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Prevalence and risk factors of retinal vein occlusion in the United States: The National Health and Nutrition Examination Survey, 2005 to 2008

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ABSTRACT

Retinal vein occlusion (RVO) is a rare, vision-threatening vascular disorder. Due to limited recovery associated with RVO, prevention is essential. There is a significant discrepancy in previously reported epidemiological studies in the United States on the prevalence and risk factors of RVO. The purpose of this retrospective, cross-sectional study was to determine the prevalence and risk factors of RVO in adults ≥40 years of age in the US using the National Health and Nutrition Examination Survey (NHANES) 2005–2008. We collected information on the demographic characteristics, medical conditions, and ocular pathology of NHANES participants. We performed weighted analysis to estimate national prevalence rates and multivariate analysis to examine associated risk factors. The main outcome measures were the prevalence of RVO and the odds ratios of associated risk factors. We included 5559 participants and found 33 cases of RVO. The overall prevalence of RVO in the US was 0.50%. Age, per 10-year increase (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.31–2.92) and elevated diastolic blood pressure, per 10 mm Hg increase (OR 1.47; 95% CI, 1.10–2.12) were significant risk factors for RVO. Race, sex, glaucoma, elevated cholesterol, and self-reported history of diabetes, stroke, and heart disease were not significant risk factors. RVO is significantly associated with older age and elevated diastolic blood pressure. Our findings should alert clinicians to identify individuals at risk for RVO.

KEYWORDS Epidemiology; National Health and Nutrition Examination Survey; public health; retinal vein occlusion

Retinal vein occlusion (RVO) is a rare, vision-threatening vascular disorder typically seen in the elderly population.[1] In central retinal vein occlusion (CRVO), the central retinal vein is blocked at or proximal to the lamina cribrosa of the optic nerve. In branch retinal vein occlusion (BRVO), the blockage typically occurs in a tributary vein at an arteriovenous intersection.[2] Patients with CRVO typically present with acute-onset painless vision loss or blurred vision, while patients with BRVO may have visual field defects or be asymptomatic. On fundoscopic examination, CRVO typically demonstrates enlargement and tortuosity of the central retinal vein and its branches with widespread retinal hemorrhages. In contrast, BRVO presents with a dilated and tortuous vein branching from the central retinal vein with localized retinal hemorrhages.[1] RVO is strongly associated with cardiovascular and systemic risk factors such as hypertension, hyperlipidemia, arteriolosclerosis, and cigarette smoking.[2–5] Due to limited treatment options for full recovery of perfusion, prevention of RVO is crucial.[4] Understanding the prevalence of RVO in different population subgroups and its associated risk factors is essential in developing appropriate, targeted preventative measures.

There is significant discrepancy in previous reported epidemiological studies in the US on the prevalence and risk factors of RVO. Most of these studies were restricted to a small number of communities and considered only cardiovascular risk factors.[6–8] The National Health and Nutrition Examination Survey (NHANES) was conducted in 30 communities across the US and collected a broad scope of demographic and health-related data. The NHANES oversampled the elderly population, making it well suited for estimating

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the prevalence of RVO.[9] In the 2005–2006 and 2007–2008 survey cycles, retinal photography of participants was performed and evaluated for pathology.

While the NHANES has been used to estimate the national prevalence of other ophthalmic diseases such as glaucoma, diabetic retinopathy, and age-related macular degeneration, there are no reported estimates on RVO prevalence using this dataset. Therefore, the aim of this study was to estimate the prevalence of RVO in the US and assess associated risk factors using the NHANES 2005–2008.

METHODS

In accordance with the Common Rule, institutional review board approval was not required for this study, as all patient data were publicly available and deidentified.

The NHANES is conducted annually by the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention. Participants were selected from 30 counties in the US, and minority groups were oversampled to enable accurate national estimates for those groups. The NHANES employs a complex, multistage probability sampling design that assigns a sample weight to each participant to compensate for oversampling and to create a nationally representative sample of the civilian, noninstitutionalized population. Weights are numerical multipliers assigned to each participant that must be correctly applied when making estimates about the national population using the NHANES survey data.[9,10] Our analysis was restricted to participants $\geq$40 years in the NHANES 2005–2008 who underwent interviews and medical examinations. We excluded participants with no retinal photographs or ungradable photographs.

Surveyors at the NHANES conducted detailed interviews at participants' homes inquiring about demographic, dietary, and health-related questions. Trained health professionals examined participants in specially designed mobile examination centers. Data collected included physiological measurements and laboratory testing. Collected demographic information included age, sex, and race/ethnicity. Interview questions regarding participants' medical conditions were used to record self-reported history of various diseases and conditions. We restricted our analysis to the self-reported history of diabetes, stroke, and cardiovascular disease.

Examination data pertaining to blood pressure, hematocrit levels, total cholesterol levels, and high-density lipoprotein (HDL) levels were collected. Blood pressure was measured by trained examiners after each participant was allowed to rest in a sitting position for 5 minutes. Average systolic and diastolic blood pressures were calculated as the mean of the first and second consecutive blood pressure measurements. Hematocrit levels were ascertained from complete blood counts. Total cholesterol and HDL levels were collected from lipid panel results for each participant. Levels of other lipids such as low-density lipoprotein (LDL) and triglycerides as well as hemoglobin A1c and fasting plasma glucose levels were excluded from analysis due to large amounts of missing data.

Participants underwent 45° nonmydriatic retinal photography of the macula and optic disc of both eyes using an ophthalmic digital imaging system (CR6-45NM; Canon USA, Melville, NY). Photographs were initially graded at the University of Wisconsin by at least two graders. In cases when the two graders disagreed on pathology, a third grader graded the eye. If agreement was not reached, an adjudicator evaluated the image to make a final decision.

Images were evaluated for the presence of BRVO and CRVO using the same protocol as used in the Multi-Ethnic Study of Atherosclerosis.[10] RVO was defined as the presence of either BRVO or CRVO in the eye. In 2012, images with a CDR of $\geq$0.6 were regraded by three glaucoma specialists at Johns Hopkins University. Each specialist reviewed the images to determine the likelihood of glaucoma with adjudication when necessary. Likelihood of glaucoma was graded as "no," "possible," "probable," or "definite." For this study, we considered a participant to have glaucoma if at least one eye was graded as "probable" or "definite."

All statistical analyses were performed using NHANES base weights to compensate for the survey's complex, multistage probability sampling design. We estimated overall prevalence of BRVO, CRVO, and any RVO in the US population at large and in subgroups defined by age and sex. In univariate analysis, continuous and categorical variables were compared across RVO status groups using Welch's t tests and χ^2 tests, respectively. We performed multivariate analysis to determine independent risk factors of RVO with a logistic regression model using GraphPad Prism (version 9.3.1; GraphPad, La Jolla, CA). In our logistic regression model, all collected variables regardless of their univariate significance were included as predictors. This step was taken to prevent biased estimates on the significance of predictor variables and to allow further elucidation of suppression and mediation effects between covariates. We considered $P < 0.05$ to be significant.

RESULTS

Of the 7081 participants $\geq$40 years of age who participated in the NHANES 2005–2008, we excluded 1552 participants with missing or ungradable retinal photographs. The final sample included 5559 participants (2771 men and 2788 women) with gradable retinal photographs that were evaluated for RVO.

The characteristics of study participants with and without RVO are displayed in *Table 1*. Of the 5559 included subjects, we identified 33 (0.59%) cases of RVO. Of these 33 cases, 27 (81.8%) cases were BRVO, and 6 (18.2%) cases were CRVO. Univariate analysis demonstrated that age (59.3 ± 12.4 years in non-RVO participants and 68.2 ± 12.4 years in RVO participants, $P < 0.001$), glaucoma (2.9% in non-RVO participants and 12.1% in RVO participants, $P = 0.009$), and total cholesterol (202.3 ± 42.4 mg/dL in non-RVO participants and 184.9 ± 40.2 mg/dL in RVO

Table 1. Characteristics and univariate analysis of study participants in the National Health and Nutrition Examination Survey, 2005–2008

Characteristic	Non-RVO (n = 5526)	RVO (n = 33)	P value
Age (y)	59.3 ± 12.4	68.2 ± 12.4	**<0.001**
Female sex (%)	50.2	39.4	0.289
Race/ethnicity (%)			0.712
Non-Hispanic White	53.9	63.6	
Non-Hispanic Black	20.3	15.2	
Mexican American	15.6	9.1	
Other Hispanic	7.0	9.1	
Other	3.2	3.0	
Glaucoma (%)	2.9	12.1	**0.009**
Self-reported diabetes (%)	15.3	21.2	0.482
Self-reported stroke (%)	5.1	12.1	0.150
Self-reported CVD (%)	12.3	21.2	0.195
Systolic blood pressure (mm Hg)	129.3 ± 20.1	134.9 ± 27.6	0.130
Diastolic blood pressure (mm Hg)	71.4 ± 13.5	72.9 ± 19.3	0.547
Total cholesterol (mg/dL)	202.3 ± 42.4	184.9 ± 40.2	**0.021**
HDL cholesterol (mg/dL)	53.5 ± 16.3	54.0 ± 14.4	0.860
Hematocrit (%)	41.8 ± 4.3	41.0 ± 4.9	0.249

Boldface indicates statistical significance ($P < 0.05$). Data are means ± standard deviation or percentages. CVD indicates cardiovascular disease; HDL, high-density lipoprotein; RVO, retinal vein occlusion

participants, $P = 0.021$) were significant risk factors. Other factors including self-reported history of diabetes, stroke, and cardiovascular disease as well as race/ethnicity and sex were not significantly different between the groups.

The weighted estimate of the prevalence of BRVO, CRVO, and any RVO in the US, along with sex- and age-based subgroup prevalence, are shown in *Table 2*. The overall national noninstitutionalized, civilian population prevalence of BRVO, CRVO, and any RVO was 0.42% (95% confidence interval [CI], 0.23–0.60), 0.08% (95% CI, 0–0.18), and 0.50% (95% CI, 0.30–0.71), respectively. Overall, the prevalence of RVO increased with age. Of all RVO cases, 84% were estimated to be BRVO and 16% were estimated to be CRVO. Men had a higher prevalence rate of BRVO than women, while women had a higher prevalence rate of CRVO than men.

Table 3 shows the multivariate logistic regression analysis with odds ratios (OR) for factors pertaining to RVO. Age, per 10-year increase (OR, 1.93; 95% CI, 1.31–2.92, $P = 0.001$) and elevated diastolic blood pressure, per 10 mm Hg increase (OR, 1.47; 95% CI, 1.10–2.12, $P = 0.032$) were significant risk factors for the prevalence of RVO. All other factors including glaucoma and total cholesterol were not significantly associated ($P > 0.05$) with the presence of RVO.

DISCUSSION

Our study focused on determining the prevalence of BRVO, CRVO, and any RVO in the US in the noninstitutionalized, civilian adult population >40 years of age using the NHANES 2005–2008. We found the overall prevalence of RVO to be 0.50% with no significant differences between sex or racial/ethnic groups. The 70 to 79 and 80+ age groups had the highest prevalence of RVO. We found 84% of RVO to be BRVO and 16% to be CRVO. In our analysis, we identified that increased age and elevated diastolic blood pressure were significantly associated with RVO. Our findings parallel those discovered by others, further underscoring the strong association between age, elevated blood pressure, and RVO.[3,6,8]

Several epidemiological studies have been conducted on RVO in the US.[6–8,11,12] A comparison of prevalence rates reported in US population-based studies is presented in Table 4. Our results are most comparable to the results from the Beaver Dam Eye Study (BDES) and the combined Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS).[6,7] The ARIC + CHS found a total of 39 cases of RVO, with 84.6% being BRVO and 15.4% being CRVO.[6] This finding is nearly identical to our identified percentages of BRVO and CRVO cases. The Multi-Ethnic Study of Atherosclerosis (MESA) reported

Table 2. Estimated prevalence of retinal vein occlusion in the United States

Group	BRVO	CRVO	Any RVO
Women			
40–49	0.29 [0, 0.80]	0	0.29 [0, 0.80]
50–59	0.41 [0, 1.08]	0.26 [0, 0.77]	0.68 [0, 1.51]
60–69	0.45 [0, 1.08]	0.12 [0, 0.36]	0.57 [0, 1.25]
70–79	0.61 [0, 1.38]	0	0.61 [0, 1.38]
80+	0.11 [0, 0.32]	0.50 [0, 1.53]	0.61 [0, 1.67]
Subtotal	0.38 [0.14, 0.63]	0.13 [0, 0.30]	0.52 [0.22, 0.81]
Men			
40–49	0.08 [0, 0.24]	0	0.08 [0, 0.024]
50–59	0.38 [0, 0.89]	0	0.38 [0, 0.89]
60–69	0.23 [0, 0.68]	0.08 [0, 0.23]	0.31 [0, 0.78]
70–79	1.44 [0.11, 2.77]	0.24 [0, 0.59]	1.68 [0.31, 3.06]
80+	2.60 [0, 5.28]	0	2.60 [0, 5.28]
Subtotal	0.45 [0.17, 0.73]	0.04 [0, 0.09]	0.49 [0.22, 0.77]
Overall			
40–49	0.19 [0, 0.46]	0	0.19 [0, 0.46]
50–59	0.40 [0, 0.88]	0.14 [0, 0.40]	0.53 [0, 1.08]
60–69	0.35 [0, 0.74]	0.10 [0, 0.24]	0.45 [0.03, 0.86]
70–79	0.98 [0.37, 1.60]	0.11 [0, 0.27]	1.36 [0.11, 2.61]
80+	1.05 [0.02, 2.08]	0.31 [0, 0.95]	1.36 [0.11, 2.61]
Total	0.42 [0.23, 0.60]	0.08 [0, 0.18]	0.50 [0.30, 0.71]

Data are percentages [95% confidence interval]. BRVO indicates branch retinal vein occlusion; CRVO, central retinal vein occlusion; RVO, retinal vein occlusion.

Table 3. Multivariate adjusted odds ratio of relevant factors of retinal vein occlusion

Factor	Odds ratio	95% CI	*P* value
Age, per 10 years	1.93	1.31, 2.92	**0.001**
Sex			
Male	1.00 reference		
Female	0.61	0.25, 1.44	0.259
Race/ethnicity			
Non-Hispanic White	1.00 reference		
Non-Hispanic Black	0.62	0.17, 1.78	0.409
Mexican American	0.91	0.21, 2.83	0.880
Other Hispanic	1.92	0.44, 5.97	0.313
Other	1.47	0.08, 7.50	0.711
Glaucoma	1.56	0.25, 5.48	0.554
Self-reported diabetes	1.40	0.52, 3.36	0.472
Self-reported stroke	0.80	0.13, 2.83	0.769
Self-reported CVD	1.02	0.36, 2.55	0.967
SBP, per 10 mm Hg increase	0.95	0.77, 1.16	0.651
DBP, per 10 mm Hg increase	1.47	1.10, 2.12	**0.032**
Total cholesterol, per 10 mg/dL increase	0.93	0.83, 1.03	0.166
HDL, per 10 mg/dL increase	1.09	0.83, 1.38	0.511
Hematocrit, per 10% increase	0.39	0.15, 1.02	0.051

Boldface indicates statistical significance ($P < 0.05$). CI indicates confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Table 4. Comparison of reported retinal vein occlusion prevalence rates in the United States

Study	Prevalence of BRVO	Prevalence of CRVO	Prevalence of any RVO	Subjects	Communities sampled
ARIC + CHS[6]	0.25%	0.05%	0.3%	15466	6
BDES[7]	0.6%	0.1%	0.7%	4856	1
MESA[8]	0.9%	0.2%	1.1%	6147	6
NHANES	0.42%	0.08%	0.50%	5559	30

ARIC indicates Atherosclerosis Risk in Communities Study; BDES, Beaver Dam Eye Study; BRVO, branch retinal vein occlusion; CHS, Cardiovascular Health Study; CRVO, central retinal vein occlusion; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; RVO, retinal vein occlusion.

higher prevalence rates than other studies, including our own.[8] This may be due in part to the unweighted survey design used in the MESA, which selected participants ≥45 years of age, while the NHANES included participants ≥40 years of age. The prevalence rate of any RVO found in our study closely aligns with the global prevalence rate of 0.52% estimated by Rogers et al in an analysis of pooled population studies.[12]

We identified increased age and elevated diastolic blood pressure to be significant risk factors for RVO. Age has been found to be a consistent risk factor for RVO across studies.[11] Although the pathophysiology of RVO is still largely unknown, the well-established association with age suggests that it may be due to age-related vascular damage.[13] Vessel damage, along with decreased perfusion in aging eyes, may contribute to the development of RVO.[14] Similar to findings in other studies, we found that race/ethnicity was not associated with RVO.[6,8,11] In contrast, other retinal diseases such as age-related macular degeneration and diabetic retinopathy have been found to have clear racial/ethnic differences.[15–17]

The association between elevated diastolic blood pressure and RVO has been seen in other population-based studies.[11] Although most previous studies have also identified elevated systolic blood pressure as a risk factor for RVO, we did not find a significant relationship between the two variables.

Similarly, a Japanese study by Arakawa et al also found diastolic blood pressure but not systolic blood pressure to be associated with RVO.[18] The cause of this inconsistency between studies is unclear and should be further explored in future epidemiological analyses. However, the consistent association of elevated blood pressure with RVO across studies suggests that hypertension-driven vascular changes may play a crucial role. Hypertension has been shown to cause retinopathy and sclerotic changes, along with hemorrhaging and occlusion of ocular microvasculature, which may contribute to RVO.[19,20]

Although they were found to be significantly associated with RVO in univariate analysis, glaucoma and total cholesterol were no longer found to be associated with RVO after multivariate analysis. One possible explanation may be that age played a mediating effect in the relationship between glaucoma and RVO. Glaucoma is known to be associated with increased age, and thus, the association seen in univariate analysis was likely due to the increased age of participants presenting with glaucoma rather than true independent associations.[21] Elevated total and LDL cholesterol have also been found to be associated with increased age and RVO.[22,23] However, our univariate analysis demonstrated a unique association of decreased total cholesterol with RVO. The causes behind this discrepancy are unclear, although it may be in part related to the missing LDL cholesterol values in many patients in the NHANES survey. Epidemiological studies with more robust collection methods may be required to further investigate this relationship.

The strengths of our study include the use of a large, nationally representative sample, masked grading of retinal photographs, and the comprehensive collection of various demographic and physiological variables. Whereas most previous studies examining RVO in the US utilized sample sizes confined to specific communities, the NHANES offers a broader and more inclusive depiction of the US population.

Our study had several limitations that require consideration. The cross-sectional design of the study limits causation analysis. The rarity of RVO and the small number of cases in our survey sample may have also affected our prevalence estimates. For some of our age- and sex-based subgroups, we found zero cases of CRVO, which naturally led to prevalence estimates of zero for those subgroups. A larger sample size may have found cases in those subgroups and allowed for more accurate prevalence estimates. Similarly, the rarity of RVO might have reduced the statistical power of our risk factor analysis. Nevertheless, the factors found to be associated with RVO in our study are the same as those found in larger studies with a greater number of cases.[11,18,24] Additionally, the design of the NHANES used questionnaires to uncover medical history for diabetes, stroke, and cardiovascular disease, which exposed our study to response and recall biases. Many individuals with diabetes and cardiovascular disease are undiagnosed or unaware of their condition, and therefore, our analysis was limited in its ability to assess the true role of these conditions as risk factors for RVO. Future studies should incorporate objective measures such as hemoglobin A1c or plasma glucose levels to better assess the relationship between diabetes and RVO. Finally, the NHANES used fundoscopic examination alone to screen for glaucoma. While characteristic optic disc changes on fundoscopy are the primary diagnostic criteria for glaucoma, other diagnostic tools such as intraocular pressure were not available, and thus, participants may have been underdiagnosed or overdiagnosed.

In conclusion, our study found RVO to be significantly associated with age and elevated diastolic blood pressure. Individuals with these characteristics should be considered at increased risk for RVO, and clinicians may consider ophthalmological screening and preventative measures targeted at these groups. Future studies with larger sample sizes may be needed to confirm our results.

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