Ophthalmic Epidemiology, 19(3), 127–136, 2012

ISSN: 0928-6586 print/ 1744-5086 online
DOI: 10.3109/09286586.2011.615452

informa
healthcare

ORIGINAL ARTICLE

Retinal Microvascular Abnormalities and Cognitive Function in Latino Adults in Los Angeles

Nicole M. Gatto[1], Rohit Varma[2,3], Mina Torres[2,3], Tien Y. Wong[4], Pam L. Johnson[3], Freddi Segal-Gidan[5], and Wendy J. Mack[3]

[1]Department of Epidemiology, School of Public Health, UCLA, Los Angeles, CA, USA, [2]Doheny Eye Institute and Department of Ophthalmology, USC Keck School of Medicine, Los Angeles, CA, USA, [3]Department of Preventive Medicine, USC Keck School of Medicine, Los Angeles, CA, USA, [4]Singapore Eye Research Institute, National University of Singapore, Singapore, and [5]Department of Neurology, USC Keck School of Medicine, Los Angeles, CA, USA

ABSTRACT

Purpose: Retinal vessels may provide a readily accessible surrogate approach to study vascular disease in brain small vessels. Previous epidemiologic studies of retinal microvascular abnormalities and cognition have not included large numbers of Latinos who have a high prevalence of diabetes and hypertension.

Methods: We used data from 809 elderly Latino participants in the Los Angeles Latino Eye Study (LALES) to assess whether retinal vessel caliber and microvascular abnormalities are cross-sectionally associated with lower cognitive function. Cognitive screening was conducted with the Cognitive Abilities Screening Instrument-Short form (CASI-S) and in-depth testing with the Spanish English Neuropsychological Assessment Scales (SENAS). Retinal photographs were used to identify retinopathy signs and measure retinal vessel caliber.

Results: A total of 65.8% had high blood pressure, 34.5% had diabetes; self-reported diagnoses of heart attack, heart failure, angina and stroke were rare. Retinal calibers and any retinopathy were not associated with the CASI-S, total SENAS or any SENAS cognitive factors assessed as continuous variables. The odds of a low CASI-S score were two times higher in subjects with generalized arteriolar narrowing (OR = 2.04, 95% CI = 1.14, 3.66), and one and half times as high in those with both generalized arteriolar narrowing and retinopathy signs (OR = 1.49, 95% CI = 0.47, 4.75) though this result was based on only four cases with both risk factors and confidence limits were wide and included the null.

Conclusion: Retinal microvasculature imaging may provide insights into small blood vessel influences on cognition in Latino populations. Additional studies in diverse populations and prospective settings are needed.

Keywords: Epidemiology, Cognition, Retina, Latinos, Microvasculature

INTRODUCTION

A substantial proportion of elderly persons do not experience normal cognitive aging and develop cognitive impairment or dementia (estimated prevalence in US adults >65 years 17% and 10%, respectively).[1] Cardiovascular disease (CVD) is known to impact cognitive function in later years,[2] and vascular and metabolic risk factors including high blood pressure, overweight and obesity, diabetes and stroke[3] have been shown to be inversely associated with cognitive function[4] among middle-aged and older adults. Some studies have found an association between atherosclerosis (ie large vessel disease) and reduced cognitive function, while others have reported weak or null associations.[5–9]

The vast majority of brain blood vessels are "small blood vessels", ie arterioles <200μm in diameter. While assessment of the cerebral microvasculature may provide the strongest test of the influence of vascular disease on cognition, it is difficult to assess *in vivo* and other approaches are required. Given similarities in anatomy and physiology[10–12] retinal vessels may provide an alternative to non-invasively study brain small vessels. Abnormalities in the retinal vasculature[10,11,13] may be markers of concomitant cerebral microvascular disease, and are closely related to hypertension, stroke, MRI-detected subclinical

Received 07 April 2011; revised 15 June 2011; accepted 09 July 2011
Correspondence: Wendy J. Mack, PhD, USC Department of Preventive Medicine, 1540 Alcazar Street, Los Angeles, CA 90089-9010, USA. Tel: +1 323 442 1820. Fax: +1 323 442 2993. E-mail: wmack@usc.edu

infarcts and white matter lesions, cerebral atrophy and stroke-related death.[14–20]

Previous epidemiologic studies of retinal microvascular abnormalities and cognition suggest that some retinopathy signs, retinal caliber measurements and arteriolar geometry characteristics are associated with cognitive dysfunction, cognitive decline or dementia.[21–26] However, these studies did not have precise measures of cognition, and thus the assessment of cognitive dysfunction may be less than optimal.

While Latinos are the fastest growing segment of the US population,[27,28] no study of retinal microvascular abnormalities has included substantial numbers of Latino participants[11] and few population-based epidemiologic studies of cognitive function among Latinos exist. In the current study we use data from the Los Angeles Latino Eye Study (LALES), designed to study the prevalence and risk factors of ocular disease in adult Latinos, to assess whether retinal vessel calibers and abnormalities in retinal microvasculature are cross-sectionally associated with cognitive dysfunction.

MATERIALS AND METHODS

Study Population

Data for these analyses were collected in the LALES population-based cohort study of Latino adults. Details of the study design, sampling plan, and baseline data have been previously reported.[29] In brief, a door-to-door census of all residents living within six census tracts in La Puente, California was conducted between 2000–2003 to identify eligible individuals (≥40 years, self-identified Latino) who were informed of the study and invited to participate. Approval was obtained from the Los Angeles County/University of Southern California Medical Center Institutional Review Board. Written consent was obtained from all participants. All study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects.

Of 7,789 eligible participants identified, 6,357 (81.6%) completed a clinical examination. In 2001, the scope of LALES was expanded to include cognitive screening with the Cognitive Abilities Screening Instrument-Short form (CASI-S) and all participants prospectively enrolled from this point forward were eligible for cognitive screening; 2,931 (46.1% of the total subjects enrolled) were screened. Starting in 2003, in-depth prospective cognitive testing with the Spanish English Neuropsychological Assessment Scales (SENAS) was initiated in an elderly subsample who had cognitive screening and who were ≥60 years old ($n = 322$, 11.0% of those screened with CASI-S; 16.3% of subjects ≥60 years old enrolled in LALES; 38.4% of those ≥60 years old and screened with CASI-S). For the current analysis, we identified LALES participants who were ≥60 years old who had both a CASI-S, an ocular examination ($n = 838$) and retinal fundus photographs taken. The analyses herein are based on two subsets for whom (1) retinal images were available and grading for quantitative measurements of retinal vessel caliber was performed ($n = 809$), and (2) retinal images were available/graded and SENAS testing was completed ($n = 281$).

Data Collection

A questionnaire assessing sociodemographic factors, ocular and medical histories and access to care was administered in English or Spanish during an in-home interview portion of the LALES study. Participants were asked to report whether they had ever been diagnosed with or received treatment for health conditions including hypertension, diabetes, or CVDs including heart disease, heart failure, angina or stroke. Smoking and depressed mood were queried. After the in-home interview was completed, appointments were scheduled for participants to receive a medical and ocular examination at which time non-fasting glucose, systolic (SBP) and diastolic (DBP) blood pressure, height and weight measurements were collected.

Assessment of Cognitive Function

Cognitive screening was conducted during the in-home interview with the CASI-S, an abbreviated version of the Cognitive Abilities Screening Instrument[30] developed as a brief screening instrument to identify potentially demented individuals of various levels of education[31], and adapted for LALES to include computer-assisted administration and scoring. The CASI-S includes four subtests: verbal registration (immediate recall of three words), temporal orientation, verbal fluency and verbal recall (delayed recall of three words) with a score range of 0–33. Sensitivity and specificity of the CASI-S to identify individuals with dementia for subjects whose education level is 10–22 years using a score ≤24 are 90% and 94%, respectively, and 96% and 80%, respectively for subjects with 4–9 years of education.[31] As the CASI-S was not designed to screen for mild cognitive impairment, we conducted in-depth cognitive testing using the SENAS, which was developed to test a range of cognitive abilities psychometrically matched between Spanish and English versions.[32] The SENAS consists of the following measures: word list learning, spatial configuration learning, category fluency (animals & supermarket), phonemic fluency (letters F & L), list sorting (two lists), digit span forward, digit span backward, verbal conceptual thinking, object naming, picture association, pattern recognition and spatial localization that assess both verbal and non-verbal aspects of cognition.[33–35] Average internal consistency reliability coefficients for

SENAS non-memory scales are 0.85 for non-Hispanic English speakers, 0.86 for Hispanic English speakers and 0.88 for Hispanic Spanish speakers, indicating uniformly high and consistent reliability across groups.[35] The SENAS has been shown to have high construct validity based on structural equation modeling relating scales to latent variables in both English and Spanish (ie inferences can legitimately be made from the cognitive areas assessed to actual cognitive abilities).[35] To reduce the number of statistical tests, we combined SENAS measures into broader cognitive factors, using loadings from a factor analysis to identify correlated measures, and then computing sums of their z-scores. Two cognitive factors were created: (1) working and semantic memory (including digit span forward and backward, list sorting, verbal conceptual thinking, object naming, picture association, pattern recognition), and (2) verbal learning and memory (word list learning tests, immediate and delayed recall). The four other SENAS tests (spatial configuration learning, spatial localization, category fluency, phonemic fluency) were examined individually because correlations with other tests were low. Thus, we examined six areas of cognitive function and also created a measure of global cognition computed as the total sum of the z-scores for all SENAS scales.

Retinal Photography

Retinal fundus photographs were shot on 35mm Ektachrome 100 slide film (Kodak, Rochester, NY) with a Topcon TRC 50EX Retinal Camera. Stereoscopic fundus photographs were graded for retinopathy signs at the Ocular Epidemiology Grading Center at the University of Wisconsin, Madison by graders masked to subject identity. Retinopathy signs assessed included microaneurysms, retinal hemorrhages, drusen (soft or hard exudates), macular edema, intraretinal microvascular abnormalities, venous beading, neovascularization on the disc or elsewhere, and vitreous hemorrhage. In subjects who had more than one ocular examination with retinal photographs taken, we selected photographs from the exam that was closest in time to cognitive assessment; all photographs selected were within 6 months of cognitive assessment.

When available, two stereoscopic slides representing field 1 centered on the temporal edge of the optic disc (OD) of each eye were sent to the Center for Eye Research Australia, University of Melbourne, for quantitative measurements of retinal vessel caliber. Slides were digitized using a Nikon Scanner at 180dpi and saved as JPEG files of 1-2MB. Digital images were uploaded into a computerized semi-automated vessel measurement program to quantify retinal arteriolar and venular calibers. This software measures the diameter of both the arterioles and venules that course through a specific region of the eye located 0.5–1.0 OD diameters from the OD margin. The average diameters for all arterioles and venules measured in this region were summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively based on formulas by Knudtson.[36]

Statistical Analysis

Subjects were identified as being diabetic if they reported having been diagnosed with diabetes; had a history of diabetes and were being treated with oral hypoglycemic medications, insulin, or diet alone; had a hemoglobin A1c (HbA1c) ≥7.0%; or had a non-fasting glucose >200 mg/dL. Hypertensive subjects were those who self-reported a diagnosis of hypertension or had a clinic-measured blood pressure >140/90 mmHg. Body mass index (BMI) was calculated (weight [kg]/height [m]^2), and three outlying values (BMI >100) were set to missing. Any retinopathy (yes, no) was defined as the presence of any of the retinopathy signs listed above. CRAE and CRVE which were strongly correlated between eyes ($r^2 = 0.51$ and $r^2 = 0.60$, respectively) were averaged across eyes. Following procedures used in other population-based cohort studies, generalized arteriolar narrowing was defined as CRAE in the lowest quartile of the population (<143 μm), while generalized venular widening was defined as CRVE in the highest quartile (≥243 μm).[37,38] Participants were categorized as having a low CASI-S or low SENAS if their total CASI-S or SENAS score was <10th percentile for their age in 5-year categories.

Multivariable general linear models were employed to calculate mean scores of cognitive measures by categories of, and estimate associations with retinal measures. We used logistic regression to estimate odds ratios (ORs) for a low CASI-S or SENAS score by the presence or absence of generalized arteriolar narrowing, generalized venular widening or any retinopathy. Simple models were adjusted for age at exam (continuous), gender, highest educational level achieved (0–5 years, 6–11 years, high school graduate, some college) and language of exam administration (Spanish, English). Full models were additionally adjusted for smoking (never, former, current) and hypertension (yes, no), and models of any retinopathy for diabetes (yes, no) to assess the effect of controlling for these additional CVD risk factors. Sensitivity analyses assessed the impact of adjustment for any CVD (self-reported diagnosis of heart disease, heart failure, angina or stroke) or depression (self-reported feelings of being downhearted and blue), as well as excluding participants with retinal images of lower grading quality.

RESULTS

Participants were predominantly Spanish-speaking females with a mean age of 70 (Table 1). The majority of participants were obese (BMI > 30 kg/m^2), had never

TABLE 1 Characteristics of LALES participants with CASI-S, SENAS and retinal imaging data included in analysis

	Mean ± SD or Number (%)	
Characteristic	Total population ($N = 809$)	Subset with SENAS ($n = 281$)
Age	70.3 ± 6.9	68.5 ± 6.9
Sex		
Male	328 (40.5)	105 (37.4)
Female	481 (59.5)	176 (62.6)
Education (years)		
0–5	318 (39.3)	92 (32.7)
6–11	282 (34.9)	114 (40.6)
12	124 (15.3)	41 (14.6)
>12	85 (10.5)	34 (12.1)
Income		
< $15,000	277 (41.0)	78 (32.6)
$15,000–$29,999	280 (41.5)	114 (47.7)
≥ $30,000	118 (17.5)	47 (19.7)
Primary language spoken		
English	195 (24.1)	53 (18.9)
Spanish	614 (75.9)	228 (81.1)
BMI (kg/m^2)	30.4 ± 5.6	30.9 ± 5.5
Waist circumference (cm)		
Males	98.7 ± 10.7	97.5 ± 10.6
Females	92.7 ± 13.3	90.5 ± 11.9
Diabetes	287 (34.5)	99 (35.2)
Treatment for diabetes	237 (82.6)	86 (86.9)
Duration of diabetes (years)	11.6 ± 10.7	9.7 ± 9.6
Non-fasting glucose (mg/dl)		
Non-diabetics	93.9 ± 14.8	95.5 ± 17.1
Diabetics	155.7 ± 75.6	142.6 ± 63.1
Systolic blood pressure (mmHg)	131.9 ± 19.7	130.0 ± 19.9
>140 mmHg	238 (29.4)	74 (26.3)
Diastolic blood pressure (mmHg)	72.6 ± 11.9	72.5 ± 11.8
>90 mmHg	55 (6.8)	18 (6.4)
Hypertension, measured or self-report	532 (65.8)	178 (63.4)
Smoking		
Never	524 (64.9)	182 (64.8)
Former	203 (25.1)	72 (25.6)
Current	81 (10.2)	27 (9.6)
Ever diagnosed with a stroke	51 (6.3)	14 (5.0)
Ever diagnosed with a heart attack	55 (6.8)	18 (6.4)
Ever diagnosed with heart failure	49 (6.1)	18 (6.4)
Ever diagnosed with angina	45 (5.6)	12 (4.3)
Any retinopathy, on ocular exam	170 (21.0)	54 (19.2)
Generalized arteriolar narrowing present*	195 (24.1)	51 (18.2)
Generalized venular widening present†	217 (26.8)	68 (24.2)
Depression‡		
None of the time	301 (43.8)	106 (40.9)
Some/little of the time	302 (43.9)	121 (46.7)
Most/all of the time	85 (12.4)	32 (12.4)
CASI-S Score, range	28.3 ± 3.9, 10–33	29.3 ± 3.4, 14–33
Total SENAS Score, range	-	25.7 ± 6.7, 5.2–41.6
Verbal learning	-	3.5 ± 1.0, 0.5– 5.5
Working and semantic memory	-	2.9 ± 0.7, 0.6– 4.7
Spatial learning	-	2.7 ± 1.0, 0– 4.9
Spatial localization	-	2.6 ± 0.9, 0– 5.0
Category fluency	-	3.6 ± 1.0, 0.8– 6.2
Phonemic fluency	-	1.8 ± 1.0, 0– 5.2

*CRAE in the lowest quartile (<143 μm); from retinal photography.
†CRVE in the highest quartile (≥243 μm); from retinal photography.
‡Self-reported feelings of being down-hearted or blue, mood variables obtained on home interview.
LALES, Los Angeles Latino Eye Study; CASI-I, Cognitive Abilities Screening Instrument-short form; SENAS, Spanish English neuropsychological assessment scales; BMI, body mass index; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

smoked, were of low income levels (<$30,000/year), and had less than a high school education. Nearly 66% of the study population had high blood pressure, and 17% reported having had at least one of the vascular conditions queried. Diabetes was prevalent in 34.5%, with the vast majority receiving treatment. Twenty-one percent had some type of positive retinopathy sign assessed on retinal fundus exam. The median CASI-S for the study population was 28.3, and 29.3 for the subset tested with the SENAS. This subset also tended to be younger than the overall study population, was somewhat more likely to speak Spanish as their primary language, and had a slightly lower prevalence of generalized retinal arteriolar narrowing. Mean total CASI-S and the total SENAS scores decreased with age (1 point per year, $P < 0.0001$, and one-quarter of a point per year $P < 0.0001$, respectively); women tended to score lower than men in their same age group across all ages (data not shown). Participants who spoke Spanish as their primary language scored lower on the CASI-S (unadjusted mean: 28.1 vs. 28.9, $P = 0.02$) and the SENAS (unadjusted mean: 24.8 vs. 29.3, $P < 0.0001$) compared to those whose primary language spoken was English. Participants with less than a high school education scored lower on the CASI-S (unadjusted mean: 27.9 vs. 29.4, $P < 0.001$) and the SENAS (unadjusted mean: 24.3 vs. 29.4, $P < 0.0001$) compared to those with at least a high school education.

Retinal caliber measures were associated with some vascular risk factors (Table 2). Subjects with any retinopathy had higher SBP compared to those without (135.3 vs. 131.0mmHg, $P = 0.02$) and had higher non-fasting blood glucose (153.3 vs. 106.4 mg/dL, $P < 0.0001$) but did not differ in DBP or BMI. Self reports

TABLE 2 Relationships between retinal caliber measurements and socioeconomic and vascular risk factors in LALES participants ($N = 809$)

Socioeconomic or Vascular risk factor	Retinal measure			
	Pearson correlation coefficient		Mean ± SD	
	CRAE (μm)	CRVE (μm)	Any retinopathy	No retinopathy
Systolic blood pressure	−0.15*	−0.01	135.3 ± 20.8	131.0 ± 19.5†
Diastolic blood pressure	−0.15*	0.01	71.6 ± 12.7	72.9 ± 11.7
Non-fasting glucose	0.11†	0.07	153.3 ± 70.8	106.4 ± 46.0*
BMI	0.02	0.05	30.9 ± 5.9	30.2 ± 5.6
	Mean ± SD		Number (%)	
Language				
English	150.5 ± 15.4	225.4 ± 20.3	50 (25.8)	144 (74.2)
Spanish	154.4 ± 14.8†	231.3 ± 21.7†	120 (19.6)	491 (80.4)
Income				
<$20,000	153.7 ± 14.9	229.7 ± 21.2	86 (20.8)	327 (79.2)
≥$20,000	153.2 ± 15.2	230.1 ± 21.5	53 (20.5)	206 (79.5)
Education				
< High school	154.4 ± 15.1	231.1 ± 21.3	126 (21.1)	472 (78.9)
≥ High school	150.8 ± 14.6†	226.2 ± 21.6‡	44 (21.3)	163 (78.7)
Hypertensive				
Yes	152.1 ± 14.6	229.3 ± 20.5	129 (24.3)	401 (75.7)†
No	156.1 ± 15.4*	230.8 ± 23.3	41 (14.9)†	234 (85.1)†
Diabetic				
Yes	155.2 ± 15.2	232.9 ± 21.8	132 (46.0)	155 (54.0)*
No	152.5 ± 14.9‡	228.1 ± 21.2†	38 (7.3)*	480 (92.7)*
Stroke				
Yes	149.6 ± 16.3	225.3 ± 21.2	17 (34.0)	33 (66.0)
No	153.7 ± 14.9**	230.1 ± 21.5	153 (20.3)††	601 (79.7)††
Heart attack				
Yes	157.1 ± 16.5	231.3 ± 21.4	18 (34.0)	35 (66.0)
No	153.2 ± 14.9**	229.8 ± 21.5	152 (20.2)††	600 (79.8)††
Heart failure				
Yes	154.6 ± 15.4	231.0 ± 20.6	13 (26.5)	36 (73.5)
No	153.4 ± 15.0	229.8 ± 21.6	157 (20.8)	599 (79.2)
Angina				
Yes	156.5 ± 17.3	233.2 ± 24.0	10 (22.2)	35 (77.8)
No	153.3 ± 14.9	229.7 ± 21.3	160 (21.1)	598 (78.9)

*$P < 0.0005$, †$P \le 0.002$, ‡$P \le 0.01$, ††$P < 0.05$, **$P \le 0.10$ from Chi-square or independent T-tests.
LALES, Los Angeles Latino Eye Study; BMI, body mass index; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

TABLE 3 Associations (β [SE(β)]) between retinal measures and cognitive tests for LALES participants*

	Cognitive measure (β [SE (β)])							
			SENAS Factors					
Retinal measure	Total CASI-S $N=809$	Total SENAS $N=281$	Verbal learning	Working and semantic memory	Spatial learning	Spatial localization	Category fluency	Phonetic fluency
Retinal arteriolar caliber								
1st quartile(<143 μm)	−0.34 (0.38)	0.60 (1.12)	0.11 (0.17)	0.06 (0.12)	0.07 (0.18)	0.10 (0.18)	0.14 (0.17)	0.16 (0.18)
2nd quartile (143–151 μm)	−0.03 (0.38)	−0.80 (0.98)	−0.08 (0.14)	−0.04 (0.10)	−0.06 (0.16)	0.30 (0.16)‡	0.08 (0.15)	−0.01 (0.16)
3rd quartile (152–161 μm)	−0.09 (0.37)	0.19 (0.93)	0.05 (0.14)	0.04 (0.10)	0.21 (0.15)	0.39 (0.15)**	−0.05 (0.14)	0.05 (0.15)
4th quartile (≥162 μm)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Generalized arteriolar narrowing (CRAE < 25th percentile)								
Present	−0.30 (0.32)	0.79 (0.97)	0.12 (0.14)	0.06 (0.10)	0.01 (0.16)	−0.13 (0.16)	0.14 (0.15)	0.15 (0.15)
Absent	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Retinal venular caliber								
1st quartile(<215 μm)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
2nd quartile (215–228 μm)	−0.44 (0.38)	−0.40 (1.01)	−0.09 (0.15)	−0.04 (0.11)	0.07 (0.17)	0.07 (0.16)	0.08 (0.15)	−0.01 (0.16)
3rd quartile (229–242 μm)	0.25 (0.38)	0.37 (0.99)	0.01 (0.15)	0.03 (0.10)	−0.25 (0.17)	−0.01 (0.16)	−0.39 (0.15)**	−0.21 (0.16)
4th quartile (≥243 μm)	−0.50 (0.38)	−1.45 (1.02)	−0.19 (0.15)	−0.14 (0.11)	−0.11 (0.17)	−0.02 (0.17)	−0.20 (0.15)	−0.26 (0.16)
Generalized venular widening (CRVE ≥75th percentile)								
Present	−0.45 (0.31)	−1.47 (0.83)††	−0.16 (0.12)	−0.15 (0.09)††	−0.04 (0.14)	−0.04 (0.13)	−0.07 (0.13)	−0.18 (0.14)
Absent	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Generalized arteriolar narrowing adjusted for generalized venular widening								
Present	−0.43 (0.32)	0.45 (0.99)	0.08 (0.15)	0.02 (0.10)	0.01 (0.16)	−0.14 (0.16)	0.12 (0.15)	0.11 (0.16)
Absent	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Any retinopathy†								
Present	−0.11 (0.37)	0.37 (1.00)	0.03 (0.15)	0.07 (0.10)	0.01 (0.16)	0.19 (0.16)	0.01 (0.15)	−0.04 (0.16)
Absent	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

*Adjusted for age at exam (continuous), gender, highest educational level (categorical), language of exam administration (Spanish, English), smoking (never, former, current), hypertension (yes, no).

†Included microaneurysms, retinal hemorrhages, drusen (soft or hard exudates), macular edema, intraretinal microvascular abnormalities, venous beading, neovascularization on the disc or elsewhere, and vitreous hemorrhage; adjusted for covariates above and diabetes (yes, no).

‡$P \leq 0.05$, **$P \leq 0.01$, ††$P \leq 0.10$ from Chi-square or independent T-tests.

LALES, Los Angeles Latino Eye Study; CASI-I, Cognitive Abilities Screening Instrument-short form; SENAS, Spanish English neuropsychological assessment scales; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

of hypertension, diabetes, and heart attack were associated with higher rates of any retinopathy compared to subjects who did not report these conditions

Associations of Retinal Measures with Continuous Cognitive Outcomes

Narrower retinal arteriolar calibers and generalized arteriolar narrowing were not associated with lower scores on cognitive measures assessed as continuous variables (Table 3). Wider retinal venular calibers were not associated with lower cognitive function, but subjects with generalized venular widening tended to have lower scores overall on the total SENAS ($\beta = -1.47$, SE[β] = 0.83, $P = 0.08$). Any retinopathy was not associated with the CASI-S, the total SENAS or any SENAS cognitive factors assessed as continuous variables (Table 3).

Associations of Retinal Measures with Lower Cognitive Function (Dichotomous Cognitive Outcomes)

Generalized arteriolar narrowing was associated with increased odds for a low CASI-S (OR = 2.04, 95% CI = 1.14, 3.66), but not with a low SENAS (Table 4). Additional adjustment for generalized venular widening strengthened the association between generalized arteriolar narrowing and low cognitive function. Generalized venular widening was associated with a low SENAS (OR = 2.28, 95% CI = 0.94, 5.54), but not a low CASI-S score. Subjects with any retinopathy tended to have low cognitive function (indicated by a low SENAS score), but confidence limits were wide and included the null.

To examine whether a greater number or severity of retinal microvascular changes had more impact on cognition, we assessed whether subjects with both generalized arteriolar narrowing and at least one of the retinopathy signs were more likely to have low CASI-S than subjects with either or neither of the retinal microvascular changes. Presence of both abnormalities was associated with one and a half times the odds of low cognitive function compared to neither change present (OR = 1.49; 95% CI = 0.47, 4.75; Table 4); however as above, confidence limits were wide and included the null, and only four subjects had both generalized arteriolar narrowing and any retinopathy. A similar analysis of low SENAS was precluded by small numbers of subjects with both generalized arteriolar narrowing and retinopathy signs.

Associations between retinal caliber measures and low CASI-S were driven by hypertension status. Generalized arteriolar narrowing was associated with two times the odds of low CASI-S in hypertensive subjects (OR = 2.09; 95% CI = 1.05, 4.17) while generalized venular widening was associated with greater odds of a low CASI-S in non-hypertensive subjects (OR = 2.65; 95% CI = 1.02, 6.88). Confidence intervals for odds ratios estimating associations between generalized

TABLE 4 Multivariable adjusted* odds ratios (95% CI) for low cognitive function (CASI-S or SENAS, <10th percentile total score) for retinal abnormalities in LALES

	Low CASI-S		Low SENAS	
Retinal measure	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Generalized arteriolar narrowing (CRAE <25th percentile)				
Present	21 (35.6)	2.04 (1.14, 3.66)	4 (13.8)	1.10 (0.32, 3.72)
Absent	38 (6.2)	1.0 *(ref)*	25 (11.0)	1.0 *(ref)*
Generalized venular widening (CRVE ≥75th percentile)				
Present	18 (8.3)	1.08 (0.59, 1.96)	11 (16.2)	2.28 (0.94, 5.54)
Absent	41 (6.9)	1.0 *(ref)*	18 (8.6)	1.0 *(ref)*
Generalized arteriolar narrowing adjusted for generalized venular widening				
Present	21 (10.8)	2.17 (1.19, 3.97)	4 (8.0)	1.39 (0.39, 4.88)
Absent	38 (6.2)	1.0 *(ref)*	25 (11.0)	1.0 *(ref)*
Any retinopathy†				
Present	5 (8.1)	1.23 (0.42, 3.54)	3 (17.7)	1.56 (0.35, 6.91)
Absent	54 (7.2)	1.0 *(ref)*	26 (10.0)	1.0 *(ref)*
Any retinopathy and generalized arteriolar narrowing†				
Both present	4 (6.8)	1.49 (0.47, 4.75)		-
Either present	23 (39.0)	0.73 (0.41, 1.30)		-
Neither present	32 (54.2)	1.0 *(ref)*		-

*Adjusted for age at exam (continuous), gender, highest educational level achieved (categorical), language of exam administration (Spanish, English), smoking (never, former, current), hypertension (yes, no).

†Included microaneurysms, retinal hemorrhages, drusen (soft or hard exudates), macular edema, intraretinal microvascular abnormalities, venous beading, neovascularization on the disc or elsewhere, and vitreous hemorrhage; adjusted for covariates above and diabetes (yes, no).

LALES, Los Angeles Latino Eye Study; CASI-I, Cognitive Abilities Screening Instrument-short form; SENAS, Spanish English neuropsychological assessment scales; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

arteriolar narrowing and venular widening and low CASI-S by diabetes status overlapped and included the null. Diabetes and hypertension stratified analyses for retinal measures and low SENAS were precluded by small numbers of subjects in strata. Results did not appreciably differ (change in βs or ORs not >6%) if an indicator of depression or any self-reported vascular condition was individually included in models, or if subjects with poor quality retinal images were excluded from analyses.

DISCUSSION

This study, the first to focus specifically on an elderly Latino population with a high prevalence of diabetes and hypertension provides limited support for associations between lower cognitive function and retinal vessel caliber or retinopathy signs. Elderly Latino adults with generalized arteriolar narrowing or venular widening were about two times as likely to have low overall cognitive function assessed by the CASI-S and SENAS, respectively. The combined presence of generalized narrowing and any of the retinopathy signs was associated with one and half times increased odds of low cognitive function. However, this result was based on only four cases with the combination of both risk factors and confidence limits included the null, thus should be interpreted accordingly.

In the Atherosclerosis Risk in Communities cohort, scores on Delayed Word Recall, Digit Symbol and Word Fluency were lower among African-American and Caucasian adult participants with some but not other retinopathies or with generalized narrowing (≤20% of the arteriole-to-venule ratio).[22] Odds of cognitive impairment (≤2 standard deviations or lower on each cognitive test) were higher with any retinopathy (ORs ~2) and generalized arteriolar narrowing. Scores on the Word Fluency test declined more over a 14-year follow-up in participants with any retinopathy.[25]

In the Cardiovascular Health Study, adjusted mean scores on the Digit Symbol Test were lower among elderly African-American and Caucasian participants with any retinopathy present compared to those without, but did not differ by the presence/absence of AV nicking, focal arteriolar narrowing, or by arteriolar or venular caliber.[23] Scores on the Modified Mini-Mental State Examination (MMSE) were lower with focal arteriolar narrowing. Prevalent dementia was also greater with focal arteriolar narrowing; among persons with hypertension, any retinopathy was associated with dementia (ORs ~2).

In the Blue Mountain Eye Study of Australian adults, retinal venular dilation but not arteriolar narrowing was associated with greater prevalence of cognitive impairment (OR ~1.8) indicated by an MMSE ≤23. Retinopathy was associated with cognitive impairment only among participants with hypertension.[26] Wider retinal venules but not narrower arterioles was associated with an increased risk of vascular dementia among elderly participants in the Rotterdam Study.[24]

Suboptimal retinal vascular network geometry was associated with decreased cognitive ability among elderly community-dwelling Scottish adults.[21] Effect sizes were small with retinal indices explaining approximately 2–3% of the variance in some cognitive tests, which approximates effect sizes for some measures in our study (ie 2.7% of variance in low CASI-S was explained by generalized arteriolar narrowing).

Taken together, previous population-based studies suggest that generalized retinal arteriolar narrowing and AV nicking, which are thought to be reflective of early stages of pathophysiological processes in the retinal circulation associated with elevated blood pressure were not associated with lower cognitive function, cognitive impairment or dementia. In contrast, cognitive associations with venular widening, which may be reflective of inflammation, cerebral hypoperfusion and cerebrovascular disease[24] are supported. Retinopathies, which are thought to reflect more advanced stages of pathophysiological processes in the retinal vasculature were generally associated with lower cognitive function, cognitive impairment and dementia. It is unclear from a mechanistic standpoint why focal narrowing and the suboptimal geometry, also reflective of earlier pathophysiological stages, were associated in other studies with lower cognitive function while others of similar severity were not. The LALES study indicates that retinal vessel changes reflective of less severe stages of pathology and retinopathies reflecting more severe pathology may not be useful to distinguish between differences in cognition across the continuous spectrum of abilities, but do correlate with reduced cognitive function evaluated categorically (ie lowest 10th percentile). Nevertheless, processes of retinal microvascular changes overlap and do not necessarily present sequentially.[11,13] In our study, about 16% of subjects who had a retinopathy did not have retinal arteriolar narrowing (ie CRAE < 25th percentile).

Our study represents the most comprehensive assessment of cognitive function, in that the SENAS allowed us to examine verbal and non-verbal aspects of six different domains of cognitive function. Nevertheless, we detected associations with both the CASI-S cognitive screener and the SENAS neuropsychological battery. Granted, the CASI-S instrument is not designed to be sensitive to more mild cognitive impairment. Moreover, only one-third of subjects included in this analysis were tested with the SENAS, limiting our power to detect more subtle associations. Furthermore, despite adjustment in our models for socioeconomic and cultural factors such as primary language spoken, it is possible that our results are still confounded by these factors that relate to cognitive test performance. However, because study subjects were recruited as residents of a specified geographic location in Los Angeles County,

they are more homogeneous in socioeconomic factors than if recruited from a larger catchment area.

While the causes, systemic associations and clinical significance of retinal microvascular changes and abnormalities are not fully understood, evidence indicates that they may parallel changes to cerebral vasculature,[12] and may be reflective of cerebral microvascular disease.[39] Furthermore, retinal microvascular abnormalities are known to reflect arteriolar damage from hypertension and other processes[11] and are consistently related with stroke, cerebral atrophy and stroke-related death.[14–20] As such, retinal microvascular abnormalities are hypothesized markers of generalized vascular disease. As with previous reports,[40] we showed that narrower retinal arteriolar caliber was correlated with increased SBP and DBP, and self-reported diagnosis of stroke.[11] Retinopathy signs were associated with diabetes and most vascular conditions assessed, in line with the level of pathology they are thought to reflect. Another possibility is that atherosclerosis in large vessels may not reflect disease in small vessels. One study found that carotid artery intima-media thickness was significantly thicker in patients with strokes attributable to large vessel disease than small vessel disease.[41]

In conclusion, this study of an elderly Latino population with high rates of diabetes and hypertension provides limited evidence for an association between lower cognitive function and generalized retinal arteriolar narrowing, providing some support for an examination of the retinal microvasculature in analyses of vascular influences on cognition. Additional studies are merited in prospective settings and in diverse populations including those at high risk for CVD to further elucidate the relationship between retinal vessel abnormalities and cognition. Our results build on evidence substantiating the utility of examining the retina as a portal into the brain, which is encouraging given that clinical tools such as retinal fundus photography provide a fairly quick and non-invasive means to visualize the retinal microvasculature.

ACKNOWLEDGMENTS

Financial Support: This work was supported by grants from NEI EY11753 and NIA P50 AG05142 and 5-T32-AG00037.

***Declaration of interest*:** The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES

1. Larrea FA, Fisk JD, Graham JE, et al. Prevalence of cognitive impairment and dementia as defined by neuropsychological test performance. Neuroepidemiology 2000;19(3):121–129.
2. O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry 2006;14(9):724–733.
3. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics – 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115(5):e69–171.
4. National Institutes of Health. Cognitive and Emotional Health Project: The Healthy Brain. 24 July 2007. Available from: http://trans.nih.gov/cehp/ReviewDocs.htm
5. Breteler MM, Claus JJ, Grobbee DE, et al. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. BMJ 1994;308(6944):1604–1608.
6. Cerhan JR, Folsom AR, Mortimer JA, et al. Correlates of cognitive function in middle-aged adults. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Gerontology 1998;44(2):95–105.
7. Johnston SC, O'Meara ES, Manolio TA, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med 2004;140(4):237–247.
8. Muller M, Grobbee DE, Aleman A, et al. Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis 2007;190(1):143–149.
9. Gatto NM, Henderson VW, St John JA, et al. Subclinical atherosclerosis is weakly associated with lower cognitive function in healthy hyperhomocysteinemic adults without clinical cardiovascular disease. Int J Geriatr Psychiatry 2009;24(4):390–399.
10. Patton N, Aslam T, Macgillivray T, et al. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 2005;206(4):319–348.
11. Wong TY, Klein R, Klein BE, et al. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. Surv Ophthalmol 2001;46(1):59–80.
12. Kwa VI, van der Sande JJ, Stam J, et al. Retinal arterial changes correlate with cerebral small-vessel disease. Neurology 2002;59(10):1536–1540.
13. Tso MO, Jampol LM. Pathophysiology of hypertensive retinopathy. Ophthalmology 1982;89(10):1132–1145.
14. Baker ML, Hand PJ, Wong TY, et al. Retinopathy and lobar intracerebral hemorrhage: insights into pathogenesis. Arch Neurol 2010;67(10):1224–1230.
15. Baker ML, Wang JJ, Liew G, et al. Differential associations of cortical and subcortical cerebral atrophy with retinal vascular signs in patients with acute stroke. Stroke 2010;41(10):2143–2150.
16. Cheung N, Mosley T, Islam A, et al. Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study. Brain 2010;133(Pt 7):1987–1993.
17. Kawasaki R, Cheung N, Mosley T, et al. Retinal microvascular signs and 10-year risk of cerebral atrophy: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2010;41(8):1826–1828.
18. Yatsuya H, Folsom AR, Wong TY, et al. Retinal microvascular abnormalities and risk of lacunar stroke: Atherosclerosis Risk in Communities Study. Stroke 2010;41(7):1349–1355.
19. Lindley RI, Wang JJ, Wong MC, et al. Retinal microvasculature in acute lacunar stroke: a cross-sectional study. Lancet Neurol 2009;8(7):628–634.
20. McGeechan K, Liew G, Macaskill P, et al. Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis. Am J Epidemiol 2009;170(11):1323–1332.
21. Patton N, Pattie A, MacGillivray T, et al. The association between retinal vascular network geometry and cognitive ability in an elderly population. Invest Ophthalmol Vis Sci 2007;48(5):1995–2000.

22. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33(6):1487–1492.
23. Baker ML, Marino Larsen EK, Kuller LH, et al. Retinal microvascular signs, cognitive function, and dementia in older persons: the Cardiovascular Health Study. Stroke 2007;38(7):2041–2047.
24. de Jong FJ, Schrijvers EM, Ikram MK, et al. Retinal vascular caliber and risk of dementia: The Rotterdam Study. Neurology 2011;76(9):816–821.
25. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. Neurology 2009;73(11):862–868.
26. Liew G, Mitchell P, Wong TY, et al. Retinal microvascular signs and cognitive impairment. J Am Geriatr Soc 2009;57(10):1892–1896.
27. US Census Bureau. American Community Survey. Washington, DC: US Census Bureau, 2008.
28. US Bureau of the Census. We the American. Hispanics. Washington, DC: U.S. Government Printing Office, 1993.
29. Varma R, Paz SH, Azen SP, et al. The Los Angeles Latino Eye Study: design, methods, and baseline data. Ophthalmology 2004;111(6):1121–1131.
30. Teng EL, Hasegawa K, Homma A, et al. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr 1994;6(1):45–58; discussion 62.
31. Teng EL, Hasegawa K, Homma A, Yukimichi I, Larson EB, Sasaki H, White LR. A practical test for cross-cultural epidemiological studies of dementia: The cognitive abilities screening instrument (CASI). In: Orimo H, Fukuchi Y, Kuramoto K, Iriki M, editors. New Horizons in Aging Science. Tokyo: University of Tokyo Press, 326–327, 1992.
32. Mungas D, Reed BR, Marshall SC, et al. Development of psychometrically matched English and Spanish language neuropsychological tests for older persons. Neuropsychology 2000;14(2):209–223.
33. Mungas D, Reed BR, Crane PK, et al. Spanish and English Neuropsychological Assessment Scales (SENAS): further development and psychometric characteristics. Psychol Assess 2004;16(4):347–359.
34. Mungas D, Reed BR, Haan MN, et al. Spanish and English neuropsychological assessment scales: relationship to demographics, language, cognition, and independent function. Neuropsychology 2005;19(4):466–475.
35. Mungas D, Reed BR, Tomaszewski Farias S, et al. Criterion-referenced validity of a neuropsychological test battery: equivalent performance in elderly Hispanics and non-Hispanic Whites. J Int Neuropsychol Soc 2005;11(5): 620–630.
36. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. Curr Eye Res 2003;27(3):143–149.
37. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet 2001;358(9288):1134–1140.
38. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology 2003;110(5):933–940.
39. Goto I, Katsuki S, Ikui H, et al. Pathological studies on the intracerebral and retinal arteries in cerebrovascular and non-cerebrovascular diseases. Stroke 1975;6(3):263–269.
40. Ikram MK, de Jong FJ, Vingerling JR, et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. Invest Ophthalmol Vis Sci 2004;45(7):2129–2134.
41. Pruissen DM, Gerritsen SA, Prinsen TJ, et al. Carotid intima-media thickness is different in large- and small-vessel ischemic stroke: the SMART study. Stroke 2007;38(4): 1371–1373.