing ethnic and sex differences.

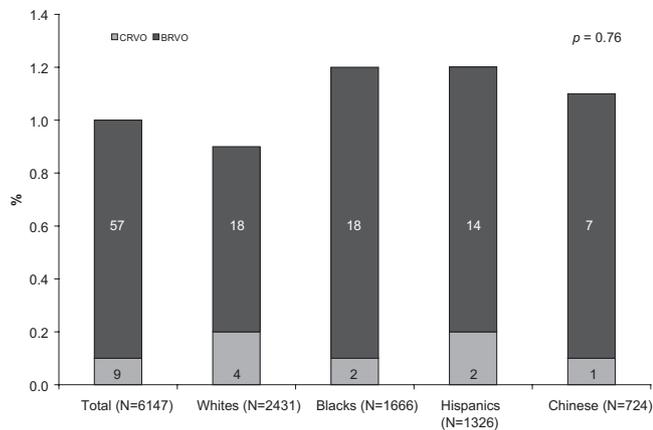


FIGURE 1. Prevalence of RVO in the MESA.

pertriglyceridemia were associated with increased odds of RVO. Diabetes and smoking were not associated with RVO.

Table 3 shows the association of RVO with novel risk factors, including biomarkers of inflammation, coagulation/hematologic abnormalities, renal dysfunction, retinal microvascular characteristics, and subclinical atherosclerosis. Of the range of risk factors examined, only hyperhomocysteinemia and increased serum creatinine were significantly associated with RVO. Other markers of inflammation (e.g., C-reactive protein) and endothelial dysfunction (e.g., soluble intercellular adhesion molecule-1) were not associated with RVO. Increased odds of RVO were also seen in participants with renal dysfunction, retinal arteriovenous nicking, and focal arteriolar narrowing. The presence of atherosclerotic disease in the carotid, coronary, and peripheral arteries was not associated with RVO.

The final multivariable model is presented in Table 4. RVO was significantly related to older age, less education, hypertension, hypertriglyceridemia, renal dysfunction, retinal arteriovenous nicking, and focal arteriolar narrowing. The association

between less education and RVO was present in all ethnic groups and was significant, even after further adjustments for income and cigarette smoking (both were not significant risk factors in our study). In supplementary analysis after excluding central RVO, the associations of branch RVO with these risk factors remained (data not shown).

We also performed several supplementary analyses (data not shown). First, to exclude nonlinear associations of RVO with the variables that were analyzed as continuous variables (e.g., per SD difference in factor VIII, D-dimer), we categorized these variables into binary traits (above versus below 90th percentile) and repeated the logistic regression analyses to assess their associations with RVO. The results were largely similar, with no additional significant associations found. Second, we have compared means and prevalence of the risk factors examined between the small number of people with central RVO and those with branch RVO. There were no significant differences. Finally, we examined potential interactions with ethnicity for the significant risk factors and found no statistically significant interactions (all $P > 0.05$, Table 4).

DISCUSSION

Our study provides new population-based data on the prevalence of RVO in a multiethnic sample of people in the general population without a history of clinical cardiovascular disease. We found an overall prevalence of RVO of 1.1%, with similar rates across four ethnic groups in the United States: whites, blacks, Hispanic, and Chinese. We also examined the associations of RVO with a wide spectrum of traditional and novel cardiovascular risk factors. Besides hypertension, we found that hypertriglyceridemia, renal dysfunction, and focal retinal arteriolar abnormalities were associated with RVO. The association between homocysteine and RVO may be a result of confounding from other vascular risk factors. Of importance, we did not find any association of RVO with many markers of systemic inflammation, endothelial dysfunction, and hematologic/coagulation diseases or with direct measures of subclin-

TABLE 2. Relationships of Traditional Cardiovascular Risk Factors and RVO in the MESA

Traditional Risk Factors	Any RVO	
	OR (95% CI)*	P
Age, increase per 10 years	1.44 (1.12–1.85)	0.005
Education (<8 y vs. ≥ 8 y)	3.87 (2.07–7.23)	<0.001
Smoking, current vs. never	1.03 (0.44–2.39)	0.95
Alcohol, current vs. never	0.79 (0.44–1.41)	0.79
Hypertension	2.32 (1.34–4.01)	0.003
Systolic blood pressure, per SD increase (mm Hg)	1.53 (1.21–1.92)	<0.001
Diastolic blood pressure, per SD increase (mm Hg)	1.71 (1.35–2.17)	<0.001
Pulse pressure, per SD increase (mm Hg)	1.41 (1.17–1.69)	<0.001
Diabetes, present vs. absent	1.18 (0.62–2.23)	0.62
BMI (WHO categories)		
Normal (<25 kg/m ²)	Reference	
Grade 1 overweight (≥ 25 but <30 kg/m ²)	0.94 (0.51–1.72)	0.83
Grade 2 overweight (≥ 30 but <40 kg/m ²)	1.06 (0.55–2.04)	0.56
Grade 3 overweight (≥ 40 kg/m ²)	1.00 (0.23–4.41)	0.99
Hypercholesterolemia, >240 mg/dL	1.08 (0.48–2.42)	0.86
LDL cholesterol, per SD increase (mg/dL)	0.91 (0.70–1.17)	0.46
HDL cholesterol, per SD increase (mg/dL)	0.93 (0.70–1.23)	0.60
Hypertriglyceridemia, ≥ 200 mg/dL	2.07 (1.17–3.69)	0.01

Risk factors examined but not significant ($P > 0.05$) include pack-years of smoking, fasting glucose, glycosylated hemoglobin, diabetes duration, medications (aspirin, oral steroids, nonsteroidal anti-inflammatory drugs, hormone replacement therapy).

BMI, body mass index; WHO, World Health Organization; LDL, low density lipoprotein; HDL, high density lipoprotein.

* OR (95% CI) adjusted for age (except for increase in age), sex, ethnicity, and study center.

TABLE 3. Relationships of Novel Inflammatory, Hematological, and Atherosclerotic Risk Factors and RVO in the MESA

Novel Risk Factors	Any RVO	
	OR (95% CI)*	P
Inflammatory factors		
C-reactive protein, per SD increase (mg/L)	0.94 (0.71-1.25)	0.66
Fibrinogen, per SD increase (mg/dL)	0.93 (0.72-1.21)	0.60
Hematologic/coagulation factors		
Hyperhomocysteinemia, >12 micromoles/L	1.88 (1.04-3.41)	0.04
Creatinine, per SD increase (mg/dL)	1.21 (1.05-1.39)	0.008
Factor VIII, per SD increase (%)	0.94 (0.73-1.21)	0.62
D-dimer, per SD increase (μ g/mL)	1.09 (0.84-1.42)	0.50
Renal dysfunction		
Absent	Reference	
Mild	2.23 (1.28-3.88)	0.005
Moderate-severe	3.73 (1.57-8.88)	0.003
Retinal microvascular characteristics		
Arteriovenous nicking	5.71 (3.04-10.70)	<0.001
Focal arteriolar narrowing	6.35 (2.17-18.61)	0.001
Subclinical atherosclerosis		
Carotid artery atherosclerosis, \geq 25% stenosis	1.34 (0.69-2.59)	0.39
Coronary artery atherosclerosis, Agatston calcium score \geq 200	1.22 (0.65-2.28)	0.54
Peripheral artery atherosclerosis, ankle-brachial index < 0.9	1.00 (0.30-3.26)	0.99

Risk factors examined but not significant ($P > 0.05$) include interleukin-6, sphingomyelin, plasmin- α_2 -antiplasmin complex, soluble intercellular adhesion molecule-1, retinal arteriolar and venular calibers.

* OR (95% CI) adjusted for age, sex, ethnicity, and study center.

ical atherosclerosis in the carotid, coronary, and peripheral leg circulation.

Although RVO is a major cause of visual loss, there are only a few population-based studies in which its prevalence has been examined. The Blue Mountains Eye Study (BMES) reported, in white Australians, the highest rate of RVO (1.6%). The pooled data report on white and black participants in the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study (ARIC & CHS) reported the lowest rate (0.3%) of RVO.^{1,3} In the predominantly white population in the Beaver Dam Eye Study (BDES), a prevalence estimate of 0.6% was reported.² It has been suggested that these variations are related to racial/ethnic differences. Our study, however, shows clearly that there are no major racial/ethnic differences in the prevalence of RVO. Thus, previously observed variations in prevalence estimates are most likely related to other differ-

ences between these studies, including study design, participant characteristics (e.g., older age corresponding to the higher prevalence rate in the BMES and cultural or environmental differences) and study methodology (e.g., retinal photography of only one eye with two fields corresponding to the lower prevalence in the ARIC & CHS, contrasting to the BMES with retinal photographs from both eyes, each with six fields).

Our data confirm the strong and known association of hypertension and related focal retinal arteriolar abnormalities with RVO, consistent with clinical knowledge and other population studies.¹⁻³ Retinal arteriolar signs, such as arteriovenous nicking and focal narrowing, represent established microvascular damage caused by long-standing elevated blood pressure. It has been suggested that sclerotic retinal arteriolar walls may compress underlying venules, especially at arteriovenous crossings. This compression in turn can transform the normal laminar venous blood flow into turbulent flow, facilitating the formation of venous thrombus and downstream venular occlusion.²² In addition, arteriolar insufficiency resulting from focal arteriosclerosis has been suggested to play a pathogenic role in RVO.^{2,23} These hypotheses are supported by prospective data from the BMES and the BDES, demonstrating that arteriovenous nicking and focal arteriolar narrowing are strong predictors of incident RVO.^{2,7,23}

We also found that people with hypertriglyceridemia and hyperhomocysteinemia were more likely to have RVO. These associations are important as both of these risk factors are modifiable and known to be associated with venous thrombosis. Several case-control studies have documented higher levels of triglyceride in patients with RVO.^{24,25} Our study extends these observations to an ethnically diverse population without overt cardiovascular disease. Alterations in platelet function, enhanced procoagulation, and plasma viscosity may contribute to the link between hypertriglyceridemia and RVO.²⁵⁻²⁷ Similarly, the elevated homocysteine level has been associated with RVO in several studies, including the BMES.^{8,28-30} It has been proposed that the oxygen free radicals generated from oxidation of homocysteine can cause venous endothelial cell dam-

TABLE 4. Relationships of Risk Factors and RVO in Multivariate Analysis in the MESA

Risk Factors	Any RVO	
	OR (95% CI)*	P
Age, increase per 10 years increase	1.34 (1.00-1.81)	0.05
Education (<8 y vs. \geq 8 y)	4.08 (2.20-7.54)	<0.001
Hypertension	2.06 (1.18-3.59)	0.01
Hypertriglyceridemia	1.98 (1.10-3.56)	0.02
Renal dysfunction (present vs. absent)	1.85 (1.01-3.39)	0.04
Creatinine, per SD increase (mg/dL)	1.20 (1.06-1.37)	0.004
Arteriovenous nicking	4.01 (2.06-7.81)	<0.001
Focal arteriolar narrowing	4.38 (1.44-13.34)	0.01
Hyperhomocysteinemia	1.40 (0.74-2.63)	0.30

* OR (95% CI) adjusted for age, sex, ethnicity, study center, systolic and diastolic blood pressure (except for hypertension), education status (except for education), and serum levels of creatinine (except for renal dysfunction), renal dysfunction (except for creatinine), homocysteine (except for hyperhomocysteinemia), and triglyceride (except for hypertriglyceridemia).

age, initiating coagulation processes that ultimately lead to formation of venular thrombosis.²⁹ Nevertheless, as shown in our multivariate analysis, the association between hyperhomocysteinemia and RVO became attenuated and lost its statistical significance, indicating that it could be a result of shared pathways from related cardiovascular risk factors, such as renal function.

Persons with higher creatinine levels and with renal dysfunction, even those with only mild impairment, were more likely to have RVO in our study. These findings agree with recent prospective data from the BDES, in which persons with elevated creatinine level (≥ 1.4 mg/dL) were shown to have 60% higher risk of RVO over 15 years of follow-up.²³ However, the underlying pathophysiological mechanisms are unclear. Since RVO and nephropathy are both closely related to hypertension, one may expect this association to be due to concomitant damage in the retinal and renal vasculature by hypertension. Although we have adjusted for blood pressure in our multivariate models, residual confounding from long-term exposure to high blood pressure cannot be totally excluded. Additional studies are clearly needed to elucidate further the mechanistic pathways that may underlie the association between renal dysfunction and RVO risk.

There has been much controversy regarding the relationship between RVO and systemic atherosclerosis.²⁸ Although some investigators believe that atherosclerosis plays a central role in the pathogenesis of RVO, previous studies have provided inconsistent results.^{1,31-35} The MESA provided a unique opportunity to resolve this question, as participants had an extensive and detailed assessment of atherosclerosis in three major arterial beds (carotid artery via ultrasonography, coronary artery via chest computer tomography, and lower-limb peripheral arteries via ankle-brachial index). Similarly, we examined a range of markers of systemic inflammation, endothelial dysfunction, and hematologic/coagulation diseases. We found no association with these measures, suggesting that in the general population, atherosclerosis, inflammation, and hematologic disease are not major risk factors for RVO.

We found a strong association between lower education and RVO, even after adjustment for potential socioeconomic (income) and lifestyle (e.g., cigarette smoking) factors. The reason underlying this association remains to be determined, but could be related to poorer control of unaccounted cardiovascular risk factors that may be important in the development of RVO (e.g., chronic or uncontrolled hypertension and dyslipidemia).

The strengths of our study include a large, multiethnic population-based sample of people, masked grading of two-field retinal photographs from both eyes with only a few ungradable cases, and standardized and comprehensive assessment of cardiovascular risk factors. However, several limitations merit consideration. First, inferences to causation are limited by the study's cross-sectional design. Second, RVOs were ascertained from two digital images per eye taken by a 45° nonstereoscopic, nonmydriatic fundus camera. Thus, our study results may not be directly comparable to those of some other population-based studies in which different methodologies were used (e.g., 30° stereoscopic photographs of six fields in the BMES and BDES).^{2,3} Third, the rarity of RVO in our population may have limited our statistical power to detect associations for some risk factors and for subanalysis of branch and central RVO. Additional studies with larger samples may be needed to verify our negative findings. Fourth, our study population was confined to persons without clinical cardiovascular disease, which may limit the generalizability of findings to people with cardiovascular disease and may also explain the lack of association with some vascular risk factors, such as diabetes and smoking.^{2,23} Nevertheless, our generally healthy

study sample can also be considered a strength, as it minimizes the effects of cardiovascular medical treatments on the results. Finally, given the large number of risk factors examined, some findings could be due to chance (e.g., education).

In summary, we showed that RVO occurs in 1% of the general adult population 45 years of age and older and does not show substantial racial/ethnic differences in prevalence. In this respect, the epidemiology of RVO is different from age-related macular degeneration and diabetic retinopathy, which demonstrate clear racial/ethnic variations. RVO is strongly associated with hypertension and retinal arteriolar abnormalities and may also be related to hypertriglyceridemia and renal dysfunction. However, in generally healthy people, measures of atherosclerosis, systemic inflammation, and hematologic dysfunction are not major risk factors for RVO.

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References

1. Wong TY, Larsen EK, Klein R, et al. Cardiovascular risk factors for retinal vein occlusion and arteriolar emboli: the Atherosclerosis Risk in Communities & Cardiovascular Health studies. *Ophthalmology*. 2005;112(4):540-547.
2. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 2000;98:133-141.
3. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. *Arch Ophthalmol*. 1996;114(10):1243-1247.
4. Liu W, Xu L, Jonas JB. Vein occlusion in Chinese subjects. *Ophthalmology*. 2007;114(9):1795-1796.
5. Klein R, Klein BE, Knudtson MD, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. *Ophthalmology*. 2006;113(3):373-380.
6. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol*. 2006;141(3):446-455.
7. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2006;124(5):726-732.
8. Chua B, Kifley A, Wong TY, Mitchell P. Homocysteine and retinal vein occlusion: a population-based study. *Am J Ophthalmol*. 2005;139(1):181-182.
9. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156(9):871-881.
10. Cheung N, Bluemke DA, Klein R, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. *J Am Coll Cardiol*. 2007;50(1):48-55.
11. Cheung N, Sharret AR, Klein R, et al. Aortic distensibility and retinal arteriolar narrowing: the Multi-Ethnic Study of Atherosclerosis. *Hypertension*. 2007;50(4):617-622.
12. Cheung N, Islam AFM, Jacobs DR, et al. Arterial compliance and retinal vascular caliber in cerebrovascular disease. *Ann Neurol*. 2007;62(6):618-624.
13. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269-2280.
14. Wong TY, Islam FM, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). *Invest Ophthalmol Vis Sci*. 2006;47(6):2341-2350.
15. Wong TY, Knudtson MD, Klein R, Klein BE, Meuer SM, Hubbard LD. Computer-assisted measurement of retinal vessel diameters in

- the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. *Ophthalmology*. 2004;111(6):1183-1190.
16. Nelson JC, Jiang XC, Tabas I, Tall A, Shea S. Plasma sphingomyelin and subclinical atherosclerosis: findings from the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. 2006;163(10):903-912.
 17. Castanon MM, Lauricella AM, Kordich L, Quintana I. Plasma homocysteine cutoff values for venous thrombosis. *Clin Chem Lab Med*. 2007;45(2):232-236.
 18. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med*. 2004;141(12):929-937.
 19. Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol*. 2007;18(4):1307-1315.
 20. Ranjit N, Diez-Roux AV, Shea S, et al. Psychosocial factors and inflammation in the multi-ethnic study of atherosclerosis. *Arch Intern Med*. 2007;167(2):174-181.
 21. Holvoet P, Jenny NS, Schreiner PJ, Tracy RP, Jacobs DR. The relationship between oxidized LDL and other cardiovascular risk factors and subclinical CVD in different ethnic groups: The Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;194(1):245-252.
 22. Verougstraete C. Is change of the vessel wall a risk factor for venous thrombosis? *Lancet*. 1999;353(9170):2158.
 23. Klein R, Moss SE, Meuer SM, Klein BEK. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol*. 2008;126(4):513-518.
 24. Brown GC. Central retinal vein obstruction with lipid exudate. *Arch Ophthalmol*. 1989;107(7):1001-1005.
 25. Dodson PM, Galton DJ, Hamilton AM, Blach RK. Retinal vein occlusion and the prevalence of lipoprotein abnormalities. *Br J Ophthalmol*. 1982;66(3):161-164.
 26. Dodson PM, Westwick J, Marks G, Kakkar VV, Galton DJ. beta-thromboglobulin and platelet factor 4 levels in retinal vein occlusion. *Br J Ophthalmol*. 1983;67(3):143-146.
 27. Moyer MP, Tracy RP, Tracy PB, van't Veer C, Sparks CE, Mann KG. Plasma lipoproteins support prothrombinase and other procoagulant enzymatic complexes. *Arteriosclerosis Thrombosis Vasc Biol*. 1998;18(3):458-465.
 28. Janssen MC, den Heijer M, Cruysberg JR, Wollersheim H, Bredie SJ. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? A meta-analysis of thrombophilic factors. *Thromb Haemost*. 2005;93(6):1021-1026.
 29. Brown BA, Marx JL, Ward TP, et al. Homocysteine: a risk factor for retinal venous occlusive disease. *Ophthalmology*. 2002;109(2):287-290.
 30. Yildirim C, Yaylali V, Tatlipinar S, Kaptanoglu B, Akpinar S. Hyperhomocysteinemia: a risk factor for retinal vein occlusion. *Ophthalmologica*. 2004;218(2):102-106.
 31. Brown GC, Shah HG, Magargal LE, Savino PJ. Central retinal vein obstruction and carotid artery disease. *Ophthalmology*. 1984;91(12):1627-1633.
 32. Rauh G, Fischereder M, Nasemann J, et al. Evaluation of atherosclerosis in patients with central retinal vein occlusion by carotid artery duplex scanning and echocardiography: a prospective case-control study. *Eur J Med Res*. 1996;1(9):429-432.
 33. Sayag D, Gotzamanis A, Brugniart C, et al. Retinal vein occlusion and carotid Doppler imaging (in French). *J Fr Ophtalmol*. 2002;25(8):826-830.
 34. Nakazato K, Watanabe H, Kawana K, Hiraoka T, Kiuchi T, Oshika T. Evaluation of arterial stiffness in patients with branch retinal vein occlusion. *Ophthalmologica*. 2005;219(6):334-337.
 35. Marin-Sanabria EA, Kondoh T, Yamanaka A, Kohmura E. Ultrasonographic screening of carotid artery in patients with vascular retinopathies. *Kobe J Med Sci*. 2005;51(1-2):7-16.