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Novel Association between Opioid Use and Increased Risk of Retinal Vein Occlusion Using the National Institutes of Health *All of Us* Research Program

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Purpose: To assess for risk factors for retinal vein occlusion (RVO) among participants in the National Institutes of Health *All of Us* database, particularly social risk factors that have not been well studied, including substance use.

Design: Retrospective, case-control study.

Participants: Data were extracted for 380 adult participants with branch retinal vein occlusion (BRVO), 311 adult participants with central retinal vein occlusion (CRVO), and 1520 controls sampled among 311 640 adult participants in the *All of Us* database.

Methods: Data were extracted regarding demographics, comorbidities, income, housing, insurance, and substance use. Opioid use was defined by relevant diagnosis and prescription codes, with prescription use $>$ 30 days. Controls were sampled at a 4:1 control to case ratio from a pool of individuals aged $>$ 18 years without a diagnosis of RVO and proportionally matched to the demographic distribution of the 2019 U.S. census. Multivariable logistic regression identified medical and social determinants significantly associated with BRVO or CRVO. Statistical significance was defined as $P < 0.05$.

Main Outcome Measure: Development of BRVO or CRVO based on diagnosis codes.

Results: Among patients with BRVO, the mean (standard deviation) age was 70.1 (10.5) years. The majority (53.7%) were female. Cases were diverse; 23.7% identified as Black, and 18.4% identified as Hispanic or Latino. Medical risk factors including glaucoma (odds ratio [OR], 3.29; 95% confidence interval [CI], 2.22−4.90; $P <$ 0.001), hypertension (OR, 2.15; 95% CI, 1.49−3.11; $P < 0.001$), and diabetes mellitus (OR, 1.68; 95% CI, 1.18−2.38; $P = 0.004$) were re-demonstrated to be associated with BRVO. Black race (OR, 2.64; 95% CI, 1.22−6.05; $P = 0.017$) was found to be associated with increased risk of BRVO. Past marijuana use (OR, 0.68; 95% CI, 0.50−0.92; $P = 0.013$) was associated with decreased risk of BRVO; however, opioid use (OR, 1.98; 95% CI, 1.41−2.78; $P < 0.001$) was associated with a significantly increased risk of BRVO. Similar associations were found for CRVO.

Conclusions: Understanding RVO risk factors is important for primary prevention and improvement in visual outcomes. This study capitalizes on the diversity and scale of a novel nationwide database to elucidate a previously uncharacterized association between RVO and opioid use. *Ophthalmology Science 2022;2:100099* © *2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Retinal vein occlusion (RVO) ranks highly among causes of vision loss due to retinal vascular disease, second only to diabetic retinopathy.[1] Several mechanisms have been postulated regarding the pathogenesis of RVO, the most studied being vein thrombosis due to compression by atherosclerotic retinal arteries, degenerative changes of the vessel wall, and hematological disorders.[1] A 2010 meta-analysis reports the prevalence of RVO at 5.2 per 1000 individuals across 11 pooled studies from the United States, Europe, Asia, and Australia.[2] Several studies have demonstrated an increasing prevalence of RVO with age, but little consensus has been reached regarding associations with race or ethnicity.[2-5] Other studies exploring medical risk factors have shown strong associations with hypertension, hyperlipidemia, diabetes mellitus, glaucoma, and cigarette smoking, as well as weaker associations with obesity, myocardial infarction, peripheral artery disease, and hypercoagulable states.[1,2,6,7] However, the majority of these studies were conducted on small, local populations limited to individuals identifying as Asian or

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White, limiting the applicability of these associations to the broader U.S. population. Additionally, few studies have investigated associations with substance use outside of cigarettes and alcohol.[7] The opioid epidemic began in the early 2000s, and as of 2019, more than 1.6 million Americans struggle with opioid use disorder. Given that long-term opioid use increases risk of cardiovascular events such as myocardial infarction, an investigation into whether opioid use increases risk of retinal vascular disease, such as RVO, is warranted.[8-11]

The National Institutes of Health *All of Us* Research Program was created in 2015 in hopes of building a nationally representative database of 1 million Americans to better represent diversity in scientific research.[12] Upon enrollment, participants answer several surveys (topics spanning demographics, health care, and lifestyle), provide access to their medical records, and provide a blood sample for genetic research. Enrollment began in May 2018.[13] As of October 2020, there were 316 760 participants enrolled, of whom 52% are White, 21% are Black, and 17% are Hispanic.[14] Given 2019 US demographics, which roughly broke down into 60% White, 13% Black, and 19% Hispanic,[15] *All of Us* is a unique database, because few others can claim similar ratios and numbers of historically under-represented populations. *All of Us* thus provides a unique opportunity to validate established risk factors for RVO and to characterize new associations.

In this study, we leveraged the size and diversity of the *All of Us* research database to elucidate a novel association between opioid use and increased risk of RVO, an important finding in the context of the worsening opioid epidemic.

Methods

Study Population

The goals, recruitment methods, and scientific rationale for *All of Us* have been described previously.[13] *All of Us* includes surveys, electronic health record (EHR) domains, and physical measurements (PM) that can be accessed and analyzed using the *All of Us* Researcher Workbench, a cloud-based platform. Survey details can be found in the Survey Explorer in the Research Hub, a website designed to support researchers.[16] Each of the surveys includes branching logic, and all surveys other than an initial basic demographics survey are optional and may be skipped by the participant. PM recorded at enrollment includes blood pressure (systolic and diastolic), height, weight, heart rate, waist and hip measurement, wheelchair use, and current pregnancy status. Electronic health record data regarding medical conditions, procedures, laboratory results, and measurements were linked for consented participants. All 3 data types (survey, PM, and EHR) are mapped to the Observational Health and Medicines Outcomes Partnership common data model v5.2 maintained by the Observational Health and Data Sciences Initiative collaborative [https://www.ohdsi.org/]. All participants provided written informed consent, and study procedures were approved by the *All of Us* Institutional Review Board.

All of Us performed data transformations across each participant record to protect participant privacy. These transformations include data suppression of codes with a high risk of identification; generalization of categories such as age, sex at birth, gender identity, sexual orientation, and race; and date shifting by a random (< 1 year) number of days. The *All of Us* Registered Tier Curated Data Repository (CDR) Data Dictionary contains formal documentation on privacy implementation and creation of the CDR.[17] Because of the data transformations and de-identification processes, secondary analyses of the CDR were considered nonhuman subjects research by the University of California San Diego Institutional Review Board. The analyses conformed to the tenets of the Declaration of Helsinki. The Researcher Workbench provides access to Registered Tier data and enables researchers to select groups of participants (Cohort Builder), save health information about cohorts (Dataset Builder), and analyze data using Jupyter Notebooks (Notebooks). Within the Notebook environment, high-powered queries and analyses can be performed using R and Python 3 programming languages.

Data Processing

The Researcher Workbench was used to extract relevant data for the analysis. We defined our case cohorts as patients aged 18 years or more with a diagnosis of branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Branch retinal vein occlusion was defined by diagnosis codes that included "branch retinal vein occlusion" with or without macular edema or neovascularization, and CRVO was defined by diagnosis codes that included "central retinal vein occlusion" with or without macular edema or neovascularization (Table S1, available at www.ophthalmologyscience.org). A total of 94 patients had a diagnosis of both BRVO and CRVO and were included in both case cohorts. A total of 1520 controls were sampled from all participants aged $\geq$ 18 years in *All of Us* who did not have a history of RVO diagnosis, proportionally matched to U.S. 2019 census demographics: 50.8% female, 76.3% White, 13.4% Black, 5.9% Asian, and 18.5% Hispanic or Latino.[15]

Next, concept sets for each predictor were built in the Workbench by selecting relevant codes (e.g., International Classification of Diseases/Systematized Nomenclature of Medicine codes for conditions or Logical Observation Identifiers Names and Codes for measurements and observations).

Predictor variables included demographics, socioeconomic status (education, housing, employment status, income, and health insurance), substance use (cigarettes, alcohol, cocaine, hallucinogens, inhalants, marijuana, stimulants, and sedatives), opioid use (incorporating relevant prescription, diagnosis, and laboratory coding, with prescription use $>$ 30 days), and published risk factors for RVO (hypertension, diabetes mellitus, obesity, hyperlipidemia, glaucoma, myocardial infarction, peripheral artery disease, deep venous thrombosis, and pulmonary embolism). Detailed lists of codes used for these predictors are provided in Tables S2 and S3 (available at www.ophthalmologyscience.org). These concept sets were then connected to the cohorts to create analysis-ready datasets that were then exported to the *All of Us* Jupyter environment. To establish a temporal relationship between predictor and outcome, predictor data were included only if they preceded the outcome diagnosis of RVO. Subsequent analyses were performed in an R notebook within the *All of Us* Workbench environment. All data extraction and cleaning procedures can be found in the referenced R notebook in our publicly available workspace.[18]

Data Analysis and Modeling

Descriptive statistics of RVO patients in *All of Us* were generated regarding age, gender, and race (Table 1).

Table 1. Demographic Data of All Adults, Controls, and Retinal Vein Occlusion Patients in *All of Us*

	All Adults (N = 311 640)	Control Patients (N = 1520)	BRVO Patients (N = 380)	CRVO Patients (N = 311)
Age (Mean, SD), yrs	52.77 (16.71)	57.12 (17.32)	70.09 (10.47)	68.71 (12.27)
Gender (n, %)				
Male Gender	119 480 (38.34%)	748 (49.21%)	176 (46.32%)	141 (45.34%)
Female Gender	192 160 (61.67%)	772 (50.79%)	204 (53.68%)	170 (54.66%)
Self-Reported Race (n, %)				
Black	67 134 (21.54%)	203 (13.36%)	90 (23.68%)	74 (23.79%)
White	173 637 (55.72%)	1159 (76.25%)	212 (55.79%)	165 (53.05%)
Asian	10 845 (3.48%)	89 (5.86%)	<20* (<5.26%)	<20* (<6.4%)
Other	60 024 (19.26%)	69 (4.54%)	66 (17.37%)	65 (20.90%)
Self-Reported Ethnicity (n, %)				
Not Hispanic or Latino	252 639 (81.07%)	1239 (81.51%)	310 (81.58%)	251 (80.71%)
Hispanic or Latino	59 001 (18.93%)	281 (18.49%)	70 (18.42%)	60 (19.29%)

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; SD = standard deviation.
*Counts < 20 (and associated percentages) cannot be shared in accordance with *All of Us* data reporting policies.

Analysis of Survey Responses

Surveys regarding socioeconomic status ("The Basics" survey) and substance use ("Lifestyle" survey) were analyzed and found to have a response rate of approximately 100% among patients with RVO. Individual response rates are available in the workspace.[19] Many of the *All of Us* survey items have historical components that do not delineate specific time periods; therefore, information on when the survey was collected in relation to RVO diagnosis was unable to be obtained. Counts less than 20 (and corresponding frequencies) are unable to be displayed individually due to *All of Us* data-sharing policies, which prohibit sharing disaggregated data due to risk of re-identification of survey participants.

Logistic Regression Modeling

Logistic regression modeling was performed via R using predictors for 380 BRVO patients, 311 CRVO patients, and 1520 controls who had all predictor data available. The following R packages were used: *ggplot2, tibble, tidyr, readr, purrr, dplyr, stringr, forcats.*

Correlation coefficients were generated for each of the predictors to identify highly correlated variables, and bivariate analyses were performed to determine statistically significant variables. Bivariate (crude/unadjusted) odds ratios (ORs), 95% confidence intervals (CIs), and associated *P* values were calculated for all predictors.

As previously described, predictors included demographic information (e.g., gender, race, ethnicity), variables from surveys, diagnosis codes (e.g., hypertension, glaucoma), and prescription codes (e.g., prescription opioids). Data on predictors were only included if they were present before the outcome (i.e., diagnosis of RVO) with the exception of self-reported survey data.

Subsequently, multivariable logistic regression modeling was performed to determine which predictors were significantly associated with increased odds of RVO diagnosis. We removed highly correlated variables (with correlation coefficient > 0.9) to avoid multicollinearity problems while modeling and used bidirectional stepwise feature selection with Akaike information criterion to select the most suited predictors for the model. Using the best-performing multivariable model, we calculated and reported adjusted ORs, their 95% CIs, and associated *P* values. For all analyses, statistical significance was defined as $P < 0.05$.

Results

General Characteristics of Patients with RVO

We identified 380 adults diagnosed with BRVO and 311 adults diagnosed with CRVO of 311 640 adults in *All of Us*. The majority of BRVO patients (n = 380, 53.68%) and CRVO patients (n = 311, 54.66%) were female. The mean (standard deviation) age of BRVO patients and CRVO patients was 70.09 (10.47) years and 68.71 (12.27) years, respectively. Black participants (n = 90) represented 23.68% of BRVO patients, whereas Hispanic or Latino participants (n = 310) represented 18.42% and Asian participants (n < 20) were the least represented at <5.26%. Similar racial and ethnic percentages were found for CRVO patients (Table 1). All RVO patients were geographically diverse, with participants recruited from 32 discrete enrollment sites across the United States.

Factors Associated with RVO Diagnosis

Factors were first individually analyzed to evaluate potential associations with developing RVO. As expected, several traditional medical risk factors were significantly associated with increased odds of developing BRVO or CRVO, including glaucoma, hypertension, hyperlipidemia, and diabetes mellitus (Table 2). Several demographic factors, notably Black race and age, were found to be associated with increased risk for BRVO or CRVO (Table 2). Several social factors were also found to be significantly associated with increased odds of developing BRVO or CRVO, including Medicare insurance and renting or owning a home (Table 2). History of substance use, such as marijuana, stimulants, and sedatives, was largely correlated with decreased risk of BRVO or CRVO. Opioid use was associated with increased odds of developing

Table 2. Bivariate Crude Odds Ratios for Variables Significantly Associated with Odds of Developing Retinal Vein Occlusion

Variable	BRVO		CRVO	
	Odds Ratio (95% CI)	*P Value*	*Odds Ratio (95% CI)*	*P Value*
Traditional Risk Factors				
Glaucoma	9.38 (6.79–13.06)	<0.001	11.20 (8.02–15.75)	<0.001
Hypertension	8.35 (6.43–10.95)	<0.001	8.47 (6.37–11.40)	<0.001
Hyperlipidemia	5.94 (4.67–7.58)	<0.001	5.64 (4.36–7.33)	<0.001
Diabetes mellitus	5.52 (4.26–7.15)	<0.001	6.59 (5.01–8.67)	<0.001
Myocardial infarction	3.42 (2.31–5.06)	<0.001	2.93 (1.89–4.49)	<0.001
Obesity	3.12 (2.42–4.03)	<0.001	3.38 (2.57–4.43)	<0.001
Pulmonary embolism	3.19 (1.55–6.46)	0.001	5.13 (2.62–10.03)	<0.001
Deep vein thrombosis	3.08 (1.54–6.05)	0.001	4.88 (2.56–9.29)	<0.001
Demographics				
Age*	1.06 (1.05–1.07)	<0.001	1.05 (1.04–1.06)	<0.001
Other race*	7.09 (3.67–14.74)	<0.001	11.98 (5.49–30.18)	<0.001
Black race*	3.29 (1.77–6.60)	<0.001	4.64 (2.19–11.42)	<0.001
Socioeconomic Status				
Medicare insurance*	4.24 (3.34–5.40)	<0.001	3.39 (2.64–4.38)	<0.001
Currently rent home*	2.40 (1.52–3.98)	<0.001	2.73 (1.64–4.82)	<0.001
Increasing years living at current address*	1.42 (1.32–1.52)	<0.001	1.42 (1.32–1.53)	<0.001
Currently employed*	0.53 (0.41–0.66)	<0.001	0.61 (0.46–0.79)	<0.001
Concerned for stable housing*	0.55 (0.39–0.76)	<0.001	0.40 (0.26–0.60)	<0.001
Currently own home*	2.17 (1.39–3.55)	0.001	2.20 (1.34–3.84)	0.003
Veterans Association health insurance*	1.99 (1.27–3.06)	0.002	2.06 (1.28–3.24)	0.002
Purchased health insurance*	1.29 (0.88–1.86)	0.182	1.71 (1.17–2.47)	0.005
Any health insurance*	2.39 (1.33–4.76)	0.007	2.70 (1.38–6.08)	0.008
Increasing education level*	0.86 (0.77–0.96)	0.008	0.84 (0.75–0.95)	0.006
Employer or union health insurance*	0.73 (0.56–0.95)	0.019	0.83 (0.62–1.09)	0.176
Never married*	0.68 (0.46–0.98)	0.039	0.70 (0.47–1.06)	0.095
Currently living with partner*	0.51 (0.25–0.95)	0.044	0.39 (0.16–0.83)	0.024
Substance Use				
Opioid use	4.28 (3.37–5.47)	<0.001	5.10 (3.90–6.73)	<0.001
Any past marijuana use*	0.40 (0.32–0.50)	<0.001	0.35 (0.27–0.46)	<0.001
Any past cocaine use*	0.56 (0.41–0.77)	<0.001	0.44 (0.30–0.64)	<0.001
Any past hallucinogen use*	0.45 (0.29–0.66)	<0.001	0.31 (0.18–0.50)	<0.001
Any past methamphetamine use*	0.43 (0.25–0.69)	0.001	0.26 (0.12–0.48)	<0.001
Any past prescription stimulant use*	0.41 (0.24–0.66)	0.001	0.42 (0.24–0.70)	0.002
Any past inhalant use*	0.44 (0.21–0.80)	0.014	0.10 (0.017–0.33)	0.002
Any past sedatives use*	0.68 (0.45–0.98)	0.045	0.47 (0.29–0.74)	0.002

BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion.
*Based on self-reported survey data.

BRVO (crude/unadjusted OR, 4.28; 95% CI, 3.37–5.47; $P < 0.001$) or CRVO (crude/unadjusted OR, 5.10; 95% CI, 3.90–6.73; $P < 0.001$; Table 2).

We used multivariable logistic regression to assess whether this association between opioid use and increased risk of RVO persisted when adjusting for other variables. Even when accounting for medical and social covariates, opioid use remained a statistically significant exposure in relation to odds of developing BRVO (adjusted OR, 1.98; 95% CI, 1.41–2.78; $P < 0.001$) or CRVO (adjusted OR, 2.32; 95% CI, 1.59–3.41; $P < 0.001$), whereas past marijuana use was associated with decreased risk of BRVO or CRVO (Table 3). Additionally, demographics such as Black race were associated with increased odds of developing BRVO or CRVO while adjusting for medical comorbidities (Table 3). Several forms of health insurance, annual income, and current employment were associated with a significantly increased risk of BRVO or CRVO (Table 3).

Discussion

Retinal vein occlusion is a leading cause of blindness in the United States; however, there remains an incomplete understanding of associated medical or socioeconomic risk factors.[20] Using a nationwide database with increased enrollment of historically underrepresented racial groups, we not only validated previously reported medical/clinical risk factors for RVO but also found associations with several social factors as well as a novel association with opioid use.

The 2 major forms of RVO, BRVO and CRVO, have been reported to have differences in epidemiology, risk factors, and prognosis and were therefore explored separately in this study. The prevalence of BRVO has been found to be greater than that of CRVO (4.42 vs. 0.8 per 1000) in a large meta-analysis.[2] Other studies suggest that hypertension is more prevalent in BRVO, whereas

Table 3. Multivariable Logistic Regression Model Predicting Development of Retinal Vein Occlusion

Variable	BRVO		CRVO	
	Odds Ratio (95% CI)	*P Value*	*Odds Ratio (95% CI)*	*P Value*
Traditional Risk Factors				
Glaucoma	3.29 (2.22–4.90)	<0.001	4.53 (3.02–6.84)	<0.001
Hypertension	2.15 (1.49–3.11)	<0.001	2.28 (1.52–3.43)	<0.001
Diabetes mellitus	1.68 (1.18–2.38)	0.004	2.03 (1.39–2.98)	<0.001
Hyperlipidemia	1.51 (1.05–2.17)	0.025	1.66 (1.11–2.48)	0.013
Pulmonary embolism	N/A (not included in model)	>0.05	2.91 (1.24–6.81)	0.014
Demographics				
Age*	1.03 (1.01–1.05)	<0.001	N/A (not included in model)	>0.05
Black race*	2.64 (1.22–6.05)	0.017	6.96 (2.60–21.22)	<0.001
Other race*	3.53 (1.47–8.89)	0.006	15.16 (5.45–47.86)	<0.001
Socioeconomic Status				
Medicare insurance*	2.32 (1.62–3.33)	<0.001	2.44 (1.68–3.57)	<0.001
Increasing time lived in residence*	1.30 (1.18–1.43)	<0.001	1.36 (1.23–1.52)	<0.001
Increasing annual income*	1.15 (1.07–1.23)	<0.001	1.18 (1.10–1.28)	<0.001
Medicaid insurance*	1.98 (1.27–3.08)	0.002	N/A (not included in model)	>0.05
Military insurance*	0.397 (0.135–1.015)	0.07	0.11 (0.019–0.48)	0.007
Currently employed*	1.59 (1.09–2.33)	0.016	1.55 (1.04–2.30)	0.031
Substance Use				
Opioid use	1.98 (1.41–2.78)	<0.001	2.32 (1.59–3.41)	<0.001
Any past alcohol use*	1.98 (1.20–3.34)	0.009	1.79 (1.06–3.10)	0.034
Any past marijuana use*	0.68 (0.50–0.92)	0.013	0.54 (0.38–0.77)	0.001
Any past prescription stimulant use*	N/A (not included in model)	>0.05	2.27 (1.07–4.58)	0.027

BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion.
*Based on self-reported survey data.

glaucoma is a stronger risk factor for CRVO.[3] Our study found that BRVO and CRVO patients largely share risk factors, with the exception of pulmonary embolism (BRVO), age (CRVO), some forms of medical insurance (both BRVO and CRVO), and reported past stimulant use (BRVO). For this reason, the forthcoming discussion proceeds with a consolidated approach by considering BRVO and CRVO together as simply RVO.

After a detailed search of multiple databases including PubMed, Google Scholar, and Web of Science, to our knowledge opioid use has not been previously well-documented as a risk factor for RVO. We developed a broad opioid use phenotype by using prescription codes, relevant opioid laboratory codes, and opioid abuse diagnosis coding. In this manner, opioid use was found to be significantly associated with subsequent diagnosis of RVO by multivariable logistic regression modeling. Several other substances were assessed; however, only past marijuana use was found to be associated with RVO which, interestingly, was protective. There are few population-based studies investigating associations between RVO and substance use, aside from smoking. The Beaver Dam Eye Study revealed an association between history of barbiturate use and incident RVO in a local Wisconsin population.[7] Several studies have investigated a correlation with alcohol use, with the only significant results showing a decreased risk of RVO with a history of alcohol use.[3,5,21] Importantly, none of these studies investigated opioid use as a risk factor for RVO, likely because they preceded the current opioid epidemic. Beginning in the late 1990s, opioid prescription for chronic, noncancer pain went from effectively prohibited in most states to almost fully liberalized in at least 20 states, largely in response to a single 1986 case series study.[22,23] Prescribing model language became increasingly permissive, and screening for pain was instituted as the "fifth vital sign" by the Joint Commission on Accreditation for Healthcare Organizations.[24] These practices quickly raised the number of opioid prescriptions from 76 to 219 million per year between 1991 and 2011.[25] The fallout was and continues to be staggering, with approximately 250 000 deaths due to overdoses involving prescription opioids from 1999 to 2019—a quadrupling of the death rates seen in the late 1990s.[26] Moreover, drug overdose deaths increased approximately 30% in 2020 alone to a record 93 000 deaths, the majority of which were due to opioid overdose and likely aggravated by the Coronavirus Disease 2019 pandemic.[27,28] Beyond overdose deaths, millions of Americans remain addicted to prescription opioids, an epidemic that already has been shown to raise the risk of cardiovascular events, depression, hormonal dysregulation, and hyperalgesia.[29] Given the recency and continued unwavering progression of the opioid epidemic, further study into other sequelae of chronic opioid use is warranted. The results of this study help to continue this ongoing investigation, because it is the first study exploring retinal vascular effects of the opioid crisis, which will hopefully generate interest in both a biological causal association and reproduction of our findings on a larger scale.

Regarding biological plausibility for opioid use leading to increased risk of RVO, there is existing evidence for a

relationship between opioid use and cardiovascular or microvascular disease. The Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain warns that long-term opioid users are at increased risk of myocardial infarction, citing both a fair-quality cohort and good-quality case-control study.[8-10] A 2014 case report documented a single case of diffuse retinal ischemia after intravenous crushed oxymorphone use,[30] demonstrating a possible link between opioid use and retinal vascular complications. Several animal studies have shown that the retina has at least 3 different opioid receptors (δ, κ, μ) that aid in retinal development and have hypothesized hemodynamic properties.[31-34] Husain et al[35,36] have repeatedly demonstrated vasodilatory and neuroprotective effects of opioid receptor stimulation in the rat retina. Someya et al[31] proposed that opioid-induced retinal vasodilation is facilitated by neuronal μ-opioid receptor-mediated nitric oxide release. However, others have found similar results with opiate antagonists or found that opioids injected intraocularly directly induce retinal ischemia.[33,34] Thus, there is evidence to suggest that opioid-induced local microvascular or possibly systemic cardiovascular changes (e.g., opioid-induced hypotension leading to venous stasis and clotting) may be responsible for an increase in risk in RVO. However, further investigation is needed to elucidate a definitive biological link between opioid use and future risk for RVO.

In addition to associations found with past substance use, we found that several socioeconomic and demographic variables were associated with RVO diagnosis. Increasing annual income, current employment, and several forms of insurance (Medicare, Medicaid, and employer) were all associated with increased risk of RVO diagnosis. Age, Black race, and other race were similarly associated with increased risk. Few publications have explored socioeconomic risk factors for RVO, and most studies do not investigate further than demographics. One notable study used the Eye Disease Case-Control Study Group and found that both increasing amounts of physical activity and higher levels of education decreased risk of RVO in a multicenter U.S. study population.[3] However, many studies have previously shown that age, male gender, and Black race are all associated with increased risk of RVO diagnosis.[4,7,20,21] Taken together, our results clearly suggest that elderly, Black patients appear to be at highest risk for RVO. Further investigation is needed to discern socioeconomic risk factors, because markers of high socioeconomic status (employer insurance, increasing annual income) and low socioeconomic status (Medicaid insurance, current employment in an elderly population) were found to increase risk of RVO diagnosis.

Finally, our results showed that hypertension, glaucoma, and diabetes mellitus were associated with increased odds of RVO, reaffirming findings from prior studies that cardiovascular risk factors and glaucoma are significant risk factors for RVO.[1-7,20,21,37-44] Several landmark studies have helped establish associations with RVO, with approaches ranging from population-based to large meta-analyses. The Beaver Dam Eye Study[7,21,39,40] and Blue Mountains Eye Study[1,41,42] demonstrated associations with hypertension and glaucoma in local Wisconsin and Australian populations, respectively. The Eye Disease Case-Control Study Group found increased risk of RVO associated with hypertension, diabetes mellitus, glaucoma, and higher body mass index in a multicenter U.S. study population.[3] Taken together, our study backs a long history of investigations that continue to demonstrate that cardiovascular risk factors and glaucoma clearly contribute to increasing risk for RVO. Our results demonstrate the relevance of the *All of Us* dataset to ophthalmic research and to increase confidence in other novel associations elucidated by this investigation.

The main strength of using data from *All of Us* is that the program places an emphasis on high enrollment, geographic diversity, and a special focus on enrolling minorities who are underrepresented in biomedical research.[45] Few studies investigating risk factors for RVO have a study population that approximates U.S. demographics; of these, almost all are limited to less than 7 sites across the United States.[3-5] In *All of Us,* patients are recruited from hundreds of U.S. sites, and in this study RVO patients were recruited from 32 different sites. Even fewer studies approach the enrollment numbers of *All of Us*, and of these none approach current U.S. demographics of 60% White, 13% Black, 19% Hispanic, and 6% Asian.[2,20] The cohort of all adults with data available in *All of Us* is diverse; 22% of *All of Us* participants identified as Black, 19% identified as Hispanic, and 62% identified as female. Such a large, nationally representative database helps to inform more accurate claims regarding risk factors for RVO and likely will help uncover new associations, as evidenced by this study.

An additional strength of this study is that the *All of Us* database includes confidential, patient-reported responses to survey questions regarding demographics and substance use. This information is useful because the content of social history information in EHRs is typically limited to drug and alcohol use, occupation, and living situation; more granular information about different dimensions of social determinants of health is not typically recorded. Furthermore, patients are often reluctant to disclose the full details of substance use in the medical office setting. Survey data help to both eliminate embarrassment of substance use and paint a fuller picture of an individual's ability to access and use health care. With this information, we have begun to illuminate the social aspects of the U.S. RVO population, which can help to inform patient outreach and prevention efforts.

Some limitations of this study include the inability to establish causal relationships because of the observational study design and inability to perform subgroup analyses due to sample size, although cohort sizes are anticipated to increase as *All of Us* continues participant enrollment. Other limitations include a reliance on survey data and diagnostic billing codes, where there is potential for erroneous subjective reporting and misclassification/inconsistencies in diagnoses, respectively. Furthermore, we were not able to verify RVO diagnosis, because the *All of Us* database does not currently provide fundoscopic images or clinical notes pertaining to patients' eye exams. These limitations are common to analyses of healthcare claims data.

In conclusion, this is the first study to report a statistically significant association between RVO and opioid use. Using nationwide data with diverse enrollment, including traditionally underrepresented minorities, we re-demonstrate associations between cardiovascular risk factors and glaucoma with RVO, as well as with several other social determinants of health. Further investigation is warranted, ideally with larger cohorts and a prospective design, as an improved understanding of ophthalmic sequelae from opioid use can help inform patient outreach and prevention efforts, especially in the context of an ongoing opioid epidemic.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at the *All of Us* approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

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Author Contributions:

Conception and design: McDermott, Ferreyra, Nudleman, Baxter

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Analysis and interpretation: McDermott, Lee, Chan, Ye, Shahrvini, Saseendrakumar, Ferreyra, Nudleman, Baxter

Obtained funding: Baxter

Overall responsibility: McDermott, Baxter

Abbreviations and Acronyms:
BRVO = branch retinal vein occlusion; **CDR** = Curated Data Repository; **CI** = confidence interval; **CRVO** = central retinal vein occlusion; **EHR** = electronic health record; **OR** = odds ratio; **PM** = physical measurements; **RVO** = retinal vein occlusion.

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