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Retinal Signs and Risk of Incident Dementia in the Atherosclerosis Risk in Communities Study

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Abstract

INTRODUCTION: The easily-imaged retinal microvasculature may reflect the brain microvasculature, and therefore be related to dementia.

METHODS: In a population-based study of 12482 adults aged 50–73 years (22% African American), we estimated the relationship of retinal characteristics from fundus photography

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RESEARCH IN CONTEXT

Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. Retinal photography is thought to be a surrogate measure of microvascular changes in the brain. A small number of population-based epidemiologic studies of the relationship between retinal photography and dementia have been conducted, but these studies are primarily cross-sectional, and are typically underpowered to investigate etiologic subtype.

Interpretation: Consistent with previous cross-sectional studies, we found a positive association between two retinal signs measured in midlife – retinopathy and generalized arteriolar narrowing – and all-cause dementia over 20 years of follow-up. Retinopathy was associated strongly with cerebrovascular, but not Alzheimer's disease-related, etiology.

Future directions: Although preventable, the contribution of microvascular disease to dementia may be underestimated given limitations of in vivo brain imaging. Future studies should determine if eye imaging techniques (e.g., optical coherence tomography angiography) provide valid surrogate indices of microvascular brain lesions to inform public health and clinical practice.

(1993–1995) with (i) incident all-cause dementia (1993–1995 to 2011–2013), and (ii) etiologic subtype of dementia/mild cognitive impairment (MCI) (2011–13).

RESULTS: 1259 (10%) participants developed dementia over a mean 15.6 years. Moderate/severe (vs. no) retinopathy (hazard ratio[HR], 1.86; 95% CI:1.36, 2.55) and central retinal arteriolar equivalent (CRAE, narrowest quartile vs. widest three quartiles; HR, 1.26; 95% CI:1.09, 1.45) were associated with all-cause dementia. Results were qualitatively stronger (but not statistically significantly different) in participants with diabetes. Retinopathy was associated with a joint outcome of cerebrovascular-related, but not Alzheimer's-related, dementia/MCI (HR, 2.29; 95% CI:1.24, 4.23).

DISCUSSION: Exploration of measures in the eye may provide surrogate indices of microvascular lesions relevant to dementia.

Keywords

Cohort studies; Dementia; Diabetes; Microvasculature; Retinal; Risk factors in epidemiology

1 INTRODUCTION

Vascular disease is a recognized, potentially modifiable, contributor to dementia in older adults.[1] Retinal fundus photography noninvasively images small vessel changes in the eye which may resemble similar changes in the brain.[2, 3] Retinal signs measured through fundus photography may therefore be a surrogate measure of microvasculature damage in the brain, and so may be related to increased dementia risk.

Retinal signs are risk factors for incident clinical stroke,[4, 5] and for early and largely silent cerebral changes,[4, 6] including ventricular enlargement,[7] silent lacune-size cerebral infarcts, incident white matter lesions and white matter hyperintensity progression.[8] However, population-based epidemiologic studies of retinal signs and dementia are few in number with limited prospective follow-up.[9]A recent systematic review underscored the need for future studies to describe the relationship between retinal signs and dementia subtypes.[9]

We addressed this research gap using data from the Atherosclerosis Risk in Communities (ARIC) Study, a large, population-based prospective cohort, to test the hypothesis that retinal signs in midlife (1993–1995) are related to increased risk of incident all-cause dementia over 20 years (1993–1995 to 2011–2013) and to etiologic subtype of a combined outcome of dementia or mild cognitive impairment in 2011–13.

2 METHODS

2.1 Study population

ARIC is a population-based prospective study of 15792 men and women aged 45–64 years at baseline (1987–1989) from four U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota (Figure 1).[10] Informed consent was obtained from all participants at each visit, or from a designated proxy with participant assent if the participant was unable to provide consent (e.g., known

dementia diagnosis). Study procedures were approved by the Institutional Review Board for each field center.

For this study, participants were excluded if race was other than black or white (N=48) or non-white from Minneapolis or Washington County sites (N=55). Also excluded were 7 participants who had a dementia diagnosis prior to when retinal photographs were collected (Visit 3, 1993–1995), 2882 who did not attend Visit 3, and 241who did not have an interpretable photograph. Participants were also excluded if missing data on retinopathy severity (N=4), education (N=19) or, given its strong relationship with retinopathy, diabetes status (N=54), yielding an analytic sample of 12482.

Excluded participants were older (55 vs. 54 years); more likely to be African American (45% vs. 22%), a current smoker (39% vs. 23%) and former drinker (26% vs. 17%); and more likely to have diabetes (19% vs. 10%), hypertension (46% vs. 32%), coronary heart disease (8% vs. 4%) and to die during follow-up (55% vs. 26%), compared to participants included in the study (Supplementary Table 1).

2.2 Diagnosis of Dementia during Follow-up

Dementia diagnosis in this cohort has been described elsewhere,[11, 12] and was ascertained for all participants, including those who died during follow-up. For all participants who survived until and attended the fifth clinic visit (2011–2013, see Figure 1), diagnosis used standardized algorithms incorporating longitudinal cognitive data and a complete neuropsychological battery that was administered at Visit 5, with all algorithmic diagnoses confirmed by expert panel review. Dementia diagnoses for participants who did not attend Visit 5 were based on a Modified Telephone Interview for Cognitive Status-Modified (TICS) interview with the participant, on modified Clinical Dementia Rating (CDR) interviews with informants confirming a hospital *International Classification of Diseases*, *Ninth Revision* (ICD-9) discharge or death certificate dementia code, or on hospital or death certificate dementia codes alone.[12, 13] Active surveillance for dementia continued through the date of last participant contact up to Sept 1, 2013. For diagnosis ascertained by codes, the date of dementia onset was estimated to be 6 months prior to the hospitalization.

2.3 MCI Diagnosis and Etiologic Subtyping of Dementia and MCI at Visit 5

Mild cognitive impairment (MCI) and etiologic subtype of dementia or MCI was adjudicated only for the subset of participants who attended the final clinic visit in 2011–13; the adjudication process has been previously described.[11] MCI diagnosis was based on full neuropsychological assessment at Visit 5, CDR, Functional Activities Questionnaire, Neuropsychiatric Inventory and brain magnetic resonance imaging (MRI). [11]

Alzheimer's disease (AD) etiology was diagnosed based on the non-abrupt onset of cognitive syndrome including memory impairment and absence of cerebrovascular (CVD), Lewy body, or other (e.g., medication-, or alcohol-induced) diagnoses.[11, 14, 15] CVD etiology was diagnosed based on history of stroke with or without reported subsequent abrupt onset of cognitive impairment using the validated National Institute of Health Stroke Scale, evidence of stroke on neurologic exam, and small vessel disease evidenced by MRI (e.g., lacunes and white matter hyperintensities volume).[11, 16]

In this analysis, AD-related dementia or MCI was defined as any case assigned an AD etiology *without* evidence of CVD-related etiology. CVD-related dementia or MCI was defined as any CVD etiology, with or without AD-related etiology.

2.4 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, with moderate-to-good intergrader reliability.[17] Presence of retinal lesions was assessed using the modified Airlie House classification, as used in the Early Treatment Diabetic Retinopathy Study (ETDRS)[17] and retinopathy severity was classified as: None (retinopathy severity level <14); Mild (14–34); Moderate (35–46); and Severe (≥ 47). Given the small number of participants with severe retinopathy (N=26), retinopathy was categorized as none, mild, or moderate/severe for analysis. Microaneurysms, retinal hemorrhages (flame- and/or blot-shaped) and soft exudates were considered present if one or more “definite” signs were present. Focal arteriolar narrowing was defined as “definite” based on number and grading of arterioles estimated to be ≥50 μm in diameter that had a constricted area ≤ 2/3 the width of proximal and distal vessel segments. AV nicking was defined as “definite” based on number and grading of at least one venous blood column(s) that was(were) tapered on both sides of its crossing underneath an arteriole. Generalized arteriolar narrowing was evaluated using enhanced images and image processing software. Arteriolar diameters within a pre-specified zone surrounding the optic nerve were quantified as the central retinal arteriolar equivalent (CRAE) using the following formula in order to adjust for branching:[18]

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

where W_c = the caliber of the trunk vessel

W_a = the caliber of the smaller branch, and

W_b = the caliber of the larger branch

Generalized narrowing was defined as the lowest CRAE quartile.[19]

Other Variables—Demographic information collected at study baseline (1987–1989) includes birthdate (for calculating age at study visit), sex, race and education (<high school, high school or equivalent, or >high school). Other covariates were measured when retinal photographs were collected (Visit 3, 1993–1995), including smoking and drinking status, each coded as never, former or current; body mass index (kg/m^2), calculated using measured weight and height; pre-hypertension, defined in persons not taking antihypertensive medication as diastolic blood pressure 80–89 mmHg or systolic blood pressure 120–139 mmHg; hypertension, defined as diastolic blood pressure ≥90 mmHg, systolic blood pressure ≥140 mmHg, or antihypertensive medication use; and diabetes defined as fasting blood glucose level ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, self-reported diabetes (as diagnosed by a physician), or use of diabetes medication. Coronary heart disease (CHD) was

defined by self-reported history at baseline and adjudicated fatal CHD, or myocardial infarction (MI), silent MI, coronary artery bypass surgery, or angioplasty through Visit 3. Prevalent stroke was defined as self-reported history of stroke diagnosed by a physician at baseline and adjudicated stroke through Visit 3. Apolipoprotein (*APOE*) genotype was categorized as the number of ε4 alleles (0 vs. ≥1).[11]

2.5 Statistical Analysis

Hazard ratios (HR) of time to dementia (1993–2013) from date of retinal photography (1993–1995) comparing participants with and without retinal signs were estimated using Cox proportional hazard models. Although our surveillance methods may not identify date of dementia onset accurately, the Cox models as implemented have been shown to yield similar results to a discrete time analysis (time divided into 5-year intervals) that relaxes assumptions about exact diagnosis date.[12] The proportional hazards assumption was verified by assessing correlation between scaled Schoenfeld residuals and transformed survival times, handling ties using the Efron method. Primary analyses were stratified by diabetes status, race and *APOE* genotype based on a priori hypotheses, with a formal test for interaction by diabetes, race, sex and *APOE* status. Analyses were adjusted for age (linear and quadratic terms), sex, an interaction between race and study site (in non-stratified models), BMI, smoking, drinking, hypertensive status (none, pre-hypertension, hypertension), diabetes (in non-stratified models), CHD and history of stroke. In a sensitivity analysis, we adjusted for hemoglobin A_{1c} measured at Visit 2 (1990–92); hemoglobin A_{1c} is not available at the time when the retinal photographs were taken.

Missing covariate and exposure data were imputed with 20 sets of multiple imputation using chained equations (MICE).[20] Number of imputed values for each variable are: AV nicking, N=1659; focal narrowing, N=2169; CRAE, N=1598; microaneurysms, N=1581; retinal hemorrhages, N=949; soft exudates, N=636; BMI, N=13; drinking status, N=8; hypertension, N=64; CHD status, N=251; and stroke status, N=26. The imputation model included all covariates in the final model, as well as the *APOE* ε4 genotype; and systolic and diastolic blood pressure, cognitive function, glucose and hemoglobin A1c measured at Visit 2.

To assess for a possible ascertainment bias, we repeated analyses censoring individuals after a hospitalization ICD-9 code for comorbidities related to retinal signs, including ischemic heart disease (400–404) or cerebrovascular disease (430–438).

Given the strong association of retinal signs with mortality in this cohort, and to aid in the interpretation of the estimated cause-specific hazards of the relationship between retinal signs and dementia, we conducted a competing risks sensitivity analysis using Cox proportional hazards models to compare risk of non-dementia death in persons with and without retinal signs, treating dementia prior to death as a censoring event.[21]

Studies on the relationship between retinal signs and dementia subtypes are needed.[9] However, in this cohort, etiologic subtype of dementia and MCI was adjudicated only in the subset of participants who survived until and attended the final clinic visit (Visit 5). Therefore, in a secondary, complementary analysis, we used generalized linear regression

with a complementary log-log link to model the hazard ratio of etiologic subtype of dementia or MCI in the subset of participants who attended Visit 5 (2011–2013) with the retinal variables assessed ~20 years previously (Visit 3, 1993–1995). As the same etiologic classification was conducted for both MCI and dementia, and because of the small numbers of events at Visit 5, dementia and MCI were modeled as a joint outcome to increase stability of the results. To minimize the likelihood of a finding due solely to chance, analysis was restricted to those retinal signs that were associated with dementia in the primary model.

Analyses were conducted in Stata 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

3 RESULTS

Of 12482 participants, 11838 (95%), 379 (3%) and 265 (2%) were classified as having no, mild or moderate/severe retinopathy, respectively (Table 1). Participants with moderate/severe retinopathy were more likely to be African-American, less educated, never drinkers; to have hypertension, coronary heart disease and history of stroke, and greater BMI; and to die during follow-up than were participants with no or mild retinopathy (Table 1). Eighty-four percent (N=222) of participants with moderate/severe retinopathy had diabetes, compared to 13% with no retinopathy.

Over a mean follow-up of 16 years, 1259 participants (10%) developed incident dementia. Twenty-five percent (N=310) of cases were diagnosed using Visit 5 data and expert review, 44% (N=552) using the TICS or dementia codes confirmed by CDR and 32% (N=397) using hospital or death codes alone. Seventeen percent of participants with moderate/severe retinopathy developed dementia during the study period, as compared to 13% for mild and 10% for no retinopathy (Table 2).

After full adjustment, the hazard ratio (HR) for incident dementia associated with mild (vs. no) retinopathy was 1.44 (95% confidence interval [CI]: 1.08, 1.92) and with moderate/severe (vs. no) retinopathy was 1.86 (95% CI: 1.36, 2.55; Table 2). After adjustment for hemoglobin A_{1c} levels, these associations were attenuated to 1.41 (95% CI: 1.05, 1.88) and 1.60 (95% CI: 1.14, 2.24), respectively. CRAE (narrowest quartile vs. widest three quartiles) was also associated with increased dementia risk; HR, 1.23 (95% CI: 1.07, 1.41; Table 2). AV nicking and focal narrowing were not associated with dementia risk (Table 2). Available-case models that did not impute missing exposure data yielded nearly identical effect estimates (Supplemental Table 2).

Retinopathy components (microaneurysms, retinal hemorrhages and soft exudates) were independently associated with greater risk of incident dementia, although the association with soft exudates was not statistically significant (Table 2).

Estimates of dementia risk associated with each retinal sign were qualitatively greater in males vs. females and, with the exception of CRAE, in persons with (vs. without) diabetes (Figure 2). However, p-values for an interaction between sex and retinal signs, as well as between diabetes and retinal signs, were not significant for any retinal exposure.

Mild retinopathy and CRAE were significantly associated with dementia risk in males but not females. For mild retinopathy, the hazard ratio was 1.57 (95% CI: 1.03, 2.40) in males vs. 1.35 (95% CI: 0.90, 2.02) in females (p-interaction=0.600); and for CRAE, the hazard ratio was 1.37 (95% CI: 1.11, 1.68) in males vs. 1.15 (95% CI: 0.95, 1.40) in females (p-interaction=0.422). Moderate/severe retinopathy was the only retinal sign in which the association was statistically significant in persons with diabetes but was not for persons without diabetes; compared to no retinopathy, moderate/severe retinopathy was associated with a 2.14 (95% CI: 1.50, 3.04) increased hazard of dementia in participants *with* diabetes and 1.29 (95% CI: 0.57, 2.90) in participants *without* diabetes; p-interaction=0.310. We did not find statistical evidence that relationships between retinal signs and dementia differed by race or *APOE* ε4 allele status.

In a sensitivity analysis that censored participants following a hospitalization code for cerebrovascular or ischemic heart disease, the HR for incident dementia associated with moderate/severe retinopathy was 3.34 (95% CI: 1.79, 6.26) and with CRAE, 1.41 (95% CI: 1.12, 1.79).

Overall, 23% of participants died prior to a dementia diagnosis during follow-up. Mortality was more common in participants with retinal signs present – moderate/severe retinopathy, 51% vs. 31% (mild) and 22% (none); AV nicking, 30% vs. 21%; focal narrowing, 29% vs. 20%; and CRAE, 23% vs. 21% (Table 3). In a competing risks sensitivity analysis, all retinal signs except CRAE were associated with increased risk of death over the 20 years of follow-up. The cause-specific hazard ratio (HR) for death associated with mild (vs. no) retinopathy was 1.22 (95% CI: 1.01, 1.48); moderate/severe (vs. no) retinopathy, 1.81 (95% CI: 1.50, 2.17); AV nicking, 1.16 (95% CI: 1.01, 1.34); focal narrowing, 1.25 (95% CI: 1.09, 1.44); and CRAE, 1.07 (95% CI: 0.97, 1.18) (Table 3).

Restricting to participants who attended Visit 5 and excluding participants with an unknown etiologic subtype, 294 (5%) participants had dementia and 1091 (19%) had MCI. For a joint outcome of MCI and dementia, N=1196 (86%) had any AD-related etiologic diagnosis, of whom N=470 (34%) had a pure AD-related etiology and 686 (14%) has an AD-related diagnosis without evidence of CVD. Only 20 participants had a pure CVD-related etiology and N=549 had a primary or secondary etiologic CVD diagnosis. In fully-adjusted models, moderate/severe retinopathy was associated with increased risk of MCI/dementia with cerebrovascular, but not AD, etiology. The hazard ratio comparing moderate/severe to no retinopathy was 1.33 (95% CI: 0.64, 2.77) for Alzheimer's disease-related dementia or MCI without evidence of CVD and 2.29 (95% CI: 1.24, 4.23) for MCI or dementia with any cerebrovascular etiology (Table 4). No associations were found for CRAE and either etiologic subtype.

4 DISCUSSION

In this study of 12482 men and women (aged 50–73 years, 22% African American), two retinal signs – retinopathy severity and CRAE, markers of small vessel integrity and vessel wall integrity and dimensions, respectively – were independently associated with increased risk of all-cause dementia over 20 years. In analyses adjusted for demographic and clinical

covariates, we observed a dose-dependent association between retinopathy severity (none, mild, moderate/severe) and dementia, with the strongest association observed for moderate/severe (vs. none) retinopathy; p-trend <0.0001. Similar associations were observed for retinopathy components (microaneurysms, retinal hemorrhages and soft exudates), although the association for soft exudates was not statistically significant, likely due to limited sample size (N=158 participants with soft exudates). Among the 25% of participants with the narrowest retinal arterioles as measured by CRAE, risk of dementia was increased by 23%.

The relationship between moderate/severe retinopathy and dementia was stronger for persons with diabetes than for persons without diabetes (HR 2.14 vs. 1.29). This might suggest that moderate/severe retinopathy is a marker for diabetes severity, rather than a specific marker for microvascular disease in the brain. However, the number of participants in this study who have moderate/severe retinopathy but not diabetes was small (N=43), limiting precision of the estimate in the group without diabetes. Additionally, in a sensitivity analysis that adjusted for hemoglobin A_{1c}, a marker of long-term hyperglycemia, moderate/severe retinopathy remained associated with dementia during follow-up, although the effect estimate was attenuated by 14%; it is a limitation of this study that hemoglobin A_{1c} was not measured concurrently with the retinal photographs, but an average of 3 years prior to the time when the retinal photographs were taken.

Our primary analysis utilized a dementia diagnosis that incorporated multiple data sources. For the majority of participants, dementia was diagnosed using a standardized algorithm and expert panel review utilizing up to 20 years of longitudinal cognitive data, including a full neuropsychological battery administered at the 5th clinic visit (2011–2013). However, because those who survived and attended Visit 5 were a select group (for example, 79% of participants with moderate/severe retinopathy did not attend Visit 5, Table 1), we ascertained dementia cases which occurred prior to the final clinic visit using community-wide hospital and death certificate surveillance. Use of this surveillance data permits our examining early dementias, which, as was reported previously,[13] are the cases most strongly associated with classical vascular risk factors. An important concern with using dementia cases ascertained in this manner is that risk of hospitalization (and therefore ascertainment and diagnosis) may be related to the exposure, which could therefore result in an overestimate of the association between retinal signs and dementia. However, retinopathy- and CRAE-dementia associations were even stronger when participants were censored following a hospitalization for ischemic heart disease or cerebrovascular disease (HR's, 3.34 and 1.41, respectively) and when cases diagnosed by only hospital or death certificate codes were excluded (OR's, 2.53 and 1.26, respectively), suggesting that our findings are not due only to ascertainment bias or misclassification of dementia.

In our primary analysis, we estimated the cause-specific hazard ratio for dementia prior to death, comparing participants with and without retinal signs. Inferences from this model type are appropriate and useful for etiologic research questions, but should not be interpreted as the effect of retinal signs on the absolute risk of the dementia over time, as the latter inference is dependent on the survival function both for dementia and for death. To aid in the interpretation of our findings, we conducted a competing risks analysis to estimate the cause-specific hazard of death prior to dementia. Estimated associations for retinopathy were

strong for both dementia and death. Although we found no association between AV nicking and focal narrowing and dementia, both signs were related to death prior to a dementia diagnosis.

In our study, MCI and etiologic diagnosis of both MCI and dementia were adjudicated using the full neuropsychological battery and MRI brain imaging administered only at Visit 5. Consistent with the hypothesis that fundus photography may provide insight into small vessel brain disease, we found that moderate/severe (vs. none) retinopathy was associated with a joint outcome of MCI and dementia for cerebrovascular-related etiologies (primary or secondary), but not for Alzheimer's disease-related etiology without evidence of CVD. Although limitations in the study design did not allow for the most appropriate methods to handle censoring for this research question (i.e., measures used to adjudicate etiology were only collected at one point in time), this secondary analysis does address an important research gap – that of the relationship between retinal signs and etiologic subtype of dementia,[9] and given the strong association with retinal signs and mortality, may be a conservative estimate of the relationship between retinal signs and the cerebrovascular subtype. These findings should be replicated in a study with dementia etiology adjudicated at more than one time point.

Only one prospective study (Rotterdam) with similar retinal measures to ARIC has been published on this topic. Unlike our study, no associations were reported. Neither baseline retinopathy (age and sex-adjusted OR: 1.2, 95% CI: 0.9, 1.5; N=6078) [22] nor CRAE (OR: 1.05, 95% CI: 0.96, 1.16; N=5553)[23] were associated with dementia risk over a mean follow-up of 11 years. The potential use of fundus photography for differentiating dementia subtypes using large, well-powered study populations was highlighted in a recent systematic review.[9] Our study addresses this research gap with a large sample size in a biracial population, retinal signs measured in midlife with up to 20 years of follow-up, and well-characterized dementia and MCI etiologic outcomes. Methodologically, we accounted for potential bias due to missing covariate data with multiple imputation and assessed the robustness of our findings to ascertainment bias in sensitivity analysis.

One minor limitation of our study is that retinal photographs were taken in only one (randomly selected) eye; although we do not expect differences between the left and right eyes, having both eyes would potentially allow for more accurate ascertainment of the presence of retinal signs. An additional limitation of this analysis is that retinal photographs were only measured at only one time point. Unmeasured and residual confounding is a threat to inference in any observational epidemiologic study. However, covariates found to be associated in prior analyses of dementia risk in this cohort that may also be related to retinal signs have been included in this analysis and defined similarly to prior investigations.[12]

This study documented an association of two midlife retinal signs – retinopathy and generalized arteriolar narrowing (measured as CRAE) – with greater 20-year risk of all-cause dementia in 12482 men and women from four US communities. This association was observed for both white and black participants and it did not differ by *APOE* ε4 genotype. Retinopathy associations were significant only in persons with diabetes, but the converse was true for CRAE – associations were strongest in persons *without* diabetes. In analyses of

midlife retinal signs and etiologic diagnoses of MCI and dementia adjudicated 20 years later, retinopathy was associated with cerebrovascular-related, but not for Alzheimer's-related impairments in the absence of CVD. Future studies should investigate the mechanism underlying these relationships. The extent of the microvascular contribution to the development of dementia may be unrecognized because of the inability to visualize the brain microvasculature in vivo. [24–28] However, fundus photography and emerging, more sensitive, imaging techniques in the eye, such as optical coherence tomography angiographic methods, may provide surrogate indices of relevant microvascular lesions. If so, these measures could possibly help to identify persons at high risk of dementia due to otherwise unrecognized vascular disease, possibly allowing for targeted interventions to reduce vascular risk. Our findings support future investigation of measures in the eye that may provide surrogate indices of microvascular lesions relevant for dementia in older adults, as well as future studies investigating if these measures may aid in clinical dementia risk prediction. Such studies should consider inclusion of variables related to diabetes control that are easily measured in the clinic (e.g., hemoglobin A1c) as well as important measures of small artery disease that are visible on brain MRI (e.g., white matter hyperintensities and lacunes). Given effective primary prevention strategies for stroke and other vascular diseases, better recognition of the total vascular contribution to dementia is critical for public health messaging and dementia prevention efforts in our aging society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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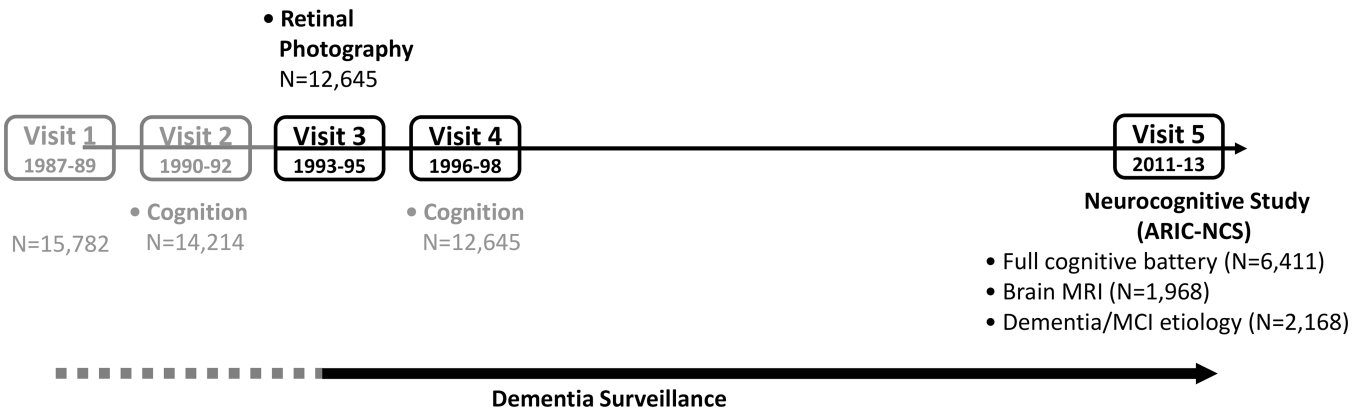

Figure 1. Atherosclerosis Risk in Communities (ARIC) Study Design

ARIC is a prospective observational study of 15782 men and women from four communities in the United States. As part of the ARIC Neurocognitive study at clinic Visit 5, all participants completed a full neuropsychological battery. A subset of participant (N=1968) also underwent brain MRI. Etiologic diagnoses were adjudicated for all participants who were diagnosed with MCI or dementia. For participants who did not attend Visit 5, active dementia surveillance continued through the date of last participant contact up to Sept 1, 2013. Dementia diagnosis was based on a Modified Telephone Interview for Cognitive Status interview with the participant, on Clinical Dementia Rating interviews with informants confirming a hospital ICD-9 discharge or death certificate dementia code, or on hospital or death certificate dementia codes alone.

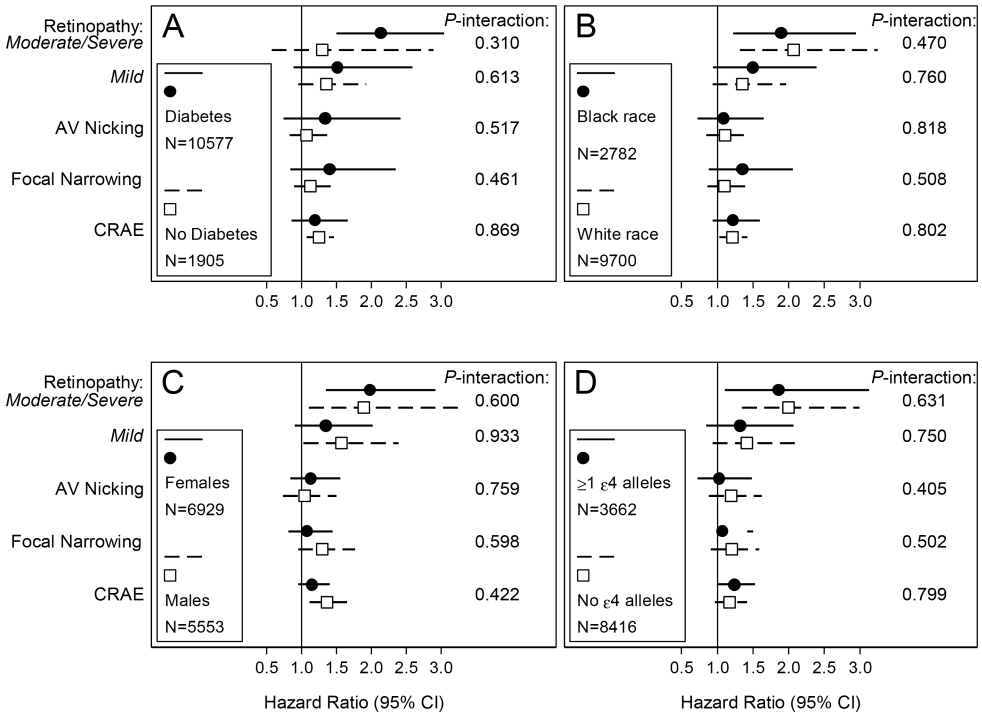

Figure 2. Multivariable-adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Relationship between Retinal Signs (Visit 3, 1993–1995) and Incident Dementia (1993–2015) by Diabetes Status, Race, and Number of *APOE* ε4 Alleles, Atherosclerosis Risk in Communities (ARIC) Study

Adjusted for age (linear and quadratic terms), education, sex, race*center interaction, BMI, drinking status, smoking status, diabetes, hypertensive status, CHD and history of stroke. Includes imputed values for missing covariate and exposure data.

Panel A: Results stratified by diabetes status (N=12482). Panel B: Results stratified by race (N=12482). Panel C: Results stratified by number of *APOE* ε4 alleles (N=12078).

Table 1.

Baseline (Visit 3, 1993–1995) Characteristics by Retinopathy Severity, Atherosclerosis Risk in Communities (ARIC) Study, N=12482

	Total (N=12482)	Retinopathy Severity			*P* value*
		None (N=11838)	Mild (N=379)	Moderate/Severe (N=265)	
	N(%)	N(%)	N(%)	N(%)	
Age (years)†	60.5 (5.7)	60.4 (5.7)	60.7 (5.7)	61.1 (5.7)	0.070
Black race	2782 (22)	2519 (21)	134 (35)	129 (49)	<0.0001
Female	6929 (56)	6580 (56)	200 (53)	149 (56)	0.540
Education					
< High school	2498 (20)	2302 (19)	97 (26)	99 (37)	<0.0001
High school	5229 (42)	4987 (42)	150 (40)	92 (35)	
> High school	4755 (38)	4549 (38)	132 (35)	74 (28)	
Body mass index (kg/m^2)†	28.5 (5.5)	28.4 (5.4)	29.4 (5.8)	31.4 (6.9)	<0.0001
Smoking status					
Never	5115 (41)	4841 (41)	155 (41)	119 (45)	0.651
Former	5158 (41)	4897 (41)	154 (41)	107 (40)	
Current	2196 (18)	2088 (18)	69 (18)	39 (15)	
Drinking status					
Never	3073 (25)	2873 (24)	108 (29)	92 (35)	<0.0001
Former	2851 (23)	2654 (22)	102 (27)	95 (36)	
Current	6545 (52)	6301 (53)	166 (44)	78 (29)	
Diabetes	1905 (15)	1581 (13)	102 (27)	222 (84)	<0.0001
Hypertension					
No hypertension	4289 (35)	4167 (35)	88 (23)	34 (13)	<0.0001
Pre-hypertension	3064 (25)	2947 (25)	75 (20)	42 (16)	
Hypertension	5065 (41)	4665 (40)	212 (57)	188 (71)	
Stroke	232 (2)	203 (2)	14 (4)	15 (6)	<0.0001
Coronary heart disease	868 (7)	794 (7)	38 (10)	36 (14)	<0.0001
APOE ε4 Genotype					
0 ε4 alleles	84162 (70)	7991 (70)	244 (66)	181 (70)	0.312
≥ 1 ε4 alleles	3662 (30)	3461 (30)	125 (34)	76 (30)	
Follow-up Status					
Died during follow-up	3234 (26)	2936 (25)	136 (36)	162 (61)	<0.0001
Living, did not attend Visit 5	3224 (26)	3069 (26)	107 (28)	48 (18)	
Attended Visit 5 (2011–13)	6024 (48)	5833 (49)	136 (36)	55 (21)	
Follow-up Time†	15.6 (4.4)	15.7 (4.3)	14.6 (5.0)	12.2 (5.9)	<0.0001
Other Retinal Measures					
Arteriovenous (AV) nicking	1641 (14)	1502 (14)	71 (19)	68 (27)	<0.0001

	Total (N=12482)	Retinopathy Severity			*P* value*
		None (N=11838)	Mild (N=379)	Moderate/Severe (N=265)	
	N(%)	N(%)	N(%)	N(%)	
Focal arteriolar narrowing	1688 (15)	1538 (14)	96 (27)	54 (22)	<0.0001
CRAE (lowest quartile)	2741 (25)	2596 (25)	92 (25)	53 (24)	0.900

Abbreviation: CRAE, central retinal arteriolar equivalent

*P-values from oneway analysis of variance test or Kruskal-Wallis test (continuous variables) or Pearson's chi2 test (categorical variables)

†Values expressed as mean (SD)

Table 2.

Multivariable-adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Relationship between Retinal Signs (Visit 3, 1993–1995) and Incident All-Cause Dementia (1993–2013), Atherosclerosis Risk in Communities (ARIC) Study

	Incident Dementia $N_{dementia}/N_{total}$ (%)	HR (95% CI)	*P*-value
Retinopathy Severity			
None	1165 / 11838 (10)	Referent	--
Mild	48 / 379 (13)	**1.44 (1.08, 1.92)**	**0.014**
Moderate/Severe	46 / 265 (17)	**1.86 (1.36, 2.55)**	**<0.0001**
Retinopathy Components			
Microaneurysms			
No	986 / 10421 (9)	Referent	--
Yes	71 / 480 (15)	**1.61 (1.25, 2.07)**	**<0.0001**
Retinal Hemorrhages			
No	1073 / 11151 (10)	Referent	--
Yes	65 / 382 (17)	**1.81 (1.40, 2.35)**	**<0.0001**
Soft Exudates			
No	1151 / 11688 (10)	Referent	--
Yes	21 / 158 (13)	1.40 (0.89, 2.19)	0.145
Arteriovenous Nicking			
No	958 / 10154 (9)	Referent	--
Yes	74 / 669 (11)	1.11 (0.88, 1.39)	0.389
Focal Narrowing			
No	865 / 9505 (9)	Referent	--
Yes	98 / 808 (12)	1.17 (0.94, 1.45)	0.161
CRAE			
No (top 3 quartiles)	749 / 8143 (9)	Referent	--
Yes (bottom quartile)	298 / 2741 (11)	**1.23 (1.07, 1.41)**	**0.004**

Abbreviations: CI, confidence interval; CRAE, central retinal arteriolar equivalent; HR, hazard ratio

Adjusted for age (linear and quadratic terms), education, sex, race*center interaction, BMI, drinking status, smoking status, diabetes, hypertensive status, CHD and history of stroke. Includes imputed values for missing covariate and exposure data.

Table 3.

Competing Risk Analysis of the Relationship between Retinal Signs (Visit 3, 1993–1995) and Mortality (1993–2013), Atherosclerosis Risk in Communities (ARIC) Study

	Deaths N_{deaths}/N_{total} (%)	HR (95% CI)	*P*-value
Retinopathy Severity			
None	2560 / 11838 (22)	Referent	--
Mild	116 / 379 (31)	**1.22 (1.01, 1.48)**	**0.035**
Moderate/Severe	136 / 265 (51)	**1.81 (1.50, 2.17)**	**<0.0001**
Retinopathy Components			
Microaneurysms			
No	2135 / 10421 (20)	Referent	--
Yes	198 / 480 (41)	**1.51 (1.30, 1.76)**	**<0.0001**
Retinal Hemorrhages			
No	2344 / 11151 (21)	Referent	--
Yes	184 / 382 (48)	**1.74 (1.48, 2.04)**	**<0.0001**
Soft Exudates			
No	2532 / 11688 (22)	Referent	--
Yes	80 / 158 (51)	**1.82 (1.45, 2.29)**	**<0.0001**
Arteriovenous Nicking			
No	2098 / 10154 (21)	Referent	--
Yes	199 / 669 (30)	**1.16 (1.01, 1.34)**	**0.040**
Focal Narrowing			
No	1919 / 9505 (20)	Referent	--
Yes	235 / 808 (29)	**1.25 (1.09, 1.44)**	**0.002**
CRAE			
No (top 3 quartiles)	1703 / 8143 (21)	Referent	--
Yes (bottom quartile)	629 / 2741 (23)	1.07 (0.97, 1.18)	0.151

Abbreviations: CI, confidence interval; CRAE, central retinal arteriolar equivalent; HR, hazard ratio

Adjusted for age (linear and quadratic terms), education, sex, race*center interaction, BMI, drinking status, smoking status, diabetes, hypertensive status, CHD and history of stroke. Includes imputed values for missing covariate and exposure data.

Table 4.

Multivariable-adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Relationship between Retinopathy Severity and CRAE (Visit 3, 1993–1995) and Etiologic Subtype of Dementia and MCI (2011–2013), Atherosclerosis Risk in Communities (ARIC) Study

	Alzheimer's disease-related			Cerebrovascular-related		
	$N_{dementia}$/MCI/N_{total} (%)	HR (95% CI)	*P*-value	$N_{dementia}$/MCI /N_{total} (%)	HR (95% CI)	*P*-value
Retinopathy Severity						
None	663/4934 (13)	Referent	--	521/4792 (11)	Referent	--
Mild	16/114 (14)	0.93 (0.56, 1.55)	0.783	15/113 (13)	0.99 (0.59, 1.67)	0.966
Moderate/Severe	7/35 (20)	1.33 (0.64, 2.77)	0.452	13/41 (32)	**2.29 (1.24, 4.23)**	**0.008**
CRAE						
No (top 3 quartiles)	449/3485 (13)	Referent	--	344/3380 (10)	Referent	--
Yes (bottom quartile)	159/1111 (14)	1.06 (0.88, 1.28)	0.578	130/1082 (12)	1.09 (0.89, 1.34)	0.391

Abbreviations: CI, confidence interval; CRAE, central retinal arteriolar equivalent; HR, hazard ratio

Adjusted for age (linear and quadratic terms), education, sex, race*center interaction, BMI, drinking status, smoking status, diabetes, hypertensive status, CHD and history of stroke. Includes imputed values for missing covariate and CRAE data.