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Cognitive decline in older adults: What can we learn from optical coherence tomography (OCT)-based retinal vascular imaging?

Alison G. Abraham PhD[1,2,3] | Xinxing Guo MD, PhD[4] | Lubaina T. Arsiwala BDS, MHS[4] | Yanan Dong MHS[3] | A. Richey Sharrett MD, DrPH[3] | David Huang MD, PhD[5] | Qisheng You MD, PhD[5] | Liang Liu MD[5] | Brandon J. Lujan MD[5] | Alexander Tomlinson BS[5] | Thomas Mosley PhD[6] | Josef Coresh MD, PhD[3] | Yali Jia PhD[5] | Aleksandra Mihailovic ScM[4] | Pradeep Y. Ramulu MD, PhD[4]

[1]Department of Epidemiology, University of Colorado, Anschutz Medical Campus, Denver, Colorado, USA

[2]Department of Ophthalmology, University of Colorado, Anschutz Medical Campus, Denver, Colorado, USA

[3]Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[4]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[5]Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA

[6]The MIND Center, University of Mississippi Medical Center, Jackson, Mississippi, USA

Correspondence
Alison G. Abraham, MHS, MS, PhD,
13001 East 17th Place, 3rd Floor, Aurora, CO 80045.
Email: alison.abraham@cuanschutz.edu

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Abstract

Introduction: Accumulated vascular damage contributes to the onset and progression of vascular dementia and possibly to Alzheimer's disease. Here we evaluate the feasibility and utility of using retinal imaging of microvascular markers to identify older adults at risk of cognitive disease.

Methods: The "Eye Determinants of Cognition" (EyeDOC) study recruited a biracial, population-based sample of participants from two sites: Jackson, MS, and Washington Co, MD. Optical coherence tomographic angiography (OCTA) was used to capture vessel density (VD) from a 6 × 6 mm scan of the macula in several vascular layers from 2017 to 2019. The foveal avascular zone (FAZ) area was also estimated. Image quality was assessed by trained graders at a reading center. A neurocognitive battery of 10 tests was administered at three time points from 2011 to 2019 and incident mild cognitive impairement (MCI)/dementia cases were ascertained. Linear mixed-effects models were used to evaluate associations of retinal vascular markers with cognitive factor score change over time.

Results: Nine-hundred and seventy-six older adults (mean age of 78.7 (± 4.4) years, 44% black) were imaged. Gradable images were obtained in 55%

(535/976), with low signal strength (66%) and motion artifact (22%) being the largest contributors to poor quality. Among the 297 participants with both high-quality images and no clinically significant retinal pathology, the average decline in global cognitive function factor score was −0.03 standard deviations per year. In adjusted analyses, no associations of VD or FAZ with longitudinal changes in either global cognitive function or with incident MCI/dementia were found.

Conclusions: In this large biracial community sample of older adults representative of the target population for retinal screening of cognitive risk, we found that obtaining high-quality OCTA scans was infeasible in a nearly half of older adults. Among the select sample of healthier older adults with scans, OCTA markers were not predictive of cognitive impairment.

KEYWORDS

Alzheimer's disease, cognitive disease, optical coherence tomography angiography (OCTA), retinal markers

INTRODUCTION

There is growing awareness that dementias including Alzheimer's dementia may relate to accumulated vascular damage. By the time symptoms occur, the damage is typically pervasive. Finding markers of pre-symptomatic disease is critical for identifying persons for whom interventions might slow or halt progression. While MRI can give a picture of pathology in the brain, MRIs are costly and cannot detect early vascular signs of cognitive impairment such as microinfarcts.[1–4]

The retina may serve as a surrogate for brain pathology. The retina and the brain share common embryological development.[5] Resulting similarities in microvascular patterns and regulation suggest that pathological signs of systemic disease may be mirrored in both vascular systems.[5–8] This is true of diabetes and hypertension, the pathology of which is apparent in the retina in the form of microvascular damage including retinopathy, arteriolar narrowing, arteriovenous nicking, flame-shaped hemorrhages, and cotton-wool spots,[6,9–13] and in the brain as subcortical infarcts, smaller lacunes, white matter hyperintensities, and microbleeds.[14–16] Studies consistently show a correlation between retinal microvascular abnormalities and signs of small-vessel disease in the brain.[17–20] Prior work in the Atherosclerosis Risk in Communities (ARIC) study demonstrated that certain rare retinal abnormalities from photographs can predict cognitive decline and incident dementia.[21–23] Together, these finding strongly suggest that the eye contains useful information about brain pathology.

Key Points

- While optical coherence tomography angiography (OCTA)-based retinal microvascular markers are promising as surrogates for cognitive disease pathology, we did not find vascular density or foveal avascular zone area associated with cognitive decline in a large biracial community sample of older adults.
- Challenges in obtaining high-quality OCTA images in older adult communities may inhibit the ability to detect asscociations between retinal vascular biomarkers and cognitive outcomes, as artifacts are common among those with physical limiations and poorer vision.

Why Does this Paper Matter?

Here we show that obtaining high-quality OCTA images is challening in older adult real-world community samples, limiting the utility of OCTA as a potential screening tool for early cognitive disease. Among the select healthier subset with high-quality images, OCTA-based retinal vascular imaging biomarkers were not associated with cognitive decline.

Optical coherence tomography angiography (OCTA)[24,25] is a recent imaging modality that detects the motion of blood cells in capillary-sized vessels of the

retina, without the need for a contrast dye. Several small case–control studies have established tentative links between OCTA-based retinal vascular signs and the presence of Alzheimer's disease or mild cognitive impairment (MCI).[26–31] However, retinal microvascular indicators of concurrent clinical disease are less relevant for intervention efforts. To be valuable, OCTA-based retinal markers need to predict dementia risk during the early, preclinical stages of cognitive decline.

Here we present data from the Eye Determinants of Cognition (EyeDOC) study, which evaluated retinal OCTA measures in an aging, biracial, community-based sample without symptomatic cognitive disease and with excellent capture of cognitive function over time. EyeDOC aimed to evaluate the feasibility and clinical value of using retinal measures to help identify older adults at risk of future cognitive impairment.

METHODS

Study population

The EyeDOC study recruited a biracial population-based sample of participants from the Atherosclerosis Risk in Communities (ARIC) study from 2017 to 2019. ARIC participants were selected by probability sampling from four communities across the United States.[32] EyeDOC recruited ARIC participants from two of these sites (Jackson, Mississippi; and Washington County, Maryland) who had Mini Mental Status Exam (MMSE) scores >23 (in Washington Co) or > 21 (in Jackson). These thresholds were used to limit the sample to participants without signs of dementia. Study sites were integrally linked with racial distribution, as the Jackson site enrolled only black participants while the Washington Co site was mostly white. For analyses of retinal microvascular parameter associations with cognitive change, we included partipants with high-quality OCTA images, as determined by an established OCTA reading center (Center for Ophthalmic Optics and Lasers, Casey Eye Institute, Oregon Health and Sciences University). Both the ARIC study and EyeDOC study were approved by the Institutional Review Boards at each ARIC site, and all participants provided written informed consent at the EyeDOC study visit. The research adhered to the tenets of the Declaration of Helsinki.

Cognitive evaluation

A 10-test neurocogntive battery spanning several cognitive domains was administered to all participants during the fifth (2011–2013), sixth (2016–2018), and seventh (2018–2019) ARIC clinic visits. Factor scores were calculated from individual tests for the domains of memory and speed of processing/executive function based on a priori cognitive test categorization and previous work in the ARIC.[33] A global composite factor score was also created from factor analysis using all 10 test scores.[33] Incident MCI and dementia classifications were made algorithmically for each ARIC-NCS participant using all available data, which included neurocognitive test performance over time, the clinical dementia rating (CDR) instrument, functional activities questionnaire responses, and a neuropsychiatric inventory; a final adjudicated classification was made by a team of expert reviewers[34] based on published criteria.[35,36]

OCT retinal microvasculature evaluation

OCTA images of both 3×3 mm^2 and 6×6 mm^2 areas of the macula were captured with an RTVue-XR Avanti system spectral OCT system (OptoVue, AngioVue) in a single eye of each participant (randomly chosen) by trained staff at study sites. The RTVue-XR is capable of an axial resolution of 5 μm full width at half-maximum in tissue and a data acquisition rate of 70,000 axial scans per second. Images were assessed for quality at the reading center using an empirically determined signal strength index (SSI) threshold of 55 and subjective determination of artifacts that would bias retinal parameter estimation. These included motion artifacts, media opacities, focusing artifacts, and poor axial positioning.[37] High-quality images were processed using a customized software.[38–40] Retinal vascular density (VD), defined as the percentage of the imaging region occupied by blood vessels, was estimated in three distinct vascular plexuses (superficial vascular complex [VD_{Sup}], intermediate capillary plexus [VD_{Int}], and deep capillary plexus [VD_{Deep}])[38] from 6×6 mm^2 images. The foveal avascular zone (FAZ) area,[41]defined as the region in the fovea devoid of retinal blood vessels, was also estimated from 3×3 mm^2 images. The images were captured from 6 days to 31 months following the ARIC V6 visit with a mean of 16 months.

Retinal pathology review

Local ocular disease was also captured through formal review of macular and optic nerve head retinal fundus images by ophthalmologists at the Wilmer Eye Institute and used to exclude images with signs of any eye disease that could affect retinal microvascular health. All photographic images were graded by one primary

ophthalmologist grader for the presence or absence of pathology; images identified as showing any pathology were graded by a second ophthalmologist. Identification of retinal pathology was in accordance with the Early Treatment Diabetic Retinopathy Study Retinal Grading Protocol.[42] The grading for the OCT images are based on the system of International Nomoenclature for Optical Coherence Tomography Panel[43] and The International Vitreomacular Traction Study Group Classification of Macular Hole.[44]

Other covariates

Vision function was assessed at the imaging visit. Presenting distance acuity was captured with current correction lenses (if any) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Precision Vision, La Salle) with a retroilluminant light box. Near-distance acuity was assessed using the MNRead card (Precision Vision). Contrast sensitivity was assessed using the MARS chart (The Mars Perceptrix Corporation, Chappaqua). Pupil diameter was measured after dilation and prior to imaging.

Other covariate values for cross-sectional analyses were drawn from ARIC visit 6, which was the closest ARIC visit consistently prior to the EyeDOC visit. ARIC V5 values were used for longitudinal analysis. Missing data were drawn from neighboring visits when available. Sex, race/community (black/Jackson or white/-Washington Co), and education were recorded at the baseline ARIC visit (1987–89). Education was reported as the highest grade or year of school completed and categorized for the analysis as less than high school (basic education), high school or equivalent (intermediate education), or more than high school (advanced education). A short physical performance battery was administed that captured information on balance and gait[45] using a performance score (from 0 to 12, with higher scores indicating better physical ability). Hypertension was defined as systolic blood pressure (mean of second and third of three measures) ≥140 mmHg or diastolic blood pressure (mean of second and third of three measures) ≥90 mmHg or use of antihypertensive medication.[46] Diabetes was defined as fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL or if medication was being taken for diabetes or if there was a physician diagnosis of diabetes as self-reported by the participant. Depression was captured using the Center for Epidemiological Studies-Depression (CES-D) scale, using 16 as the threshold for clinically meaningful depressive symptoms.[47] Current alcohol use was categorized into drinker or nondrinker. Current cigarette smoking was categorized into smoker or nonsmoker.

Statistical methods

First, to understand factors that affected the image quality of OCTA images, we used quality data and ARIC V6 covariate data to characterize correlates of image failure among the full sample, and used *t*-tests, chi-squared, and exact tests as appropriate to compare the characteristics between particpants with quality-passed versus quality-failed images. Logistic regression was also used in a multivariable analysis to examine independent predictors of failed images. Then, to examine factors univariably associated with retinal microvascular parameters, we limited the sample to those with high-quality OCTA images and used linear regression analysis to examine the relationship between individual demographic, behavioral, and vision characteristics (drawn from ARIC V6 and the EyeDOC visit) with VD in the three layers and with FAZ.

To understand cross-sectional relationships between retinal microvascular parameters and cognitive function, we further limited the analysis to those without evidence of the following eye diseases as determined from retinal pathology review of images: glaucoma, advanced macular degeneration (including neovasuclarization and geographic atrophy), proliferative retinopathy, and retinopathy with edema. We drew from the ARIC V6 neuropsychological battery and used factor scores describing overall and domain-specific (memory and executive function) cognitive function as outcomes. Linear regression analysis was used to examine multivariable adjusted associations of VD and FAZ with overall and domain-specific cognition. Regressions were progressively adjusted for demographic and socioeconomic status (SES) factors (age, income, education) including race/community (black/Jackson or white/Washington Co), and then for comorbid and behavioral factors (current smoking, physical activity, hypertention, and diabetes) to evaluate the progressive influence of these factors on associations between retinal biomarkers and cognition.

We used the longitudinal cognitive factor scores from ARIC V5, V6, and V7 to examine the relationship between retinal microvascular parameters and longitudinal change in cognition over appromiately 7 years of follow-up. Covariate values for possible confounding factors were drawn from V5, the baseline visit for our capture of longitudinal change. The relationship of VD and FAZ with the slope of cognitive change was modeled using linear mixed-effects regression with random effects for the intercept and slope across time, and unstructured covariance to account for correlation of cognitive scores between the repeated visits. As a secondary outcome for longitudinal analysis, we also examined relationships of VD and FAZ with incident MCI or dementia in V7 using

logistic regression. These analyses were limited to participants without evidence of MCI/dementia at V5, the baseline visit, and whose EyeDOC visits fell between V6 and V7. Regressions were progressively adjusted for demographics and SES (age, sex, race/community, education) and comorbidity and behaviors (physical activity, hypertention, and diabetes).

Nonlinear relationships between cognitive outcomes and retinal microvascular parameters were evaluated using cubic polynomials. Models stratified by race/community were also estimated. Sensitivity analyses were done including data from all images regardless of quality.

RESULTS

There were 1073 indivduals who came for an EyeDOC visit, of whom 1064 also attended ARIC V6 and had V6 covariate data. Of these, four individuals of self-reported Asian race were excluded. There were 87 participants who refused or could not complete OCTA, leaving a final sample of 976 individuals (Figure S1). Overall characteristics of the community sample, stratified by OCTA image quality, are described in Table 1. Among those with gradable images, the average age was 78 years, 43% self-identified as black, and 62% were female. Based on retinal and optic nerve photograph review, 6% had likely glaucoma, 7% had signs of AMD with evidence of choroidal neovascularization (CNV) or geographic atrophy, and less than 1% had proliferative retinopathy for a total of 14% with one or more of these conditions.

Feasiblity of OCTA imaging in an older adult population and predictors of poor-quality images

Gradable images were obtained in 55% (535/976) of those who were imaged. For the remainder, images were judged to be too poor to yield reliable retinal vascular measures. Of the failed scans, the primary reasons for poor quality included low SSI (66%), motion artifact (22%), defocus (<1%), significant media opacity (5%), problems with axial positioning (4%), and other artifacts (2%).

In univariable comparisons, several factors differed between those with and without gradable OCTA images including age, physical ability, near and distance visual acuity, contrast sensitivity, significant retinal/optic nerve pathology, and global cognitive score. In multivariable regression, only three predictors of unsuccessful imaging persisted: worse presenting distance visual acuity (1.2 times the odds of a failed scan per one line decrement in visual acuity; $p < 0.001$), worse contrast sensitivity (1.1 times the odds of a failed scan for 0.1 log CS poorer contrast sensitivity; $p = 0.026$), and, unexpectedly, the absence of retinal pathology seen in retinal photos (0.6 times the odds when AMD, likely glaucoma, or retinopathy was observed in images; $p = 0.010$).

Distribution and predictors of vascular density

Among the 535 eyes with gradable images (Figure S1), distributions of VD_{Sup}, VD_{Int}, and VD_{Deep} were nearly normal. The mean VD_{Sup} was 47% with an interquartile range (IQR) of 43%–52% in the sample. The mean VD_{Int} was 38% with an IQR from 34% to 42% in the sample, while mean VD_{Deep} was 22% with an IQR from 17% to 28% in the sample. The VD_{Int} and the VD_{Deep} were highly correlated with a Spearman correlation coefficient of 0.81, while the VD_{Int} and VD_{Sup} had a weak positive correlation of 0.15 and the VD_{Deep} and VD_{Sup} had a weak negative correlation of -0.14. The factors that most strongly univariably related to higher VD_{Sup} included lower age, white race/Washington Co, higher physical ability, better vision, and larger pupil diameter. The factors that most strongly univariably related to higher VD_{Deep} included black race/Jackson, no alcohol intake, smaller pupil diameter, and higher SSI. No factors were consistently associated with VD in a similar direction across the layers (Table S1). Notably, diabetes was not significantly associated with VD in any layer.

Mean FAZ area was 0.30 mm^2 with an IQR from 0.21 to 0.37 mm^2 in the sample. FAZ area was most strongly correlated with VD_{Sup} ($\rho = -0.20$), and the correlation was negative as expected. The univariable predictors of greater FAZ area included black race/Jackson, female sex, no alcohol intake, smaller pupil diameter, and higher SSI (Table S1).

Cross-sectional associations between retinal signs and prevalent cognitive status

As local eye disease can directly affect retinal microvascular health, we limited the sample to the 480 participants with no clinically significant retinal pathology (Figure S1). In this sample, univariable relationships between global cognitive function and VD appeared nearly linear across the full range of VD except for VD_{Sup} (Figure S2); however, polynomial terms did not improve the fit, so the relationship was modeled as linear. As VD_{Int} and VD_{Deep} were highly correlated, we did not

evaluate cross-sectional relationships with VD_{Int}. Table 2 shows the linear associations from regression analysis in nested models adjusted for potential confounders. Associations of VD with global cognitive function and with the subdomains were null in final models for all layers. Race/community was found to be the primary confounder that nullified associations, suggesting a strong relationship of race/community context (beyond standard

TABLE 1 Characteristics of the 976 older adults from Jackson, MS, and Washington Co, MD, imaged in the EyeDOC study comparing those with gradable and ungradable images

	Without gradable images ($N = 441$)	With gradable images($N = 535$)	
Participant characteristics from ARIC V6	**Mean (SD) or %**		***p***
Demographics and SES factors			
Age (years)	79.3 (4.5)*	78.2 (4.2)*	<0.001
Body mass index (kg/m^2)	29.3 (5.5)	29.6 (5.7)	0.418
Black race/Jackson (%)	45.4	43.4	0.560
Female	64.2	61.9	0.465
Household income			0.272
< $35,000/year	49.9	44.9	
$35,000 to 74,999/year	29.5	33.6	
> $75,000/year	14.3	14.4	
Education			0.431
Basic education	18.6	16.3	
Intermediate education	38.8	42.4	
Advanced education	42.6	41.1	
Behaviors and comorbidities			
Current smoking	8.6	8.4	0.909
Current alcohol intake	40.8	38.1	0.430
Clincally significant depressive symptoms	0.2	0.4	1.000
Diabetes	38.1	38.7	0.642
Hypertension	81.6	82.4	0.802
Physcial performance score	8.2 (2.9)*	8.6 (2.6)*	0.037
Vision and eye			
Eye imaged			0.563
Left	49.9	51.0	
Right	50.1	49.0	
Near visual acuity (log MAR)	0.3 (0.3)*	0.2 (0.3)*	0.012
Presenting distance visual acuity (logMAR)	0.3 (0.2)*	0.2 (0.2)*	<0.001
Contrast sensitivity (log CS)	1.3 (0.3)*	1.4 (0.2)*	<0.001
Pupil diameter (mm)	6.3 (1.9)	6.5 (1.8)	0.338
Significant retinal/optic nerve pathology	9.3*	13.8*	0.029
Cognition and cognitive status			
Global cogntition score	−0.2 (0.9)*	−0.1 (0.8)*	0.012
Cognition status			0.679
Normal cogntition	83.4	85.2	
Mild cognitive impairment	13.8	12.7	
Dementia	2.7	2.1	

Note: Column percentages not summing to 100% represent factors with missing data.

*Statistical significance at an α level of 0.05.

TABLE 2 Cross-sectional associations of vessel density (VD) in the superficial vascular complex and deep capillary plexus and foveal avascular zone (FAZ) area with cognitive performance (global and domain specific) among 480 particpants in EyeDOC without retinal pathology

Factor score outcome	Model 0: Crude coefficient estimate (*p* value)[a]	Model 1: Demographics, SES, and race/community adjusted[b]	Model 2: Model 1 + comorbidity and behavior adjusted[c]
Exposure: Superficial vascular complex vessel density (per 10%)			
Global function	0.26 (0.15, 0.37)*	−0.02 (−0.07, 0.01)	−0.02 (−0.7, 0.01)
Memory	0.07 (−0.02, 0.17)	−0.03 (−0.13, 0.06)	−0.03 (−0.13, 0.06)
Executive function	0.27 (0.16, 0.38)*	0.03 (−0.06, 0.12)	−0.02 (−0.07, 0.11)
Exposure: Deep capillary plexus vessel density (per 10%)			
Global function	−0.09 (−0.19, 0.01)	−0.01 (−0.06, 0.09)	−0.01 (−0.06, 0.09)
Memory	−0.03 (−0.12, 0.06)	−0.01 (−0.09, 0.08)	−0.01 (−0.10, 0.08)
Executive function	−0.10 (−0.20, 0.01)	−0.03 (−0.05, 0.11)	0.02 (−0.06, 0.10)
Exposure: Foveal avascular zone area (mm^2)			
Global function	−1.62 (−2.22, −1.02)*	0.11 (−0.42, 0.65)	0.23 (−0.31, 0.77)
Memory	−0.38 (−0.93, 0.16)	0.05 (−0.54, 0.64)	0.17 (−0.44, 0.78)
Executive function	−1.61 (−2.25, −0.98)*	0.17 (−0.40, 0.73)	0.24 (−0.33, 0.81)

[a]Interpreted as the difference in cognitive function factor score per 10% increase in VD (area covered by vessels) or by 1 mm^2 larger FAZ area.
[b]Model 1: Adjusted for age, sex, income, education, black race/Jackson study site.
[c]Model 2: Adjusted for age, sex, income, education, black race/Jackson study site, current smoking, physical activity, hypertention, and diabetes.
*Statistical significance at an α level of 0.05.

SES factors) with both retinal miscrovascular health and cognition. Consistent with this finding, univariable associations were null when stratfied by race/community.

FAZ area was also examined as an exposure, and assocations with cognitive function level were similary null in final models, with race/community being the primary confounding factor that attenuated associations (Table 2). In race/community stratified models, there was some evidence of differences in crude associations between blacks from Jackson and whites from Washington County (blacks: –0.88 [95%CI: –1.68, −0.08] versus whites: 0.38 [95%CI: –0.47, 1.22)], but differences were attenuated and associations became nonsignificant after adjustment for other factors.

Associations of retinal signs with cognitive change and incident MCI

Lastly, we looked at change in cognitive function and incident MCI among the 297 participants with no baseline (ARIC visit 5) indication of MCI or dementia, and an EyeDOC visit prior to V7 (Figure S1). In linear mixed-effects models of the linear change in global cognitive function, the estimated average decline in global cognitive function factor score was −0.03 standard deviations per year (95%CI –0.04, −0.03) between ARIC V5 and V7, representing very little change over time in this relatively healthy population. Graphs of the estimated linear slope of global cognitive function from V5 to V7 versus VD_{Sup}, VD_{Int}, VD_{Deep}, and FAZ indicated no notable relationships (Figure 1). Echoing the graphical analysis, in models including VD and interactions with time, no associations of either VD_{Sup} or VD_{Deep} with longtitudinal change in global cognitive factor score in crude or adjusted models were found; point estimates for the relationship were approximately null (Table 3). We also examined incident MCI or dementia in the V7 ARIC follow-up visit, which was a median of 3 months after the EyeDOC visit. There were 37 incident cases among the incident sample of 297 for a cumulative incidence of 12%. Point estimates of the association with VD were again nearly null in both crude and adjusted models, though the direction indicated slower declines in cognitive function with higher VD. Similarly, no meaningful associations were found between FAZ area and either linear change in global cognitive function or incident MCI/dementia.

Sensitivity analyses using full sample without regard for image quality

Using an expanded sample that included all OCTA data regardless of image quality, we reran the analyses. In 670 older adults with no clinically significant retinal pathology, the estimated relationship between VD_{Sup} and global

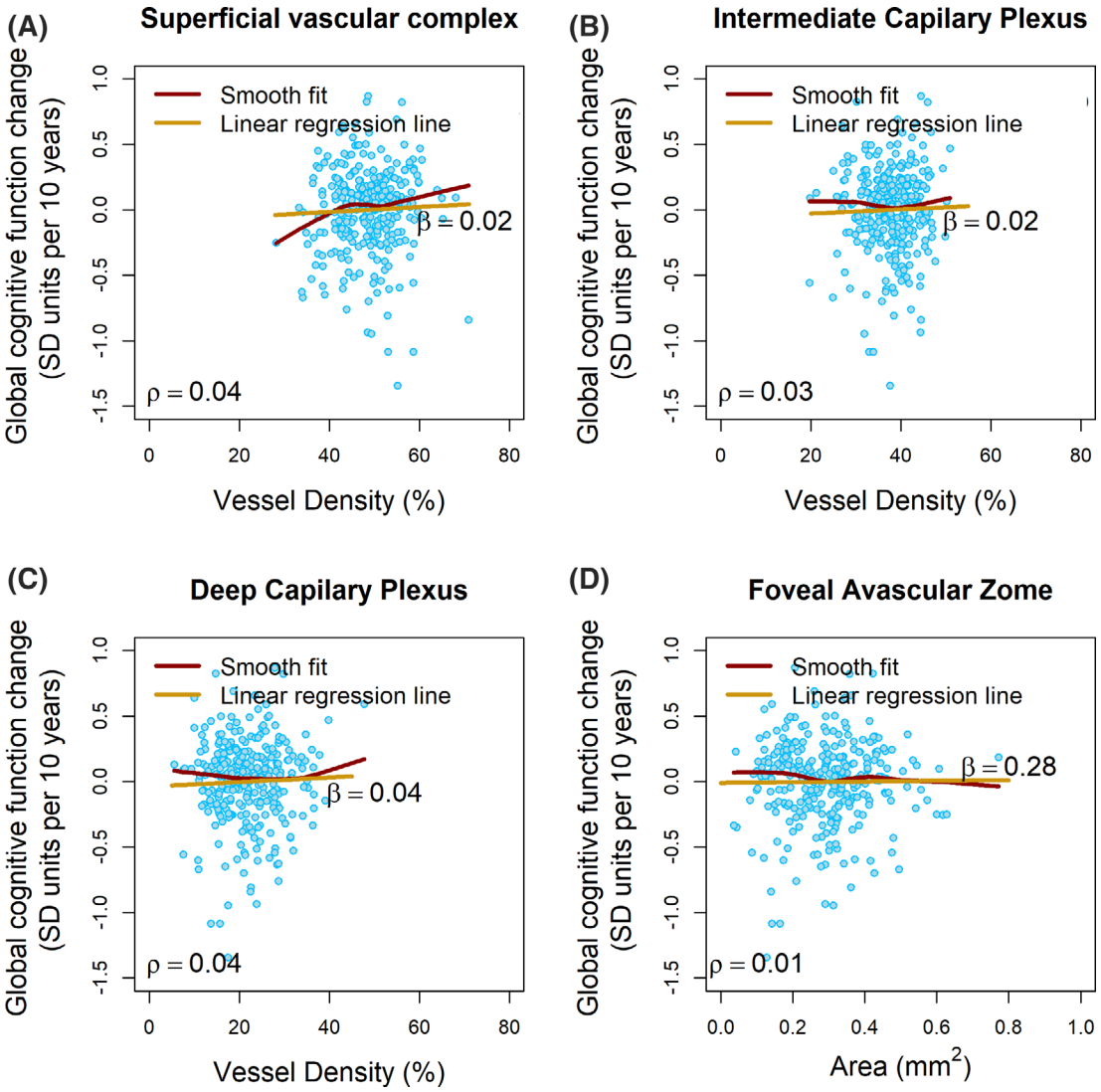

FIGURE 1 Relationship of the estimated change in global cognitive function over 7 years with retinal vascular features in 297 older adults from Jackson, MS, and Washington Co, MD, imaged in the EyeDOC study. Panels A, B, and C show vessel density (VD) in the superficial vascular plexus intermediate capillary plexus and deep capillary plexus layers of the retina, respectively, while panel D shows foveal avascular zone area (FAZ). Solid line is the locally weighted scatterplot smoothing (LOWESS) fit, while the broken line is the univariate linear regression fit with the slope estimate β, interpreted as the 10-year difference in cognitive function z-score per 10% change in VD (area covered by vessels) or 1 mm^2 change in FAZ. Pearson correlation ρ is shown in the bottom left of each figure

cognitive function level was 0.04 SDs (95% CI −0.08, 0.15; $p = 0.532$) in the fully adjusted model. In an expanded sample of 423 with no baseline (ARIC visit 5) indication of MCI or dementia and an EyeDOC visit prior to V7, the fully adjusted effect estimate for the 10-year difference in global cognitive function z-score per 10% change in VD_{Sup} was 0.07 SDs (95% CI: −0.08, 0.02; $p = 0.364$).

DISCUSSION

Findings markers of pre-symptomatic cognitive disease is key to identifying persons for whom interventions might slow or halt progression before brain pathology becomes pervasive and functional loss becomes irreversible. While studies suggest retinal features may serve as biomarkers of cogntivie disease, they must be feasible to obtain in a real-world sample and provide information early in the disease process.

The current study used a biracial, community-based sample of healthy older adults to evaluate the feasibility of obtaining OCTA-based retinal vascular markers and their value for discriminating cognitive function decline. Our results suggest two main conclusions: First, given the current OCTA technology, obtaining sufficiently high-quality scans is often infeasible in a real-world

TABLE 3 Longitudinal associations of vessel density (VD) in the superficial vascular complex and deep capillary plexus and foveal avascular zone area (FAZ) with change in cognitive performance between ARIC V5 and V7 and incident MCI/Dementia among 297 particpants without baseline MCI/Dementia and EyeDOC visits prior to ARIC Visit 7

Outcome	Crude	Fully adjusted: Demographics, SES, and comorbidity[a]
Exposure: Superficial vascular complex vessel density (per 10%)		
Coefficient estimate (95% CI)[b]		
Change in global function (SDs over 10 years)	0.02 (−0.08, 0.13)	0.04 (−0.07, 0.15)
Odds ratio (95% CI)[c]		
Incident MCI/dementia	0.99 (0.93, 1.04)	0.99 (0.94, 1.04)
Exposure: Deep capillary plexus vessel density (per 10%)		
Coefficient estimate (95% CI)[b]		
Change in global function (SDs over 10 years)	0.04 (−0.07, 0.15)	0.03 (−0.08, 0.14)
Odds ratio (95% CI)[c]		
Incident MCI/dementia	0.98 (0.93, 1.03)	0.98 (0.94, 1.04)
Exposure: Foveal avascular zone area (per mm^2)		
Coefficient estimate (95% CI)[b]		
Change in global function (SDs per 10 years)	0.28 (−0.31, 0.87)	0.24 (−0.35, 0.83)
Odds ratio (95% CI)[c]		
Incident MCI/Dementia	0.93 (0.73, 1.18)	0.93 (0.72, 1.22)

[a]Adjusted for age, sex, black race/Jackson, education, physical activity, hypertention and diabetes.
[b]Interpreted as the 10-year difference in cognitive function z-score per 10% change in VD (area covered by vessels) or 1 mm^2 change in FAZ.
[c]Interpreted as the OR for incident MCI/dementia per 10% change in VD (area covered by vessels) or 1 mm^2 change in FAZ.

population. We were able to obtain high-quality images in only 55% of our older adult community sample. Those successfully imaged differed from those not successfully imaged in a number of ways including slightly better cognitive scores. This is particularly concerning for the use of OCTA as a tool for studying cognition, as it suggests those most at risk of poor cognitive outcomes were least likely to have interpretable scans, though sensitivity analyses indicated that the exclusion of those with poorer images did not greatly impact estimates. Improvements in imaging software and image processing algorithms could substantially increase image quality and yield more representative samples. Notably, both pupil diameter (which speaks to both the amount of light and the aperture through with images can be captured) and SSI were associated with VD, suggesting that image quality measures need to be captured and accounted for in studies of retinal vascular markers.

=Second, among older adults in whom high-quality scans can be obtained, vascular markers were not strongly correlated with cognitive decline or risk of incident MCI/dementia. While earlier work in the ARIC using retinal photographs found associations between retinopathy and cognitive decline in longitudinal analyses, retinopathy is a severe sign of retinal microvascular damage seen in <1% of our sample.

These findings contrast with studies of OCTA-based retinal vascular markers and prevalent Alzheimer's disease, which have found associations[26–31] with only a few exceptions.[48,49] However, studies of earlier cogntive disease have been mixed. One study found higher VD in preclinical AD,[50] while a second found relationships for AD but not MCI.[31] Cross-sectional studies of cognitive status are particularly prone to confounding bias due to myriad demographic and SES factors that drive cognitive function levels. Our own cross-sectional analysis found that associations were confounded by race/community.

The main limitation of the current study was the selective sample of older adults with high-quality OCTA images, representing a subgroup of the ARIC cohort with generally good health. This is not a limitation unique to the present study and likely will continue to be a limitation in general in studies of OCTA-based retinal vascular measures in community samples—which serve as the best source populations for understanding the -population-based associations and feasibility. We had a relatively small number of older adults developing MCI/dementia in ARIC V7, which limited our power to

detect associations. In addition, the timing of the EyeDOC visit meant we could not ensure the temporality between assessment of VD and the development of MCI/dementia ascertained at V7.

In conclusion, obtaining high-quality OCTA images is challening in older adult communities, limiting the utility of OCTA as a potential screening tool for early cognitive disease. Among the select healthier subset with high-quality images, OCTA-based retinal vascular imaging biomarkers were not associated with cognitive decline. While rapid improvement in OCTA technology and image processing algorithms may remove barriers to obtaining good images in the broader population of older adults in the future, its unclear whether this will reveal associations between OCTA-based retinal vascular imaging biomarkers and early cognitive decline.

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Conflict of Interest

David Huang has significant financial interests in Optovue, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. Financial interests in Optovue include patent royalty, stock ownership, research grant, and material support. No conflicting relationship exists for any other author.

Author Contributions

Alison G. Abraham, Pradeep Y. Ramulu, A. Richey Sharrett, Xinxing Guo, Josef Coresh, and Thomas Mosley were involved in data collection; David Huang, Qisheng You, Liang Liu, Alexander Tomlinson, and Yali Jia were responsible for imaging protocols, image processing, and image data quality. Alison G. Abraham, Xinxing Guo, Lubaina T. Arsiwala, and Xinxing Guo were responsible for data management, data quality assurance, and analysis. Alison G. Abraham, Pradeep Y. Ramulu, Aleksandra Mihailovic, A. Richey Sharrett, Xinxing Guo, Lubaina T. Arsiwala, and YaNan Dong were responsible for the interpretation of results and writing.

Sponsor's Role

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ORCID

Alison G. Abraham https://orcid.org/0000-0002-6863-0565

Alexander Tomlinson https://orcid.org/0000-0002-6778-9590

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Figure S1: Flowchart showing the sample selection for the Eye Determinants of Cognition study and each analytic sample.
Figure S2: Scatter plot of global cognitive function versus vessel density (VD) in the superficial vascular plexus, intermediate capillary plexus, and deep capillary plexus in 480 older adults from Jackson, MS, and Washington Co, MD, imaged in the EyeDOC study. Solid line is the locally weighted scatterplot smoothing (LOWESS) fit, whereas the broken line is the univariate linear regression fit. Pearson correlation (ρ) is shown at the bottom of each figure.
Table S1: Univariate associations of participant characteristics with vascular density (VD) and foveal avascular zone (FAZ) area in 535 older adults from Jackson, MS, and Washington Co, MD, imaged in the EyeDOC study.

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