Published Ahead of Print on February 28, 2018 as 10.1212/WNL.0000000000005205

ARTICLE

Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study

Jennifer A. Deal, PhD, A. Richey Sharrett, MD, DrPH, Andreea M. Rawlings, MS, PhD, Rebecca F. Gottesman, MD, PhD, Karen Bandeen-Roche, PhD, Marilyn Albert, PhD, David Knopman, MD, Elizabeth Selvin, PhD, MPH, Bruce A. Wasserman, MD, Barbara Klein, MD, MPH, and Ronald Klein, MD, MPH

Correspondence
Dr. Deal
jdeal1@jhu.edu

Neurology® 2018;0:e1-e9. doi:10.1212/WNL.0000000000005205

Abstract

Objective

To test the hypothesis that retinal vascular signs are associated with greater cognitive decline over 20 years in 12,317 men and women 50 to 73 years of age at baseline.

Methods

A composite cognitive score was created with 3 neuropsychological tests measured at 3 time points (1990–1992 to 2011–2013). Retinal signs were measured with fundus photography (1993–1995). Differences in cognitive change by retinal signs status were estimated with linear mixed models. Cognitive scores were imputed for living participants with incomplete cognitive testing.

Results

In multivariable-adjusted analyses that controlled for attrition, loss of vascular integrity (retinopathy and its components) was associated with greater 20-year decline (difference in 20-year cognitive change for moderate/severe vs no retinopathy −0.53 SD, 95% confidence interval −0.74 to −0.33). Estimated differences were similar in participants with and without diabetes mellitus and in white and black participants.

Conclusions

Retinopathy was associated with accelerated rates of 20-year cognitive decline. These findings support the exploration of more sensitive measures in the eye such as optical coherence tomography angiography, which may provide surrogate indexes of microvascular lesions relevant to cognitive decline in older adults.

From the Departments of Epidemiology (J.A.D., A.R.S., A.M.R., R.F.G., E.S.), Neurology (R.F.G., M.A.), Biostatistics (K.B.-R.), and Radiology and Radiological Sciences (B.A.W.), Johns Hopkins University, Baltimore, MD; Department of Neurology (D.K.), Mayo Clinic, Rochester, MN; and Department of Ophthalmology and Visual Sciences (B.K., R.K.), University of Wisconsin School of Medicine and Public Health, Madison.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

GLOSSARY

ARIC = Atherosclerosis Risk in Communities; **CHD** = coronary heart disease; **CI** = confidence interval; **CRAE** = central retinal arteriolar equivalent; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **OR** = odds ratio; **3MS** = Modified Mini-Mental State Examination.

Cerebral small vessel disease is likely a more important contributor to cognitive decline and dementia in older adults than disease of larger arteries.[1] Vascular disease at autopsy, microinfarcts <1 mm, may be more strongly related to late-life cognitive impairment than vascular lesions detectible by standard brain imaging.[1–4] The overall effect of vascular disease in the pathogenesis of cognitive decline is therefore likely to be greater than previously estimated.[2,5]

Retinal fundus photography noninvasively visualizes small vessel changes in the eye. Because blood vessels in the eye and brain are anatomically and physiologically similar, retinal photography may provide indexes of a broad range of small vessel changes within the brain,[6] including lesions too small to be visualized with brain imaging.

Previous prospective studies show that retinal signs are risk factors for ventricular enlargement,[7] incident clinical stroke,[8,9] and early and largely silent cerebrovascular changes,[7,8,10–12] including white matter lesions progression[11] and incident subclinical lacunes.[12]

Cross-sectional studies suggest an association between retinal signs and poorer cognitive function[13,14]; however, longitudinal studies are few, have limited follow-up, and show mixed results.[15–17]

We used data from the Atherosclerosis Risk in Communities (ARIC) Study to test hypotheses relating retinal signs (1993–1995) to 20-year cognitive decline (1990–1992 to 2011–2013). We hypothesize decline to be related to 2 types of retinal vessel signs: loss of vascular integrity (retinopathy and its components) and changes in the arteriolar wall (arteriovenous nicking, and focal and generalized arteriolar narrowing).

Methods

Study population

ARIC is a population-based prospective study of 15,792 men and women 45 to 64 years of age at baseline (1987–1989) from 4 US communities. Cognitive testing was performed at visit 2 (1990–1992), and retinal photographs were collected at visit 3 (1993–1995) (figure e-1, links.lww.com/WNL/A277). Of 14,348 participants who attended visit 2, a total of 12,466 had a retinal photograph. Participants were excluded if race was other than black or white (n = 38) or nonwhite from Minneapolis or Washington County (n = 42). Nineteen and 30 participants were missing information on education and diabetes mellitus, respectively, yielding an analytic sample of 12,317 (figure e-2). Excluded participants were older and more likely to be black; to have less than a high school education; to be current smokers and current drinkers; to have diabetes mellitus, hypertension, and coronary heart disease (CHD); and to die during follow-up (table e-1, links.lww.com/WNL/A278).

Standard protocol approvals, registrations, and patient consents

Informed consent was obtained from all participants, and study procedures were approved by the Institutional Review Board for each field center.

Cognitive outcomes

Three tests representing different domains were administered in 1990 to 1992 (visit 2), 1996 to 1998 (visit 4), and 2011 to 2013 (visit 5): memory (Delayed Word Recall Test), language (Word Fluency Task), and executive function/attention (Digit Symbol Substitution Test). These tests were also administered to participants ≥55 years of age at 2 study sites in 1993 to 1995 (visit 3) and to the same persons who participated in the Brain MRI Substudy (2003–2005). The primary analysis used cognitive data from the 3 occasions when collected in all participants (visits 2, 4 and 5; n = 12,317). Because retinal photographs were collected at visit 3 (1993–1995), a sensitivity analysis was restricted to participants who had cognition measured at visit 3 and used all subsequent cognitive data (visit 4, Brain MRI Substudy, and visit 5; n = 2,003) (figure e-2, links.lww.com/WNL/A277).

Cognitive test scores were standardized as z scores. Test-specific z scores at each testing occasion were scaled to the mean and SD on first testing (visit 2). A composite score was created by summing the 3 test-specific z scores at each visit[18,19] and scaling so that 1 unit equals 1 SD of that score at visit 2. Our primary outcome was the trajectory of 20-year change in the composite z score. In secondary analyses, we estimated trajectories of 20-year test-specific decline.

Retinal exposures

Photographs (visit 3) were obtained in a single, randomly selected eye for each participant by trained technicians using nonmydriatic fundus cameras. All photographs were assessed at a central reading center by trained, certified graders masked to participant characteristics.[20]

Retinopathy severity was defined according to the Airlie House classification, as used in the modified Early Treatment Diabetic Retinopathy Study (ETDRS)[20] and classified as

none (retinopathy severity level <14), mild (14–34), moderate (35–46), and severe (≥47). Microaneurysms, retinal hemorrhages (flame or blot shaped), and soft exudates were considered present if ≥1 definite signs were present.

Focal arteriolar narrowing was defined as definite on the basis of the number and grading of arterioles estimated to be ≥50 μm in diameter that had a constricted area two-thirds or less of the width of proximal and distal vessel segments. Arteriovenous nicking was defined as definite on the basis of the number and grading of at least 1 venous blood column that was tapered on both sides of its crossing underneath an arteriole. Generalized arteriolar narrowing was evaluated with enhanced images and image processing software. Arteriolar diameters within a prespecified zone surrounding the optic nerve were quantified as the central retinal arteriolar equivalent (CRAE) with the following formula used to adjust for branching[21]:

$$\text{Arterioles } W_c = \sqrt{0.87 \times W_a^2 + 1.01 \times W_b^2 - 0.22 \times W_a \times W_b - 10.76}$$

where W_c is the the caliber of the trunk vessel, W_a is the caliber of the smaller branch, and W_b is the caliber of the larger branch.

Generalized narrowing was defined as the lowest CRAE quartile.[15]

Other variables

Demographic information collected in 1987 to 1989 included age, sex, race, and education (less than high school, high school or equivalent, or more than high school). Other covariates were measured at visit 2 (1990–1992): smoking, coded as never, former, or current; body mass index (kilograms per meter squared), calculated from visit 2 weight and visit 1 height; hypertension, defined as diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, or antihypertensive medication use; and diabetes mellitus, defined as fasting blood glucose level ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, self-reported diabetes mellitus (as diagnosed by a physician), or use of diabetes medication. CHD was defined by reported history at visit 1 (1987–1989) and adjudicated fatal CHD, myocardial infarction, silent myocardial infarction, coronary artery bypass surgery, or angioplasty between visits 1 and 2. Prevalent stroke was defined as history of stroke diagnosed by a physician at visit 1 and adjudicated stroke through visit 2.

Statistical analysis

Rates of cognitive change were estimated with linear mixed models. An interaction term between retinal sign and time was used to test whether change rates differed by presence of retinal signs (1993–1995). A 2-piece linear spline with knot at year 6 was included to allow rates to differ before and after visit 4 because 6 years is the mean follow-up time between the first and second cognitive testing occasions, after which there is a 16-year testing gap. A random effect was included for intercept and 2 for slopes before and after visit 4. An independent variance-covariance matrix was assumed for the random effects.

Because of attrition that was strongly related both to cognitive decline and exposure status, we used multiple imputation with chained equations to impute missing cognitive scores at the median visit follow-up time for participants who were alive at the time of the visit but did not complete cognitive testing. Multiple imputation with chained equations models included all covariates in the fully adjusted model (model 2), as well as the *APOE* ε4 genotype; Telephone Interview for Cognitive Status[22] scores; suspect dementia status[23]; Clinical Dementia Rating[24] scores; self-reported poor health; an indicator (yes/no) of whether a proxy was needed for the telephone call; a count of the number of hospitalizations; test scores for the Delayed Word Recall test, Word Fluency Test, and Digit Symbol Substitution Test at visits 2, 4, and 5; and interaction terms between suspect dementia and education, race-field center, prior visit *z* scores, Clinical Dementia Rating score, diabetes mellitus, and hypertension.

Missing exposure and covariate data were imputed with 10 sets of imputations. This method has been described and validated in this cohort as producing unbiased imputations.[23]

Analyses were adjusted for age (linear and quadratic terms), sex, interaction between race and study site (in nonstratified models), body mass index, smoking, drinking, CHD, diabetes mellitus (in nonstratified models), hypertension, history of stroke, and interaction terms between time and age, time and sex, and time and race-field center. We also report analyses stratified by diabetes status and race.

Although visit 2 cognitive data precede the retinal photographs (visit 3), the primary analysis used cognitive data from visits 2, 4, and 5 (n = 12,317) because it is unlikely that cognitive decline from visit 2 to 3 is a cause of the observed retinal signs and cognitive data at visit 3 are limited to a small subset of participants. However, we performed sensitivity analyses restricted to the 2,003 participants who had cognition measured at visit 3 using all subsequent cognitive data.

The primary estimands for inference in this study were the attrition-adjusted differences in 20-year change in the composite cognitive score from the fully adjusted models for 1 measure of loss of vascular integrity (retinopathy severity) or 3 measures of arteriolar changes (arteriovenous nicking, focal narrowing, and CRAE). Analyses were conducted with Stata 13 (Stata Statistical Software, release 13, StataCorp, College Station, TX, 2013).

Results

Of 12,313 participants, 11,692 (95%), 365 (3%), and 256 (2%) were classified as having no, mild, or moderate/severe

retinopathy, respectively (table 1). On average, participants with moderate/severe retinopathy were more likely to be black, less educated, and never drinkers; to have diabetes mellitus, hypertension, CHD, and history of stroke; to have a poorer cognition at visit 2 and greater body mass index; and to die during follow-up (table 1). Eighty-three percent (n = 212) of participants with a moderate/severe retinopathy had diabetes mellitus compared to only 12% of those with no retinopathy.

During 20 years of follow-up, 3,171 (26%) participants died and 3,237 (26%) were lost to follow-up (table 1). Attrition was associated with poorer visit 2 cognitive performance and was more common among participants with retinopathy; 20% of participants with moderate/severe retinopathy attended the final study visit compared to 49% of participants with no retinopathy (table 1).

In available-case analyses (n = 9,300, n observations = 21,936), the average 20-year change in cognitive function in participants with moderate/severe retinopathy was −1.22 SD (95% confidence interval [CI] −1.43 to −1.00) compared to −0.91 SD (95% CI −0.96 to −0.87) for participants with no retinopathy, a difference of −0.31 SD (95% CI −0.52 to −0.09) (table 2, model 1). Associations between retinal severity and 20-year cognitive decline were stronger in analyses accounting for informatively missing cognitive data (n = 12,317, n observations = 33,658); the difference in average 20-year change comparing participants with moderate/severe retinopathy and those with no retinopathy in these models was −0.57 SD (95% CI −0.76 to −0.38) (table 2, model 2). The difference in sensitivity analysis restricted to participants who had cognition measured at the same time as the retinal photography (2 study sites only, n = 2,003) was −0.49 SD (95% CI −0.92 to −0.05) (table 2, sensitivity analysis).

Patterns for retinopathy components (microaneurysms, retinal hemorrhages, and soft exudates) were similar. All measures were independently associated with greater 20-year cognitive decline in models accounting for attrition, with the greatest difference in 20-year cognitive decline estimated for retinal hemorrhages (−0.36 SD, 95% CI −0.52 to −0.20, table 2, model 2).

Both focal narrowing and CRAE were independently related to 20-year cognitive change in analyses that were minimally adjusted for age, education, sex, and race. The difference comparing participants with and without these retinal signs in models adjusted for attrition was −0.19 SD (95% CI −0.28 to −0.10) and −0.09 SD (95% CI −0.14 to −0.05) for focal narrowing and CRAE, respectively (data not shown). However, associations did not persist after adjustment for the full set of covariates (table 2, models 1 and 2). Arteriovenous nicking was not related to cognitive decline (table 2).

Generally, associations of retinal signs with 20-year cognitive change were similar in persons with and without diabetes mellitus (figure 1). The estimated difference in rate of 20-year cognitive decline comparing participants with and without diabetes mellitus was −0.47 SD (95% CI −0.72 to 0.23, n = 1,713) vs −0.30 SD (95% CI −0.67 to 0.06, n = 10,604) for moderate/severe retinopathy, −0.12 (95% CI −0.44 to 0.20) vs −0.05 SD (95% CI −0.14 to 0.04) for focal narrowing, and −0.09 (95% CI −0.27 to 0.09) vs −0.03 (95% CI −0.08 to 0.02) for CRAE (figure 1). We estimated greater cognitive decline for retinopathy components in persons with diabetes mellitus; however, the numbers of events for the components were small, especially in participants without diabetes mellitus (e.g., 111 soft exudates in participants with diabetes mellitus vs 38 in participants without diabetes mellitus).

Associations were also similar in black and white participants (figure 2).

All retinal signs except arteriovenous nicking were consistently associated with greater 20-year declines in executive function/attention. We also estimated greater decline in memory for participants with moderate/severe retinopathy and retinal hemorrhages and greater decline in language for all retinopathy components (table 3, models used imputed data).

Discussion

In this study of 12,317 men and women (age 50–73 years, 22% black), measures of loss of vascular integrity (retinopathy) were associated with faster 20-year cognitive decline. In analyses adjusted for attrition, estimates of the difference in rates of 20-year cognitive change for moderate/severe retinopathy and its components ranged from −0.21 to −0.57 SD. Measures of arteriolar changes (CRAE and focal narrowing) were associated with declines in demographic-adjusted models but not after full adjustment, perhaps because these signs are simply reflective of the risk factors included in the model. Associations in our study were similar in blacks and whites and in persons with and without diabetes mellitus. To put the magnitude of these associations in perspective, a previous study estimated the 20-year effect of baseline diabetes mellitus on cognitive decline using the same methods to account for informative censoring to be −0.21 SD (95% CI −0.31 to −0.12).[19] If retinal signs are adequate surrogates for homologous changes in the brain, these differences could represent reasonable estimates of the otherwise not estimable net contribution of cerebral small vessel disease (including microinfarction) to cognitive decline in older adults, independently of declines due to Alzheimer disease and other processes with a pathogenesis that is not primarily vascular.

Previous analyses in this cohort showed a cross-sectional association of retinal signs with midlife cognitive performance[21] and in a small selected subset of this population (n = 803, only 2 study sites) with greater cognitive decline on the Digit Symbol Substitution Test[25] and the Word Fluency

Table 1. Baseline (visit 2, 1990–1992) characteristics by retinopathy severity, ARIC Neurocognitive Study (n = 12,313)[a]

		Retinopathy severity			
	Total (n = 12,313)	None (n = 11,692)	Mild (n = 365)	Moderate/severe (n = 256)	*p* Value[b]
Age, mean (SD), y	60 (6)	60 (6)	61 (6)	61 (6)	0.04
Black race, n (%)	2,689 (22)	2,442 (21)	123 (34)	122 (48)	<0.0001
Female, n (%)	6,837 (56)	6,498 (56)	190 (52)	145 (57)	0.384
Education, n (%)					
Less than high school	2,426 (20)	2,241 (19)	91 (25)	94 (37)	<0.0001
High school	5,179 (42)	4,941 (42)	145 (40)	91 (36)	
More than high school	4,712 (38)	4,510 (39)	129 (35)	71 (28)	
BMI, mean (SD), kg/m^2	28 (5)	28 (5)	29 (6)	31 (7)	0.0001
Smoking status, n (%)					
Never	5,064 (41)	4,793 (41)	156 (43)	113 (44)	0.794
Former	4,723 (38)	4,497 (38)	133 (36)	92 (36)	
Current	2,530 (21)	2,402 (21)	76 (21)	51 (20)	
Drinking status, n (%)					
Never	2,740 (22)	2,563 (22)	91 (25)	84 (33)	<0.0001
Former	2,457 (20)	2,284 (20)	83 (23)	89 (35)	
Current	7,106 (58)	6,832 (59)	191 (52)	82 (32)	
Diabetes mellitus, n (%)	1,713 (14)	1,405 (12)	96 (26)	212 (83)	<0.0001
Hypertension, n (%)	4,195 (34)	3,849 (33)	177 (48)	167 (65)	<0.0001
Stroke, n (%)	180 (2)	158 (1)	10 (3)	12 (5)	<0.0001
CHD, n (%)	631 (5)	577 (5)	28 (8)	26 (10)	<0.0001
Cognitive *z* score, mean (SD)	0.00 (1.00)	0.02 (0.99)	−0.25 (1.05)	−0.63 (0.99)	0.0001
Follow-up status					
Died during follow-up, n (%)	3,171 (26)	2,886 (25)	129 (35)	155 (61)	<0.0001
Living, did not attend visit 5, n (%)	3,237 (26)	3,082 (26)	102 (28)	51 (20)	
Attended visit 5, n (%)	5,909 (48)	5,724 (49)	134 (37)	50 (20)	
Follow-up time, mean (SD), y	13.1 (7.6)	13.3 (7.6)	11.3 (7.4)	8.8 (6.6)	<0.0001
Other retinal measures, n (%)					
Focal arteriolar narrowing	797 (8)	706 (7)	55 (16)	36 (17)	<0.0001
Arteriovenous nicking	657 (6)	590 (6)	35 (10)	32 (14)	<0.0001
CRAE (lowest quartile)	2,700 (25)	2,562 (25)	86 (24)	51 (24)	0.820
Retinopathy components, n (%)					
Microaneurysms	462 (4)	17 (0.1)	196 (54)	249 (99)	<0.0001
Hemorrhages	370 (3)	29 (0.3)	127 (35)	214 (85)	<0.0001
Soft exudates	149 (1)	13 (0.1)	36 (10)	100 (40)	<0.0001

Abbreviations: ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; CHD = coronary heart disease; CRAE = central retinal arteriolar equivalent.
[a] Because of 4 participants missing retinopathy, n = 12,313.
[b] *p* Values from 1-way analysis of variance or Kruskal-Wallis test (continuous variables) or Pearson χ^2 test (categorical variables).

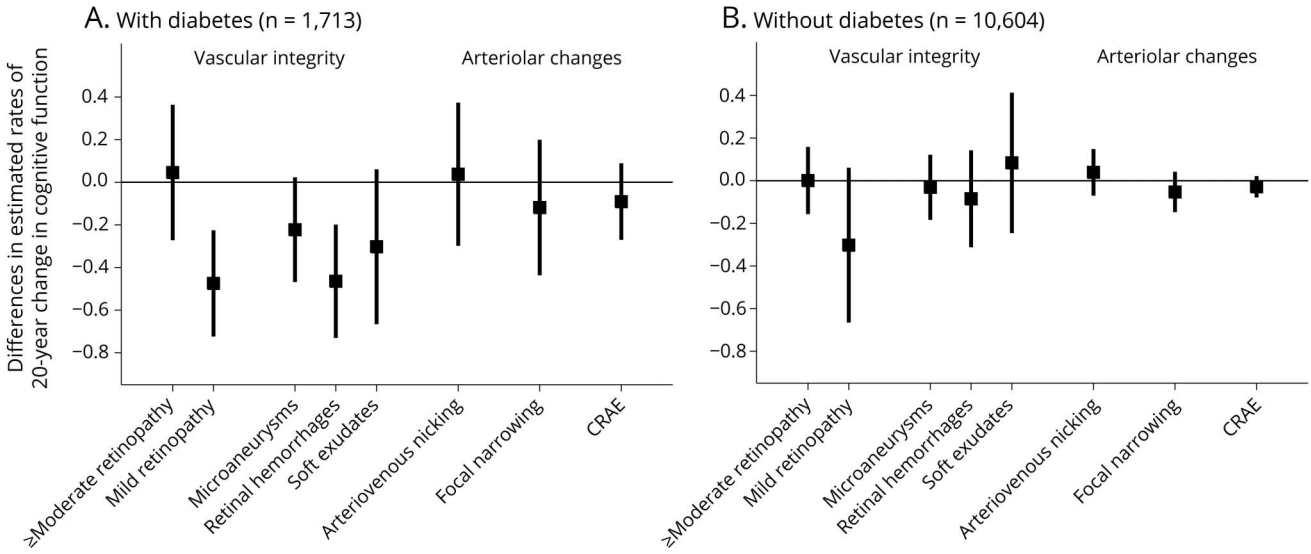
Table 2. Multivariable-adjusted differences in rates of cognitive change by presence of retinal signs, ARIC Neurocognitive Study (n = 12,317)

	20-y Change				17-y Change (sensitivity analysis)	
	Model 1[a] (n = 9,300)		Model 2[b] (n = 12,317)		Model 2[b] (n = 2,003)	
	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value
Retinopathy severity						
Mild vs none	−0.03 (−0.16 to 0.10)	0.685	−0.01 (−0.16 to 0.13)	0.847	−0.05 (−0.34 to 0.24)	0.731
Moderate/severe vs none	−0.31 (−0.52 to −0.09)	0.005	−0.57 (−0.76 to −0.38)	<0.0001	−0.49 (−0.92 to −0.05)	0.028
Retinopathy components						
Microaneurysms	−0.11 (−0.25 to 0.02)	0.098	−0.21 (−0.34 to −0.07)	0.002	−0.14 (−0.42 to 0.13)	0.307
Retinal hemorrhages	−0.22 (−0.41 to −0.04)	0.015	−0.36 (−0.52 to −0.20)	<0.0001	−0.35 (−0.66 to −0.03)	0.030
Soft exudates	−0.19 (−0.43 to 0.05)	0.125	−0.29 (−0.52 to −0.06)	0.015	−0.71 (−1.23 to −0.19)	0.008
Arteriovenous nicking	−0.01 (−0.10 to 0.09)	0.981	0.04 (−0.06 to 0.14)	0.441	0.07 (−0.17 to 0.30)	0.572
Focal narrowing	−0.07 (−0.16 to 0.01)	0.085	−0.05 (−0.14 to 0.04)	0.259	−0.01 (−0.23 to 0.23)	0.983
CRAE	−0.01 (−0.06 to 0.03)	0.554	−0.03 (−0.08 to 0.01)	0.155	0.02 (−0.15 to 0.12)	0.826

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; CRAE = central retinal arteriolar equivalent.
[a] Model 1 (available case; n = 9,300, n observations = 21,936).
[b] Model 2 (includes imputed values for missing covariate, exposure, and outcome data; n = 12,317, n observations = 33,658; sensitivity analysis n = 2,300, n observations = 6,412).

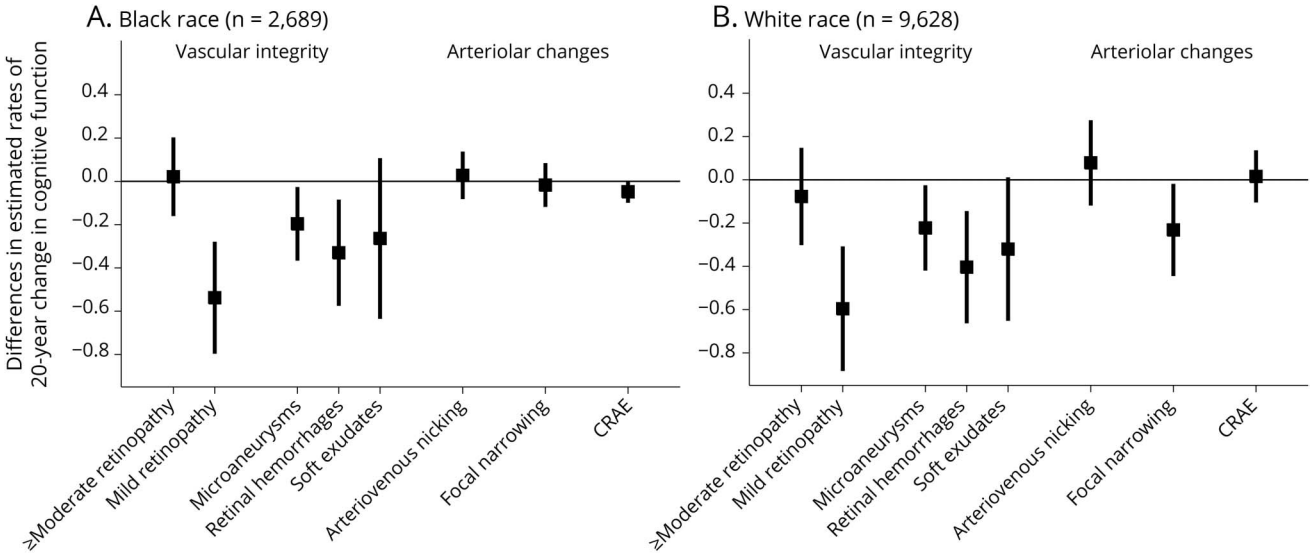
Task[26] over 14 years.[15] Here, we expanded on that work and the generalizability of study findings by quantifying the relationship between retinal signs and cognitive change in 12,317 participants from all 4 ARIC Study sites over 20 years of follow-up. With the expected better accuracy, the current study finds differences in detail in both the retinal predictors and the cognitive domains predicted. No other study provides such a long follow-up, particularly at a time in which participants experience accelerating cognitive decline, with comparable sample size from a biracial population.

Figure 1 Multivariable-adjusted differences in estimated rates of 20-year change in cognitive function by retinal signs and diabetes status, ARIC Neurocognitive Study, 1990 to 1992 to 2011 to 2013, n = 12317



(A) Participants with diabetes mellitus (n = 1723). (B) Participants without diabetes mellitus (n = 10604). *p* Values for interaction between diabetes mellitus and retinal sign: mild retinopathy $p = 0.862$, moderate/severe retinopathy $p = 0.316$, microaneurysms $p = 0.083$, retinal hemorrhages $p = 0.016$, soft exudates $p = 0.134$, arteriovenous nicking $p = 0.890$, focal narrowing $p = 0.588$, and CRAE $p = 0.709$. ARIC = Atherosclerosis Risk in Communities; CRAE = central retinal arteriolar equivalent.

Figure 2 Multivariable-adjusted differences in estimated rates of 20-year change in cognitive function by retinal signs and race, ARIC Neurocognitive Study, 1990 to 1992 to 2011 to 2013, n = 12317



(A) Black race (n = 2689). (B) White race (n = 9628). *p* Values for interaction between race and retinal sign: mild retinopathy $p = 0.470$, moderate/severe retinopathy $p = 0.645$, microaneurysms $p = 0.681$, retinal hemorrhages $p = 0.595$, soft exudates $p = 0.821$, arteriovenous nicking $p = 0.637$, focal narrowing $p = 0.073$, and CRAE $p = 0.642$. ARIC = Atherosclerosis Risk in Communities; CRAE = central retinal arteriolar equivalent.

Our findings are consistent with previous cross-sectional studies in other cohorts. In 2,211 adults (age 69–97 years) in the Cardiovascular Health Study, retinopathy was associated with lower Digit Symbol Substitution Test scores but not with scores from the less sensitive Modified Mini-Mental State Examination (3MS).[27] Retinopathy and focal narrowing were associated with dementia but were significant only in participants with hypertension (odds ratio [OR] 3.0, 95% CI 1.5–6.0 vs OR 2.1, 95% CI 1.0–4.2).[13] Among Blue Mountain Eye Study participants with hypertension, cross-sectional associations were seen between retinopathy and 3MS score[28] ≤23 (OR 1.7).[14] However, cross-sectional studies compared with longitudinal studies cannot account as well for stable characteristics that affect cognitive test performance (e.g.,

Table 3. Multivariable-adjusted differences in rates of 20-year cognitive change in memory, language, and executive function/attention by presence of retinal signs, ARIC Neurocognitive Study, 1990 to 1992 to 2011 to 2013 (n = 12,317)

	Memory		Language		Executive function/attention	
	Estimate (95% CI)	***p* Value**	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Retinopathy severity						
Mild vs none	0.10 (−0.13 to 0.33)	0.399	−0.11 (−0.24 to 0.01)	0.085	−0.10 (−0.24 to 0.03)	0.134
Moderate/severe vs none	−0.54 (−0.97 to −0.11)	0.014	−0.24 (−0.41 to −0.06)	0.009	−0.60 (−0.84 to −0.36)	<0.0001
Retinopathy components						
Microaneurysms	−0.16 (−0.36 to 0.05)	0.139	−0.21 (−0.34 to −0.09)	0.001	−0.28 (−0.45 to −0.12)	0.001
Retinal hemorrhages	−0.33 (−0.63 to −0.03)	0.029	−0.32 (−0.63 to −0.03)	0.029	−0.43 (−0.61 to −0.25)	<0.0001
Soft exudates	−0.10 (−0.49 to 0.29)	0.611	−0.22 (−0.44 to −0.01)	0.048	−0.38 (−0.58 to −0.18)	<0.0001
Arteriovenous nicking	0.01 (−0.16 to 0.17)	0.952	0.06 (−0.01 to 0.14)	0.097	0.04 (−0.04 to 0.12)	0.305
Focal narrowing	−0.02 (−0.19 to 0.14)	0.793	−0.01 (−0.09 to −0.06)	0.789	−0.09 (−0.17 to −0.01)	0.047
CRAE	0.01 (−0.09 to 0.12)	0.810	−0.03 (−0.08 to −0.02)	0.236	−0.06 (−0.11 to −0.02)	0.004

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; CRAE = central retinal arteriolar equivalent.
Models include imputed values for missing covariate, exposure, and outcome data.

education level and long-term social and occupational cognitive activities or exposures related to those influences). In a longitudinal analysis of 511 women ≥65 years of age from the Women's Health Initiative, retinopathy was associated with lower 3MS scores (mean difference 1.01 points, $p = 0.02$) after 10 years, but the difference was not significant ($p = 0.07$).[16] In 6,078 participants in the Rotterdam Study (mean age 68 years), baseline retinopathy was associated with prevalent but not incident all-cause dementia during 11 years of follow-up (hazard ratio 1.15).

One limitation of our study is that the retinal photographs were taken in only 1 (randomly selected) eye. In addition, we did not adjust for multiple comparisons. However, our findings were hypothesized in advance and are consistent with previous studies. We found significant differences in 20-year composite cognitive score decline by retinal sign status for 3 of the 4 primary exposures of interest (retinopathy severity, focal narrowing, and CRAE) (table 2, model 2).

Our study has several strengths, including large sample size, a biracial population, retinal signs measured at a relatively young age (mean age 60 years, range 50–73 years), and long follow-up. We accounted for bias due to missing data, including informative censoring of the cognitive outcome. Informative censoring arises when the mechanism generating the missing outcome values is related to the mechanism that determines the outcome. In this study, cognitive decline is associated with death and dropout (table 1). Critically, attrition in this study is also associated with the exposure, inducing a selection bias so that available-case analyses are expected to underestimate associations. In our study, when a retinal sign was related to cognitive decline, compared to naive estimates ignoring attrition, declines associated with those retinal signs were consistently larger in models accounting for attrition. Differences between naive and imputed estimates were greater for measures related to retinopathy, which is not surprising because retinopathy is more strongly associated with dropout than measures of arteriolar changes. Eighty percent of participants with moderate/severe retinopathy at baseline were lost to follow-up (table 1) compared to 52% with CRAE (table e-2, links.lww.com/WNL/A278).

This study documented a strong, consistent association between retinopathy measured at a mean age of 60 years (range 53–70 years) and greater 20-year decline in cognitive performance among 12,317 men and women from 4 US communities. This association was observed in participants with and without diabetes mellitus and for both white and black participants. The total extent of the contribution of cerebral small vessel disease to the development of cognitive decline and dementia is unknown, largely because of the inability of cerebral imaging to visualize its microvascular component. Retinal photography captures small vascular signs, and emerging imaging techniques in the eye such as optical coherence tomography angiography may have the sensitivity to provide surrogate indexes of even microvascular lesions that may be most relevant to cognitive decline in older adults.

Author contributions

Jennifer A. Deal: study concept and design, analysis and interpretation of data, statistical analysis, drafted and revised manuscript. A. Richey Sharrett: study concept and design, acquisition of data, interpretation of data, critical revision of manuscript for intellectual content. Andreea M. Rawlings: study concept and design, critical revision of manuscript for intellectual content. Rebecca F. Gottesman: critical revision of manuscript for intellectual content. Karen Bandeen-Roche: interpretation of data, critical revision of manuscript for intellectual content. Marilyn Albert, David Knopman, Elizabeth Selvin, and Bruce Wasserman: critical revision of manuscript for intellectual content. Barbara Klein and Ronald Klein: acquisition of data, critical revision of manuscript for intellectual content.

Acknowledgment

The authors thank the staff and participants of the ARIC study for their important contributions.

Study funding

The ARIC study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, NIH, Department of Health and Human Services, under contracts HHSN268201700001I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I, and HHSN2682017000021. Neurocognitive data are collected by U01 HL096812, HL096814, HL096899, HL096902, and HL096917, with previous brain MRI examinations funded by R01-HL70825 and additional support from the National Institutes of Neurologic Disorders and Stroke. Dr. Deal is also supported by NIH/National Institute on Aging grant K01AG054693. Dr. Selvin is also supported by NIH/National Institute of Diabetes and Digestive and Kidney Diseases grant K24DK106414.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received May 3, 2017. Accepted in final form December 19, 2017.

References

1. White L. Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia Aging Study. J Alzheimers Dis 2009;18:713–725.
2. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672–2713.
3. Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007;62:406–413.
4. Jellinger KA. Pathology and pathogenesis of vascular cognitive impairment: a critical update. Front Aging Neurosci 2013;5:17.
5. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–2204.
6. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. 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;206:319–348.
7. 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;41:1826–1828.
8. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67–74.
9. Kuller LH, Longstreth WT Jr, Arnold AM, et al. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke 2004;35:1821–1825.
10. Cooper LS, Wong TY, Klein R, et al. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. Stroke 2006;37:82–86.
11. Cheung N, Mosley T, Islam A, et al. Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study. Brain 2010;133:1987–1993.
12. Hanff TC, Sharrett AR, Mosley TH, et al. Retinal microvascular abnormalities predict progression of brain microvascular disease: an Atherosclerosis Risk in Communities Magnetic Resonance Imaging Study. Stroke 2014;45:1012–1017.
13. 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;38:2041–2047.
14. Liew G, Mitchell P, Wong TY, et al. Retinal microvascular signs and cognitive impairment. J Am Geriatr Soc 2009;57:1892–1896.
15. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. Neurology 2009;73:862–868.
16. Haan M, Espeland MA, Klein BE, et al. Cognitive function and retinal and ischemic brain changes: the Women's Health Initiative. Neurology 2012;78:942–949.
17. Heringa SM, Bouvy WH, van den Berg E, Moll AC, Kappelle LJ, Biessels GJ. Associations between retinal microvascular changes and dementia, cognitive functioning, and brain imaging abnormalities: a systematic review. J Cereb Blood Flow Metab 2013;33:983–995.
18. Gottesman RF, Schneider AL, Albert M, et al. Midlife hypertension and 20-year cognitive change: the Atherosclerosis Risk in Communities Neurocognitive Study. JAMA Neurol 2014;71:1218–1227.
19. Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. Ann Intern Med 2014;161:785–793.
20. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. Ophthalmology 1999;106:2269–2280.
21. 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;33:1487–1492.
22. Brandt J, Spencer M, Folstein MF. The telephone interview for cognitive status. Neuropsychiatry Neuropsychol Behav Neurol 1988;1:111–117.
23. Rawlings AM, Sang Y, Sharrett AR, et al. Multiple imputation of cognitive performance as a repeatedly measured outcome. Eur J Epidemiol 2016;32:55–66.
24. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.
25. Wechsler D. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp; 1981.
26. Benton AL, Hamsher K, Sivan AB. Multilingual Aphasia Examination. 3rd ed. Iowa City: AJA Associates; 1994.
27. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) Examination. J Clin Psychiatry 1987;48:314–318.
28. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study

Jennifer A. Deal, A. Richey Sharrett, Andreea M. Rawlings, et al.

Neurology published online February 28, 2018
DOI 10.1212/WNL.0000000000005205