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## Relationship between Retinal Vascular Occlusions and Cognitive Dementia in a Large Cross-Sectional Cohort

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### Abstract

- **PURPOSE:** To examine the association between cognitive dementia and retinal vascular occlusions.
- **DESIGN:** A retrospective, cross-sectional study.
- **METHODS:** Single-institution study population: we reviewed the electronic medical records of 37,208 individuals older than 65 years of age who were evaluated by an ophthalmologist or an optometrist and who also had a medical visit to our institution over a 6-year period. Individuals with and without retinal vascular occlusions were identified by International Classification of Diseases, version 10 (ICD-10) diagnostic codes.
- **MAIN OUTCOME:** we analyzed the association between dementia and retinal vascular occlusions after adjusting for covariates which included age, sex, stroke, diabetes mellitus, and hypertension using multiple logistic regression analyses.
- **RESULTS:** Compared to subjects without retinal vascular occlusions, those with retinal vascular occlusions had a higher prevalence of dementia (6.7% vs. 9.3%, respectively;  $P < .001$ ). After adjusting for either age or stroke, there were no significant associations between retinal vascular occlusions and dementia.
- **CONCLUSIONS:** Individuals with retinal vascular occlusions have a higher prevalence of dementia. However, this association is secondary to shared underlying risk factors in this population, such as older age and stroke.

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Dementia is a leading cause of morbidity and mortality in the elderly, and the increasing worldwide burden of dementia has sparked interest in identifying risk factors related to dementia.<sup>1–8</sup> Retinal imaging has demonstrated that retinal vascular changes are detectable in individuals with dementia<sup>9–11</sup> and that retinal vein occlusions have been recently shown to confer an increased risk of dementia.<sup>3</sup> However, individuals with dementia and retinal vascular occlusions share common risk factors such as older age, cardiovascular disease, and stroke.<sup>1, 4–6, 12–31</sup> What is unknown is whether retinal vascular occlusions are associated with increased risk of dementia, independent of these common risk factors.

## METHODS

This was a retrospective, cross-sectional study conducted in accordance with the Health Insurance Portability and Accountability Act. Internal Review Board (IRB) approval was obtained from the University of California San Diego Health System.

We reviewed the records of 37,208 individuals older than 65 years of age, who were evaluated by an ophthalmologist or an optometrist and who also had a medical visit to our institution between January 1, 2015, and December 31, 2020. Individuals with retinal vascular occlusions were identified through International Classification of Diseases, edition 10 (ICD-10) diagnostic codes. In addition, we identified individuals with dementia (vascular dementia, ICD-10 F01; dementia in other diseases classified elsewhere, ICD-10 F02; unspecified dementia, ICD-10 F03; Alzheimer's disease, ICD-10 G30), stroke (cerebral infarction, ICD-10 I63), essential hypertension (ICD-10 I10) and type 2 diabetes mellitus (ICD-10 E11). Baseline characteristics of subjects with and without retinal vascular occlusions were compared using Student's *t*-test and Pearson's  $\chi^2$  test, where applicable. Multivariate logistic regression models were used to analyze the association between retinal vascular occlusions and dementia. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical analyses and graphs were generated using R version 4.0.3 software (R Foundation, Vienna, Austria).

## RESULTS

We identified 904 individuals with and 36,304 individuals without retinal vascular occlusions. Demographics and baseline characteristics of the study cohort are shown in Table 1. Individuals with retinal vascular occlusions were older than those without (79 vs. 76 years of age, respectively;  $P < .001$ ), and the proportion of females was lower in the retinal vascular occlusion group (51.0 vs. 57.2%, respectively;  $P < .001$ ). There were no significant differences in race between the groups ( $P = .62$ ). Compared to individuals without, those with retinal vascular occlusions had a higher prevalence for dementia (6.7% vs. 9.3%, respectively;  $P = .003$ ), stroke (7.3% vs. 18.1%, respectively;  $P < .001$ ), hypertension (62.1% vs. 77.0%, respectively;  $P < .001$ ) and diabetes mellitus (26.9% vs. 36.4%, respectively;  $P < .001$ ).

Given that dementia and retinal vascular occlusions share similar risk factors, we analyzed the association between dementia and retinal vascular occlusions after adjusting for each of

the significant covariates including age, sex, stroke, hypertension, and diabetes mellitus by using multiple logistic regression analyses.

After we adjusted for sex, hypertension, or diabetes, or all 3 covariates, retinal vascular occlusions were still significantly associated with dementia, with OR of 1.42 (95% CI: 1.12–1.78), 1.27 (95% CI: 1.01–1.59), 1.36 (95% CI: 1.08–1.70), and 1.27 (95% CI: 1.00–1.58), respectively (Table 2). However, after we adjusted for either age or stroke there was no significant association between retinal vascular occlusions and dementia, OR 1.10 (95% CI: 0.86–1.38) and 1.12 (95% CI: 0.88–1.41), respectively (Table 2).

We also analyzed the following associations between dementia and retinal vascular occlusions in different age groups: 65–74 years of age ( $n = 18,382$ ), 75–84 years of age ( $n = 12,777$ ), and  $\geq 85$  years of age ( $n = 6,049$ ). Within each age group, there were no statistically significant differences in age between individuals with and without retinal vascular occlusions. There were no significant associations between retinal vascular occlusions and dementia in any of the 3 age groups. The OR were 0.93 (95% CI: 0.39–1.82) for individuals 65–74 years of age; 1.01 (95% CI: 0.66–1.48) for individuals 75–84 years of age; and 1.20 (95% CI: 0.86–1.63) for individuals  $\geq 85$  years of age, respectively (Table 2).

Finally, we analyzed the association between dementia and all of the covariates including retinal vascular occlusions. Stroke, older age, diabetes, and hypertension were each associated with dementia, whereas retinal vascular occlusions and female sex were not significantly associated with dementia (Figure). For retinal vascular occlusions, the OR of dementia was 0.88 (95% CI: 0.69–1.12).

## DISCUSSION

We examined the association between the retinal vascular occlusions and dementia in a retrospective cohort of individuals older than 65 years of age. We found that individuals with retinal vascular occlusions have increased odds of having dementia, in line with a recently published report.<sup>3</sup> However, after we adjusted for age or stroke, there were no significant associations between retinal vascular occlusions and dementia.

The major strengths of our study are the large sample size and adjustment for confounding risk factors for dementia. Limitations of this study include the inherent weakness of retrospective study design. Because we relied on diagnostic billing codes, there was a possibility for misclassification of diagnoses. Additionally, dementia is often underdiagnosed in the clinical setting. We also did not examine the association between retinal vascular occlusions and individual subtypes of dementia such as Alzheimer's disease, vascular dementia, and dementia with Lewy bodies. Additionally, the contributions of other factors associated with cognitive decline, including genetic risk factors and socioeconomic status, were not assessed. Finally, the cohort was composed mainly of Whites (66.8%) and Asians (12%), which limited the generalizability of our findings to other populations.

In conclusion, we demonstrate that the increased association between retinal vascular occlusions and dementia is secondary to shared underlying risk factors in this population, mainly older age and presence of stroke.

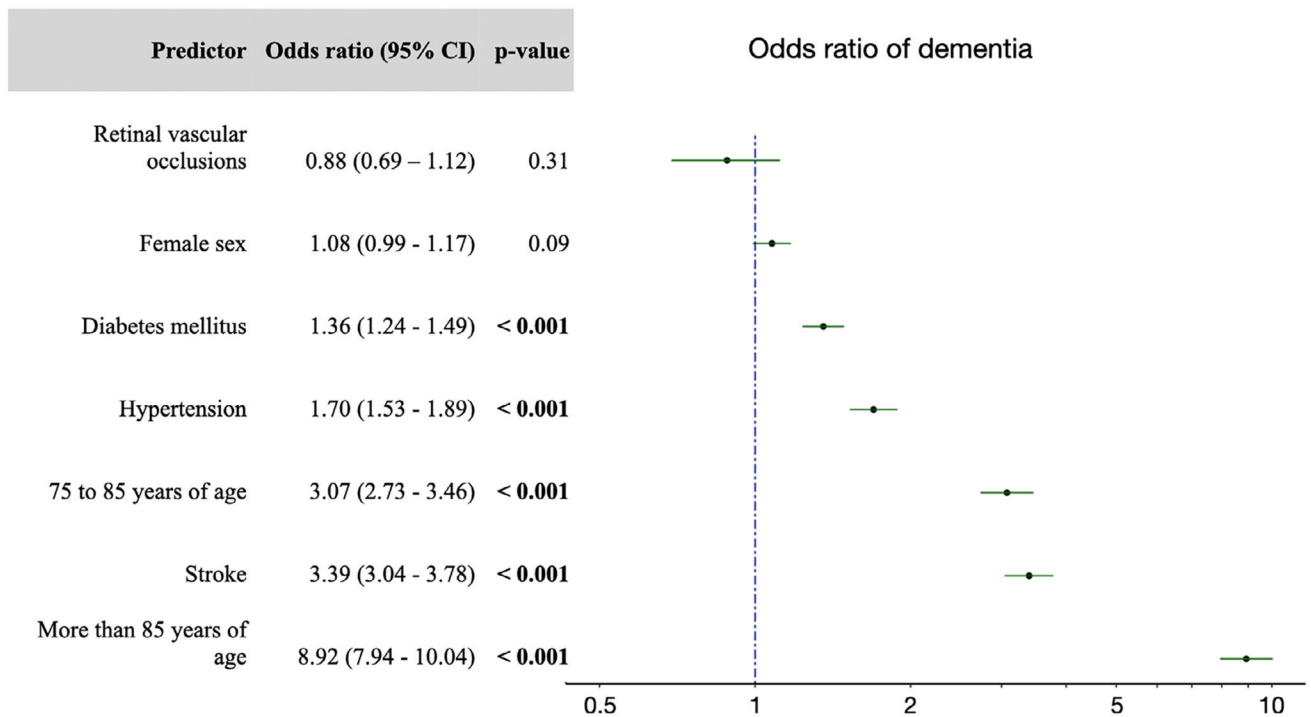
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**FIGURE.** Odds ratios for dementia. A multivariate logistic regression model was used to identify the presence of dementia. Covariates included stroke, female sex, hypertension, diabetes mellitus, and age groups 75–84 years of age and ≥ 85 years of age, with a reference age group of 65–74 years of age. Error bars represent 95% confidence intervals. The dotted line indicates an odds ratio of 1.

**TABLE 1.**

Characteristics of the Study Cohort<sup>a</sup>

	Retinal Vascular Occlusions Present n = 904	Retinal Vascular Occlusions Absent n = 36,304	P Value
Mean ± SD age, y	79 ± 8	76 ± 8	< .001
Females	461 (51.0)	20,756 (57.2)	< .001
Race			.62
White	603 (66.7)	24,269 (66.8)	
Asian	112 (12.4)	5,011 (13.8)	
Black	33 (3.7)	1,067 (2.9)	
Native Hawaiian or Pacific Islander	4 (0.4)	154 (0.4)	
American Indian or Alaska Native	3 (0.3)	133 (0.4)	
Other	154 (17.0)	5,770 (15.9)	
Dementia	84 (9.3)	2,440 (6.7)	.003
Stroke	164 (18.1)	2,645 (7.3)	< .001
Hypertension	696 (77.0)	22,556 (62.1)	< .001
Diabetes mellitus	329 (36.4)	9,768 (26.9)	< .001

Table values are mean ± SD and n (%).

<sup>a</sup>Mean and standard deviations are reported for age. Percentages are reported for females, races, dementia, stroke, hypertension, and diabetes mellitus.

**TABLE 2.**

OR for Presence of Dementia in Individuals with Retinal Vascular Occlusions <sup>a</sup>

Age groups (n)	Covariates adjusted for	OR	95% CI	P Value
65 y (37,208)	None	1.42	1.12–1.78	.003
	Sex	1.42	1.12–1.78	.003
	Hypertension	1.27	1.01–1.59	.04
	Diabetes mellitus	1.36	1.08–1.70	.008
	Age	1.10	0.86–1.38	.44
	Stroke	1.12	0.88–1.41	.34
	Sex, hypertension and diabetes mellitus	1.27	1.00–1.58	.04
	Age and stroke	0.94	0.73–1.18	.59
65–74 y (18,382)	None	0.93	0.39–1.82	.85
75–84 y (12,777)	None	1.01	0.66–1.48	.96
85 y (6,049)	None	1.20	0.86–1.63	.27

OR: Odds ratio; CI: confidence interval.

Odds ratios are shown for the presence of dementia in individuals with retinal vascular occlusions, after adjusting for different covariates using multivariable logistic regression models.