Cognitive function and retinal and ischemic brain changes

The Women's Health Initiative

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For the Women's Health
Initiative Memory
Study and the
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ABSTRACT

Objective: To examine the association between retinopathy and cognitive decline or brain lesions and volumes in older women.

Methods: This study included 511 women aged 65 and older who were simultaneously enrolled in the Women's Health Initiative Memory Study and the Sight Examination Study. In this analysis, we examined the link between retinopathy, assessed using fundus photography (2000–2002), cognitive performance over time assessed by the modified Mini-Mental State Examination (3MSE) (1996–2007), and white matter hyperintensities and lacunar infarcts in the basal ganglia.

Results: Presence of retinopathy was associated with poorer 3MSE scores (mean difference = 1.01, SE: 0.43) ($p = 0.019$) over a 10-year follow-up period and greater ischemic volumes in the total brain (47% larger, $p = 0.04$) and the parietal lobe (68% larger, $p = 0.01$) but not with measures of regional brain atrophy.

Conclusions: The correspondence we found between retinopathy and cognitive impairment, along with larger ischemic lesion volumes, strengthens existing evidence that retinopathy as a marker of small vessel disease is a risk factor for cerebrovascular disease that may influence cognitive performance and related brain changes. Retinopathy may be useful as a clinical tool if it can be shown to be an early marker related to neurologic outcomes. *Neurology*® 2012;78:942–949

GLOSSARY

3MSE = modified Mini-Mental State Examination; **AMD** = age-related macular degeneration; **CEE** = conjugated equine estrogen; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **ICV** = intracranial volume; **ILV** = ischemic lesion volume; **MPA** = medroxyprogesterone acetate; **WHI HT CT** = Women's Health Initiative Clinical Trial of Hormone Therapy; **WHIMS** = Women's Health Initiative Memory Study; **WHIMS-MRI** = Women's Health Initiative Memory Study-Magnetic Resonance Imaging Study; **WHISE** = Women's Health Initiative Sight Exam Study.

Retinopathy is a well-known complication of both type 2 diabetes and hypertension¹ which have been linked in a number of observational studies to a higher risk of dementia and poorer cognitive performance.^{2–7} Vascular brain changes, often manifested as an increase in white matter hyperintensities, and larger and more frequent ischemic lesions, even in the absence of a stroke,⁸ are found more frequently among older adults with diabetes and hypertension. In a middle-aged population,⁹ greater sulcal and ventricular size were associated with presence of retinopathy even in those without diabetes or hypertension. It is reasonable to hypothesize that retinopathy may serve as a marker of early microvascular changes that signal increased risk for cognitive deficits and neuroradiologic findings consistent with neurodegenerative or vascular disease.

We examined the associations between retinopathy and cognitive performance, ischemic brain lesions, and regional brain volumes using data from 3 ancillary studies within the Women's Health Initiative Clinical Trial of Hormone Therapy (WHI HT CT).¹⁰ We studied women aged 65 and

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Supplemental Data

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Figure 1 Study timelines

3MSE = modified Mini-Mental State Examination; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; WHIMS-MRI = Women's Health Initiative Memory Study-Magnetic Resonance Imaging Study; WHISE = Women's Health Initiative Sight Exam Study.

older who had cognitive assessments and structural brain scans as part of the Women's Health Initiative Memory Study (WHIMS) and the WHIMS Magnetic Resonance Imaging Study (WHIMS-MRI),¹¹⁻¹³ respectively, as well as standardized retinopathy evaluations as part of the Women's Health Initiative Sight Exam Study (WHISE).^{10,14}

METHODS The WHIMS, an ancillary study to the WHI HT CT, has been described elsewhere.¹⁵⁻¹⁸ The NIH and Institutional Review Boards for all participating institutions approved the protocols and consent forms. Women were reconsented to continued follow-up with clinic-based cognitive testing through September 2007.

WHIMS-MRI was designed to compare MRI outcomes by active vs placebo therapy in WHI HT CT.¹¹ WHIMS-MRI exclusion criteria included the presence of pacemakers, defibrillators, neurostimulators, certain medical implants, and foreign bodies that were contraindicated for MRI. Other exclusion criteria included shortness of breath or inability to lie flat and conditions exacerbated by stress (e.g., anxiety panic disorders, claustrophobia, uncontrolled high blood pressure, or seizure disorders) severe enough to preclude MRI. Readable MRI scans were obtained from 1,403 women enrolled in the WHIMS-MRI study. Women were scanned an average of 3.0 (in the conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) trial) or 1.4 (in the CEE alone trial) years after the cessation of the CEE therapy trials. The mean age at scanning was 78.5 (SD = 3.7) years. These women were enrolled beginning in 1996 and each contributed up to 9 annual cognitive assessments with an average of 6.6 (1.2) assessments.

The women in the WHISE study were recruited between 2000 and 2002 from among those who were enrolled in 1 of 21 clinical sites participating in the WHI HT CT.¹⁰ To be eligible for WHISE, a woman had to be aged 65 years or older at the time of her eye examination and have at least one eye that could be photographed using standard methods of fundus photography. Participants included 4,688 women who consented to participate in WHISE; 4,349 completed enrollment with photographs of at least one eye, 97% of the enrollment goal of 4,500 participants. Of these, 511 WHISE participants were also participants of WHIMS-MRI. Figure 1 shows the study timeline

beginning from baseline enrollment (3.8 years average) to eye examination to MRI (average 4.2 years).

Fundus photography. After pupillary dilation to at least 6 mm, the photographer took 30° or 35° stereoscopic fundus photographs. Fundus photographs were taken following a specified protocol that was adapted for this study by photography consultants at the University of Wisconsin.¹⁰ Participants without diabetes were photographed using a modified 3-standard field protocol: 2 stereoscopic fundus photographs of the modified optic disc field (Early Treatment Diabetic Retinopathy Study [ETDRS] field 1M), 2 of the modified macula field (ETDRS field 2), and an additional nonstereoscopic photograph temporal to the macula (ETDRS field 3M) were taken. Participants with diabetes had photographs taken of the 7 standard fields consisting of 2 stereoscopic photographs of each of the following fields: optic disc, macula, temporal to macula, superior temporal, inferior temporal, superior nasal, and inferior nasal. If the participant had evidence of new vessels or a preretinal or vitreous hemorrhage, an additional photograph was taken to document the lesion. All participants had 2 fundus (red reflex) photographs taken to allow the Reading Center's graders to take opacities of the media into consideration when reviewing photographic quality. The quality control for the grading system included a preliminary and detailed grading followed by an edit of the photograph and adjudication, if necessary. Upon completion of this detailed grading, a comparison was made between preliminary grading and detailed grading. If there was a disagreement in the levels assigned for specific lesions, the eye photograph was sent to another grader for an edited grade of those lesions. In our quality control system for which there are 21 levels of retinopathy, exact agreement between 2 detailed graders is 58.3% to 60% and for one step (off the diagonal) the agreement is 80.0% to 85.0%.

Eye examination and interview. All participants included in this analysis had an eye examination and completed a questionnaire which collected ocular and medical history on conditions such as cataracts, glaucoma, diabetes, early and late age-related macular degeneration (AMD), retinal detachment, trauma, and previous treatment or ocular surgery. Visual acuity was tested using a pinhole and, in this analysis, was summarized by the average number of letters correctly identified for the left and right eye.

Cognitive testing. Cognitive function was assessed annually from 1996 to 2007 using the modified Mini-Mental State Examination (3MSE).¹⁹ Possible scores range from 0 to 100, with a

Table 1 Distribution of risk factors for cognitive impairment by retinopathy status at time of enrollment into WHI

Risk factor for cognitive impairment	Retinopathy status		p Value
	None present (n = 472)	Present (n = 39)	
Age at WHI enrollment, y, n (%)			
65-69	252 (53.4)	9 (23.1)	0.65
70-74	160 (33.9)	14 (35.9)	
75-80	60 (12.7)	16 (41.0)	
Education, n (%)			
Not HS grad	21 (4.4)	2 (5.1)	0.69
HS grad	121 (25.6)	12 (30.8)	
Post HS	178 (37.7)	16 (41.0)	
College graduate	152 (32.2)	9 (23.1)	
Smoking status, n (%) ^a			
Never	289 (61.5)	21 (53.8)	0.64
Former	159 (33.8)	16 (41.0)	
Current	22 (4.7)	2 (5.1)	
Body mass index, kg/m ² , n (%) ^a			
<25	135 (28.7)	9 (23.1)	0.40
25-29	173 (36.8)	13 (33.3)	
30-34	108 (23.0)	9 (23.1)	
≥35	54 (11.5)	8 (20.5)	
Hypertension status, n (%) ^b			
No	248 (52.5)	15 (38.5)	0.09
Yes	224 (47.5)	24 (61.5)	
Prior CVD, n (%) ^c			
No	445 (94.3)	35 (89.7)	0.25
Yes	27 (5.7)	4 (10.3)	
Diabetes, n (%) ^d			
No	459 (97.2)	31 (79.5)	<0.001
Yes	13 (2.8)	8 (20.5)	
WHI HT assignment, n (%)			
HT	233 (49.4)	19 (48.7)	0.94
Placebo	239 (50.6)	20 (51.3)	

Abbreviations: HS = high school; WHI HT = Women's Health Initiative Hormone Therapy.

^a Smoking status and body mass index were missing for 2 women.

^b Measured to be less than or more than 140/90 mm Hg.

^c Defined as myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, or stroke (n = 1).

^d Diabetes defined according to WHI criteria (self-report, medication use).

higher score reflecting better cognitive functioning. The test includes specific items that measure temporal and spatial orientation, immediate and delayed recall, executive function (mental reversal, 3 stage command), naming, verbal fluency, abstract reasoning (similarities), praxis (obeying command, sentence writing), writing, and visuoconstructional abilities (copying). The 3MSE tests were administered during a WHI screening visit and annually thereafter by a technician who was trained and certified in its administration and masked to randomization assignment and reports of symptoms. Tests scores for the 3MSE were available on 505 (98.8%) of the 511 women at WHI baseline enrollment. Throughout WHI follow-up, these women provided an

average of 10.4 (in those without retinopathy) and 10.1 (in those with retinopathy) 3MS examinations. Of these, averages of 4.5 and 4.6 3MSEs occurred prior to the fundus photography, respectively, and 5.9 and 5.5 3MSEs occurred after fundus photography. 3MSE measures for this analysis included scores from the eye examination through 2007.

MRI protocol. The standardized MRI scanning protocol was developed by investigators at the MRI Quality Control Center in the Department of Radiology, University of Pennsylvania, Philadelphia.¹² T1-weighted volumetric MRI scans were first preprocessed according to a standardized protocol for alignment, removal of extracranial material, and segmentation of brain parenchyma into gray matter, white matter, and CSF.¹³ Volumes of brain lesions and periventricular abnormal white matter were measured separately via the same procedure.¹² Ischemic lesion volume defined by this methodology generally corresponds to what has been called small vessel ischemic disease (ischemic white matter disease and lacunar infarctions). Our methodology classifies all brain tissue into either normal or abnormal gray or white matter. Although it does not distinguish between infarcts and other abnormal appearing tissue, abnormalities in the white matter correspond to “white matter hyperintensities” whereas abnormal tissue in the basal ganglia is thought to reflect lacunar infarcts. Intracranial volume (ICV) was estimated as the total cerebral hemispheric volumes, including ventricular CSF and the CSF within the sulcal spaces. Ventricular volume was calculated as the difference between the ICV and the total brain volume.

Risk factors for cognitive impairment. Baseline demographic, lifestyle, and clinical factors were collected via self-report and standardized assessments from the interview at the WHI randomization visit.¹⁸ Diabetes at WHI baseline was defined by self-report of a physician diagnosis or current drug therapy. Hypertension was defined as a self-report of a physician diagnosis, current drug therapy, or measurement of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained; the NIH and Institutional Review Boards for each participating institution approved the protocols and consent forms for both the WHIMS and WHISE studies.

Statistical methods. In this analysis, retinopathy was coded as present or absent without regard to diabetic status and included mild, moderate, and severe cases in either eye. The worst eye was chosen for analysis. Comparisons of ILV and brain volumes grouped by retinopathy status were conducted using analyses of covariance. Two models were fit: with limited covariate adjustment (age at WHI enrollment, age at retinal scan, age at MRI scan, clinical site, WHI treatment assignment, and intracranial volume) and full covariate adjustment (adding education level, smoking status, body mass index, hypertension, prior cardiovascular disease, and diabetes). Ischemic lesion volumes (ILV) were right-skewed and were log-transformed prior to analyses. Fitted means from these analyses were transformed back to their original units (with standard errors developed by the delta method) for reporting. Comparisons of annual 3MSE exam data were made using generalized linear models fitted by restricted maximum likelihood.²⁰ The 3MSE score was left-skewed and was transformed in analyses as natural Log (102 3MSE score) to reduce skewness.

Table 2 Fitted mean ischemic lesion volumes with limited and full covariate adjustment^a

Brain region	Mean (SE) ischemic lesion volume (cc)		p Value
	No retinopathy (n = 472)	Retinopathy (n = 39)	
Model 1 ^b			
Frontal lobe	1.91 (0.10)	2.77 (0.43)	0.03
Occipital lobe	0.37 (0.02)	0.47 (0.08)	0.15
Parietal lobe	0.97 (0.06)	1.65 (0.30)	0.01
Temporal lobe	0.96 (0.05)	1.39 (0.23)	0.05
Total brain	4.50 (0.22)	6.86 (1.13)	0.02
Non-basal ganglia	4.04 (0.20)	6.21 (1.01)	0.01
Basal ganglia	0.58 (0.03)	0.87 (0.13)	0.03
Model 2 ^c			
Frontal lobe	1.92 (0.10)	2.65 (0.43)	0.07
Occipital lobe	0.37 (0.02)	0.44 (0.08)	0.36
Parietal lobe	0.97 (0.06)	1.63 (0.26)	0.02
Temporal lobe	0.96 (0.05)	1.35 (0.23)	0.08
Total brain	4.51 (0.23)	6.63 (1.13)	0.04
Non-basal ganglia	4.06 (0.20)	5.94 (1.01)	0.04
Basal ganglia	0.59 (0.03)	0.84 (0.13)	0.05

^a Estimates were generated from log-transformed data and then back-transformed to the original scale.

^b Adjusted for age at Women's Health Initiative enrollment, age at MRI scan, clinical site, Women's Health Initiative treatment assignment, and intracranial volume.

^c Adjusted for model 1 + education level, smoking status, body mass index, hypertension, prior cardiovascular disease, and diabetes.

RESULTS A total of 511 members of the WHIMS-MRI study were also enrolled in the WHISE study. At WHI HT CT randomization, the mean $\pm$ SD (range) age of these women was 69 ± 4 (64–79) years. These women were evaluated in WHISE for retinopathy an average (range) of 3.8 ± 0.8 (1.9–6.7) years after they had enrolled in the WHI. Their MRI scans in WHIMS were obtained an average of 8 (6–10) years after WHI enrollment, when their average age was 78 ± 4 (72–88). MRI was done an average of 4.2 ± 0.5 (3.0–5.4) years after WHISE eye examinations. Overall, the race/ethnic composition of this sample was 0.8% (n = 4) Asian, 4.1% (n = 21) African American, 2.1% (n = 10) Hispanic/Latina, 91.9% (n = 470) Caucasian, and 0.9% (n = 5) other/multiple race/ethnicity.

Thirty-nine (7.6%) women were classified as having retinopathy: of these 8 were mild, 15 with only microaneurysms, 2 moderate, 1 severe, and 13 other (fibrous proliferation). The number of cases in a specific severity category was too small for subanalyses. Table 1 compares potential risk factors for cognitive impairment by retinopathy status. Of all these comparisons, only diabetes status differed significantly by retinopathy status.

Table 2 compares mean ILV by retinopathy status by for 4 brain regions and for the total brain. In

addition, ILVs within or outside of the basal ganglia were compared, with basal ganglia ILVs more likely to reflect lacunar infarcts. Women with retinopathy had greater levels of total lesion volumes (52% larger in model 1 and 47% in model 2). Mean frontal lobe lesion volumes were approximately 45% greater in women with compared to those without retinopathy ($p = 0.03$); additional covariate adjustment reduced the difference to 38% ($p = 0.07$). Regional differences in lesion volumes by retinopathy status were present in model 1 for the parietal (70% larger) and temporal lobes (46% larger) but not in the occipital lobe. ILV differed significantly between retinopathy groups both within and outside the basal ganglia (42% larger within the BG and 46% larger outside the BG). Adjustments for covariates in model 2 did not substantially change these patterns. Ischemic lesions for the total brain volume, the parietal lobe, and the basal ganglia location remained significantly different by retinopathy status after covariate adjustment. In contrast to the associations between retinopathy and ILVs, there were no substantive or significant differences in the total or regional brain volumes or ventricle volume associated with retinopathy, without and with full covariate adjustment (table 3).

Across follow-up, covariate-adjusted mean 3MSE scores were significantly lower for women with retinopathy compared to others throughout follow-up: mean (SE) difference 1.01 (0.43), $p = 0.019$. Prior to the time of the eye examination, the mean relative deficit averaged 0.72 (0.38) units. Following the eye examination, the mean relative deficit averaged 1.10 (0.53) units (figure 2). Based on test for interaction between retinopathy and time period, the difference between the means for these 2 time periods was not significant ($p = 0.07$). Including all the MRI measures in tables 2 and 3 as additional covariates in these models decreased the average differences between 3MS examination scores only slightly, to 0.86 (0.41). However, the retinopathy differences in cognitive function remained statistically significant: $p = 0.04$.

We also divided the components of the 3MS according to whether or not they were dependent on vision. Compared to those without retinopathy, women with retinopathy performed worse on both the vision-dependent ($p = 0.036$) and nonvision-dependent ($p = 0.017$) items over time. Visual acuity, as summarized by the average number of letters correctly identified for the left and right eye, was similar for women with and without retinopathy, with means (SD) 47.4 (9.9) and 46.9 (9.5), respectively: $p = 0.77$. Acuity had a moderately positive association with the 3MSE score (β slope = 0.33, $p = 0.06$)

Table 3 Mean regional brain volumes with limited and full covariate adjustment

Brain region	Mean (SE) brain volumes (cc)		p Value
	No retinopathy (n = 472)	Retinopathy (n = 39)	
Model 1 ^a			
Frontal lobe	284.14 (0.70)	282.96 (2.43)	0.64
Occipital lobe	101.89 (0.38)	101.08 (1.31)	0.55
Parietal lobe	152.32 (0.41)	150.56 (1.44)	0.24
Temporal lobe	183.55 (0.53)	184.44 (1.84)	0.64
Total brain	798.47 (1.68)	795.25 (5.86)	0.59
Ventricle	36.83 (0.63)	36.29 (2.21)	0.81
Model 2 ^b			
Frontal lobe	284.06 (0.69)	283.91 (2.51)	0.95
Occipital lobe	101.88 (0.37)	101.13 (1.36)	0.57
Parietal lobe	152.30 (0.41)	150.83 (1.49)	0.35
Temporal lobe	183.55 (0.53)	184.46 (1.90)	0.66
Total brain	798.33 (1.66)	796.91 (5.99)	0.81
Ventricle	36.86 (0.63)	35.90 (2.29)	0.69

^a Adjusted for age at Women's Health Initiative enrollment, age at MRI scan, clinical site, Women's Health Initiative treatment assignment, and intracranial volume.

^b Adjusted for model 1 + education level, smoking status, body mass index, hypertension, prior cardiovascular disease, and diabetes.

in a mixed model repeated measures analysis. When visual acuity was included as a covariate in analyses, associations between retinopathy and mean 3MS scores remained statistically significant: $p = 0.02$.

Lesion volumes were consistently higher in those with retinopathy and covariate adjustment did not substantially affect the magnitude of these findings although only total volume, parietal and basal gan-

glia lesion volumes remained statistically significant. In contrast, covariate adjustment reduced the association between diabetes and lesion volume by about 10%. Similarly, lesion volumes were significantly higher in those with hypertension. Covariate adjustment had little influence on differences between hypertensive and nonhypertensive patients.

DISCUSSION In this analysis, we found that retinopathy was associated with greater deficits over time in global cognitive function and with larger ischemic lesion volumes. Moreover, we found that associations between retinopathy and ILVs in white matter (white matter hyperintensities) and ILVs in basal ganglia (presumed infarcts) were similar within and outside the basal ganglia, although the latter are more likely to reflect infarcts rather than the ischemic/demyelinating changes associated with white matter ILV. These results are supportive of a role for small vessel disease in relation to cognitive outcomes as shown in some other studies^{21,22} which report that the number of microinfarcts is associated with higher risk of dementia.

Retinopathy and other markers of retinal microvascular abnormalities have been widely linked to cerebrovascular disease.^{9,23–27} For example, the Atherosclerosis Risk in Communities study in a cohort of middle-aged men and women, 8% of whom had diabetes at baseline, reported greater initial deficits and 14-year rates of decline on tests of executive function and psychomotor speed in those with retinopathy.^{28–30} This link may provide some clinical advantage in that the retina provides an opportunity to

Figure 2 Modified Mini-Mental State Examination (3MSE) scores over time for women by retinopathy status at eye examination forward derived from an adjusted × mixed linear regression model

Covariate adjustment for age, clinical site, education, smoking, body mass index, hypertension, prior cardiovascular disease, diabetes, examination year, and Women's Health Initiative treatment assignment.

observe vascular pathologies directly. This is likely why we found these associations to be stronger than for diabetes and hypertension alone, which are less direct markers of cerebrovascular disease.

There have been several reports that retinopathy is also associated with markers of brain atrophy. These include ventricular enlargement^{9,30} and lower gray matter density,³¹ but to our knowledge there have been no reports of associations with brain volumes, which is consistent with our findings. It may be that the coarser measures of larger regions that we examine miss more subtle changes, such as subcortical cerebral ischemia rather than cortical atrophy.^{28,32} Two studies^{23,33} reported robust relationships between retinopathy and markers of vascular disease in the brain such as white matter and cerebral infarcts. Others have shown that measures of retinopathy were linked to ventricular enlargement over time but not to sulcal widening.³⁰

We have previously reported that increased ILVs were associated with cognitive deficits in women enrolled in the WHIMS-MRI study,³⁴ yet, in our analysis, including all MRI measures as covariates did not materially attenuate relationships we observed between retinopathy and cognitive deficits. This lack of a mediation effect may be attributed to the imprecision of our measures. It may also reflect that multiple mechanisms are involved. Microvascular disease may be most directly related to mechanisms related to impaired perfusion, but it is also a risk factor for inflammation and glucose dysregulation, which also adversely affect cognitive function.^{35–37} Thus, the inability of our measures of ischemia and atrophy to account fully for the observed cognitive deficits is not surprising.

Limitations of this study include a relatively small sample size and a modest number of retinopathy cases. We were not able to determine which aspects of the broader retinopathy measure were more important in influencing cognitive function or ischemic lesions. Only a measure of global cognitive function was available and it was not possible to evaluate specific cognitive domains. Our approach to quantification of ILVs does not allow us to distinguish white matter infarcts from other white matter signal abnormalities. Diabetes status was based on self-report of a physician diagnosis and use of diabetic medications; this approach has been validated within the WHI cohort.³⁸ Our cohort consisted of women aged 65 and older who were predominantly of European descent. There may be gender and race/ethnic differences in exposure to small vessel disease or retinopathy and their influences on brain function.

This analysis has revealed that retinopathy is associated with larger ILV in older women. It was also associated with relative deficits on a test of global cognition.

Over 61% of the retinopathy cases occurred in women who were hypertensive, reflecting the fact that hypertension is a common antecedent condition for both ischemic brain lesions and for retinopathy. There was no difference by retinopathy status in measures of total or regional brain volumes/atrophy. These findings may point toward an additive model, in which ischemia and infarction lower the threshold at which cognitive impairment occurs. Microvascular disease may lead to higher levels of brain amyloid, and accelerate the appearance of cognitive symptoms. The correspondence between retinopathy and cognitive impairment, along with larger ILV, strengthens existing evidence that retinopathy as a marker of small vessel disease is a risk factor for cerebrovascular disease. Retinopathy may be useful as a clinical tool if it can be shown to be an early marker related to neurologic outcomes.

AUTHOR CONTRIBUTIONS

Dr. Haan: statistical analyses, drafting and revision of manuscript, data collection. Dr. Espeland: statistical analyses, drafting and revision of manuscript, data collection. Dr. Klein: drafting and revision of manuscript, data collection. Dr. Casanova: statistical analyses. S.A. Gaussoin: statistical analyses. Dr. Jackson: revision of manuscript, data collection. Dr. Millen: revision of manuscript. Dr. Resnick: revision of manuscript, data collection. Dr. Rossouw: revision of manuscript, data collection. Dr. Shumaker: revision of manuscript, data collection. Dr. Wallace: revision of manuscript, data collection. K. Yaffe: revision of manuscript, data collection.

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DISCLOSURE

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