



## Original Contribution

# Associations between Findings on Cranial Magnetic Resonance Imaging and Retinal Photography in the Elderly

## The Cardiovascular Health Study

W. T. Longstreth, Jr.<sup>1</sup>, Emily K. Marino Larsen<sup>2</sup>, Ronald Klein<sup>3</sup>, Tien Yin Wong<sup>4,5</sup>, A. Richey Sharrett<sup>6</sup>, David Lefkowitz<sup>7</sup>, and Teri A. Manolio<sup>8</sup>

<sup>1</sup> Departments of Neurology and Epidemiology, University of Washington, Seattle, WA.

<sup>2</sup> Department of Biostatistics, University of Washington, Seattle, WA.

<sup>3</sup> Department of Ophthalmology, University of Wisconsin, Madison, WI.

<sup>4</sup> Centre for Eye Research Australia, University of Melbourne, East Melbourne, Victoria, Australia.

<sup>5</sup> Singapore Eye Research Institute, National University of Singapore, Republic of Singapore.

<sup>6</sup> Department of Epidemiology, Johns Hopkins University, Baltimore, MD.

<sup>7</sup> Department of Neurology, Wake Forest University, Winston-Salem, NC.

<sup>8</sup> Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, MD.

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Associations between findings on cranial magnetic resonance imaging (MRI) and retinal photographs have been described mostly in middle-aged people. In the Cardiovascular Health Study, 1,717 elderly participants underwent MRI and retinal photography between 1991 and 1999. Associations were sought between MRI findings and four findings of retinal microvascular disease: retinopathy, focal arteriolar narrowing, arteriovenous nicking, and the arteriovenous ratio—the last based upon semiautomated measurements of arterioles and venules. After controlling for age and gender, the authors found associations between MRI findings and the smaller arteriovenous ratio (per standard deviation decrease): prevalent infarcts (odds ratio = 1.18, 95% confidence interval: 1.05, 1.34;  $p = 0.007$ ), white matter grade (regression coefficient, 0.093;  $p = 0.011$ ), incident infarct (odds ratio = 1.26, 95% confidence interval: 1.09, 1.46;  $p = 0.002$ ), and worsening white matter grade (odds ratio = 1.12, 95% confidence interval: 0.98, 1.29;  $p = 0.09$ ). Arteriovenous nicking was also associated with prevalent (odds ratio = 1.84, 95% confidence interval: 1.23, 2.76;  $p = 0.003$ ) and incident (odds ratio = 1.84, 95% confidence interval: 1.15, 2.94;  $p = 0.011$ ) infarcts. Adjustment for hypertension and diabetes had minimal effect. Evidence of small vessel disease in the retina increases the likelihood of finding it in the brain. Associations were less prominent in this elderly population than have been described in middle-aged people.

arteriosclerosis; brain infarction; leukoaraiosis; magnetic resonance imaging; microcirculation; retinal artery; retinal vein

Abbreviations: ARIC, Atherosclerosis Risk in Communities; MRI, magnetic resonance imaging.

Retinal examinations provide the only readily available views of blood vessels in the human body. Blood vessels in the retina and brain share many features, raising the possi-

bility that characteristics of blood vessels in the retina may provide clues about blood vessels in the brain. In studies of mostly middle-aged people, findings on retinal photographs

Correspondence to Dr. W. T. Longstreth, Jr., Department of Neurology, Box 359775, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104-2420 (e-mail: wl@u.washington.edu).

**TABLE 1. Comparison of participants (*n* = 4,249) who had study visits in 1997 and 1998 and were included or not in the analyses, Cardiovascular Health Study**

Characteristic*	Not included ( <i>n</i> = 2,532)		Included ( <i>n</i> = 1,717)		<i>p</i> value
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	
Age, years		80.2 (5.3)		78.3 (4.3)	<0.001
Men	927 (36.6)		682 (39.7)		0.042
Non-White	475 (18.8)		276 (16.1)		0.024
Current smoker	151 (6.9)		119 (7.0)		0.949
History of cardiovascular disease	1,174 (46.3)		409 (23.8)		<0.001
History of hypertension	1,069 (47.8)		791 (46.1)		0.304
Hypertension	1,259 (66.1)		967 (56.3)		<0.001
Diabetes	342 (20.2)		216 (13.0)		<0.001
Systolic blood pressure, mmHg		133.3 (21.2)		131.4 (19.2)	0.006
Diastolic blood pressure, mmHg		66.8 (11.6)		66.9 (10.8)	0.655
Body mass index, kg/m <sup>2</sup>		27.0 (4.9)		26.8 (4.4)	0.221
Serum glucose, mg/dl		105.2 (35.5)		100.4 (28.0)	<0.001
Total serum cholesterol, mg/dl		202.1 (39.5)		202.6 (39.6)	0.721

\* Characteristics from around the time of the 1997–1998 visit were expressed as the mean (standard deviation (SD)) for continuous variables and the number (%) for dichotomous variables.

have been associated with findings on cranial magnetic resonance imaging (MRI), as well as with clinical events such as stroke (1). In the Cardiovascular Health Study, a longitudinal population-based study, 1,716 elderly participants had both cranial MRI and retinal photography around the same time, thus affording the opportunity to seek correlations between abnormalities in the brain and retina that likely reflect consequences of small vessel disease.

## MATERIALS AND METHODS

Participants in the Cardiovascular Health Study were recruited from a random sample of people on Medicare eligibility lists for four US communities. Participants had to be 65 years or older and could not be institutionalized, wheelchair bound in the home, or under active treatment for cancer (2). The 5,888 participants in the Cardiovascular Health Study have been followed longitudinally since recruitment started in 1989 (3). They were invited to undergo cranial MRI scanning between 1991 and 1994 and again about 5 years later. Importantly, the 3,660 (62 percent) participants who underwent initial scan were healthier than those who were never scanned (4, 5), and the 2,116 (36 percent) participants who underwent two scans were healthier than those who underwent a single scan (6, 7). In addition to the follow-up MRI scan, surviving participants were also invited in 1997 and 1998 to undergo retinal photography. In total, 1,639 participants did not attend study evaluations in 1997 and 1998, and 2,215 participants lacked one of the studies, leaving 2,034 participants who completed both follow-up MRI scan and retinal photography. These analyses are limited to the 1,717 participants who did not have missing results from these studies (*n* = 143) and did not have a history of transient ischemic attack or stroke before follow-up MRI scans (*n* = 174). Table 1 compares participants who came to

study visits in 1997 and 1998 and were included in these analyses or not. Overall, those included were healthier than those who were not included. The institutional review board at each participating center approved the study, and each participant gave informed consent.

## Evaluations

Eligible and consenting participants underwent extensive baseline evaluations at enrollment including standard questionnaires, physical examination, performance measures, and laboratory testing. Parts of the baseline evaluations have been repeated annually. The variables considered in these analyses were those from the examinations closest in time to brain and retinal imaging in 1997 and 1998. Participants were screened for vascular diseases at baseline and during follow-up, including transient ischemic attack, stroke, angina, myocardial infarction, and congestive heart failure. Participants were said to have cardiovascular disease if they had one or more of these conditions. As previously (8), hypertension was defined as present if the participant had systolic blood pressure greater than or equal to 140 mmHg, diastolic blood pressure greater than or equal to 90 mmHg, or the combination of self-reported high blood pressure diagnosis and use of antihypertensive medications. Diabetes mellitus was defined according to American Diabetes Association criteria, namely, having either a fasting blood sugar measurement of 126 mg/dl (7.0 mmol/liter) for those not currently using any hypoglycemic agents or treatment with oral hypoglycemic agents, insulin, or both (9).

## Brain imaging

Scanning protocols included sagittal T1-weighted localizer images and axial T1-weighted, spin density-, and

T2-weighted images. All axial images had 5-mm thickness without interslice gaps. Blinded to any information about participants or retinal photographs, neuroradiologists at the reading center identified infarcts (5, 6) and estimated white matter grade using a 10-point system from 0 to 9, higher being more abnormal (4, 7). An MRI-defined brain infarct was an area of abnormal signal intensity 3 mm in size or greater in a vascular distribution and without mass effect.

### Retinal imaging

Procedures concerning retinal photographs are detailed elsewhere (8, 10). In brief, after 5 minutes of dark adaptation, participants underwent a 45-degree retinal photograph of one eye centered between the optic disc and the macula. Blinded to any information about participants or MRI scans, one of two trained graders at the reading center assessed photographs for four retinal microvascular abnormalities using a standard protocol. Retinopathy was defined as the definite or probable presence of any of the following lesions in any of four quadrants of the retina: microaneurysms, blot or flame-shaped hemorrhages, soft exudates or cotton wool spots, hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, vitreous hemorrhage, and laser photocoagulation scars. The definition of retinopathy excluded signs of age-related maculopathy, such as exudative maculopathy, and retinal artery or vein occlusions. Similarly, focal arteriolar narrowing and arteriovenous nicking were defined by their definite or probable presence in any of four quadrants. In addition, retinal photographs were digitized, and the diameters of all arterioles and venules coursing through an area from one-half to one-disc diameter from the optic disc margin were measured. Summary variables were calculated, yielding central retinal arteriolar and venular equivalents, and were expressed as arteriolar:venular equivalent ratios, which reflect the relative diameters of arterioles to venules, adjusting for magnification. Duplicate readings indicated that retinal measures were reliable. Intragrader kappa statistics ranged from 0.57 for focal arteriolar narrowing to 0.90 for retinopathy, whereas intergrader kappa statistics ranged from 0.31 for focal arteriolar narrowing to 0.88 for retinopathy. For the arteriovenous ratio, the intragrader intraclass correlation coefficient was 0.74, and intergrader, 0.81.

### Analyses

Correlations were sought between the MRI-defined variables of infarct and white matter grade and four variables derived from the retinal photographs. Because of small numbers in the higher white matter grades, grades five and more were combined. Dependent variables were MRI variables, and independent variables, retinal variables. Variables were coded as in table 2. We controlled for age and gender in all analyses using logistic regression for infarcts and linear regression for white matter grade. Considering both the initial and follow-up MRI, we also sought associations with the dichotomous dependent variables incident MRI-defined infarcts (6) and worsening white matter by one or more

**TABLE 2. Findings on cranial magnetic resonance imaging scans and retinal photographs, Cardiovascular Health Study, 1997–1998**

Characteristics	Total no.	Summary*	
		No. (%)	Mean (SD)
Prevalent infarcts	1,717	496 (28.9)	
White matter grade	1,715		2.5 (1.6)
Incident infarcts	1,285	356 (27.7)	
Worsening white matter	1,431	395 (27.6)	
Retinopathy	1,346	133 (9.9)	
Microaneurysm	1,345	70 (5.2)	
Retinal hemorrhage	1,654	84 (5.1)	
Soft exudate	1,669	25 (1.5)	
Focal arteriolar narrowing	1,393	130 (9.3)	
Arteriovenous nicking	1,435	108 (7.5)	
Arteriovenous ratio	1,333		0.87 (0.084)
Arteriolar equivalent ( $\mu\text{m}$ )	1,333		165.6 (19.3)
Venular equivalent ( $\mu\text{m}$ )	1,333		191.0 (18.3)

\* Findings were expressed as the mean (standard deviation (SD)) for continuous variables and the number with the characteristic (% of total) for discrete variables.

grades (7). We sought evidence of confounding and effect modification by age, gender, hypertension, and diabetes mellitus. Not all MRI scans and photographs yielded usable results on all variables, so the numbers in analyses vary.

SPSS for Windows software (version 11; SPSS, Inc., Chicago, Illinois) was used for analyses, which were based on the updated Cardiovascular Health Study database incorporating corrections through September 2003.

### RESULTS

Findings on MRI scans and retinal photography are summarized in table 2. The interval between brain and retina imaging studies ranged from 0 to 737 days, with a mean of 121 and a standard deviation of 122. Retinopathy, focal arteriolar narrowing, and arteriovenous nicking were significantly and positively associated with each other. The arteriovenous ratio was significantly and positively associated with only retinopathy. MRI-defined infarcts on scans done around the time of retinal photographs were significantly associated with arteriovenous nicking and the smaller arteriovenous ratio after controlling for age and gender (table 3) but not with retinopathy or focal narrowing. The white matter grade was significantly associated with only the smaller arteriovenous ratio (table 3). Patterns of associations with incident MRI-defined infarcts and worsening white matter (table 4) were similar to patterns seen in cross-sectional analyses (table 3). Associations were always stronger for smaller retinal arteriolar equivalents than for larger venular equivalents, for which none of the associations was significant (tables 3 and 4).

**TABLE 3. Associations between findings on retinal photographs and cranial magnetic resonance imaging scans performed in 1997 and 1998, Cardiovascular Health Study**

Retinal characteristic	Prevalent infarcts				White matter grade		
	No.	Odds ratio*	95% confidence interval*	<i>p</i> value	No.	Regression coefficient†	<i>p</i> value‡
Retinopathy	1,346	0.94	0.63, 1.41	0.777	1,344	-0.042	0.728
Focal narrowing	1,393	1.20	0.81, 1.78	0.354	1,391	0.097	0.425
Arteriovenous nicking	1,435	1.84	1.23, 2.76	0.003	1,433	0.210	0.106
Arteriovenous ratio (per SD‡ decrease)	1,333	1.18	1.05, 1.34	0.007	1,332	0.093	0.011
Arteriolar equivalent	1,333	1.15	0.99, 1.26	0.082	1,332	0.050	0.167
Venular equivalent	1,333	1.05	0.93, 1.19	0.450	1,332	0.035	0.338

\* Odds ratios and 95% confidence intervals were calculated from logistic regression controlling for age and gender.

† Coefficient and *p* value were calculated from linear regression controlling for age and gender.

‡ SD, standard deviation.

The effects of adding variables for the presence or absence of hypertension, diabetes mellitus, or both to models for arteriovenous nicking and the arteriovenous ratio are shown in table 5. Hypertension slightly weakened measures of association, more so for white matter grade than infarct. Diabetes mellitus had a minimal effect on measures of association.

Small numbers hampered searches for effects differing by strata defined by age, gender, hypertension, and diabetes mellitus. Multiple analyses suggested only one significant statistical interaction. The association between white matter grade and arteriovenous nicking differed for women and men. The age-adjusted regression coefficient was 0.469 ( $p = 0.004$ ) for women and -0.216 ( $p = 0.326$ ) for men.

Sensitivity analyses included examining other categorization schemes for white matter grade and the arteriovenous ratio, using other analytical approaches, such as multinomial logistic regression, including participants with a history of transient ischemic attack or stroke, and including the interval between brain and retina imaging studies in the

multivariable models. The results of these analyses are not shown because they were similar to those presented in tables 3 and 4. Using quintiles for the arteriovenous ratio in these analyses did not suggest a nonlinear relation or threshold effect. We made certain that important associations would not become apparent when multiple vascular risk factors were added to models; no associations between brain and retinal findings became substantially stronger or became statistically significant in these analyses. Finally, we reasoned that associations might be stronger if we considered only small vessel lacunar infarcts, defined as a subcortical infarct less than 20 mm in its greatest diameter (5). Nonetheless, results were similar if 62 participants whose follow-up MRI showed exclusively nonlacunar infarcts were excluded.

## DISCUSSION

In this group of elderly people, we sought to identify associations between findings on brain MRI and retinal

**TABLE 4. Associations between findings on retinal photographs and changes on cranial magnetic resonance imaging scans performed on average 5 years apart, Cardiovascular Health Study, 1991–1994 and 1997–1998**

Retinal characteristic	Incident infarct				Worsening white matter grade			
	No.	Odds ratio*	95% confidence interval*	<i>p</i> value	No.	Odds ratio*	95% confidence interval*	<i>p</i> value
Retinopathy	1,002	0.92	0.56, 1.52	0.919	1,118	1.31	0.72, 1.76	0.600
Focal narrowing	1,057	1.17	0.73, 1.86	0.519	1,162	1.44	0.95, 2.18	0.084
Arteriovenous nicking	1,089	1.84	1.15, 2.94	0.011	1,204	1.21	0.76, 1.93	0.414
Arteriovenous ratio (per SD† decrease)	1,004	1.26	1.09, 1.46	0.002	1,117	1.12	0.98, 1.29	0.090
Arteriolar equivalent	1,004	1.17	1.01, 1.35	0.037	1,117	1.17	1.03, 1.34	0.019
Venular equivalent	1,004	1.05	0.91, 1.22	0.480	1,117	0.93	0.82, 1.07	0.303

\* Odds ratios and 95% confidence intervals were calculated from logistic regression controlling for age and gender.

† SD, standard deviation.

**TABLE 5. Effects on associations of controlling for hypertension, diabetes mellitus, or both, Cardiovascular Health Study, 1991–1994 and 1997–1998**

Variable	Prevalent infarcts		White matter grade		Incident infarct		Worsening white matter	
	Odds ratio	<i>p</i> value	Regression coefficient	<i>p</i> value	Odds ratio	<i>p</i> value	Odds ratio	<i>p</i> value
Arteriovenous nicking*	<i>n</i> = 1,386		<i>n</i> = 1,384		<i>n</i> = 1,049		<i>n</i> = 1,166	
Model 1	1.79	0.006	0.240	0.068	1.77	0.019	1.22	0.417
Model 2	1.74	0.009	0.223	0.088	1.76	0.022	1.20	0.459
Model 3	1.78	0.006	0.241	0.067	1.76	0.021	1.21	0.434
Model 4	1.74	0.009	0.225	0.086	1.75	0.023	1.19	0.467
Arteriovenous ratio*	<i>n</i> = 1,285		<i>n</i> = 1,284		<i>n</i> = 965		<i>n</i> = 1,081	
Model 1	1.17	0.011	0.088	0.017	1.25	0.004	1.12	0.100
Model 2	1.14	0.044	0.069	0.065	1.22	0.011	1.10	0.167
Model 3	1.17	0.011	0.088	0.017	1.25	0.004	1.12	0.103
Model 4	1.14	0.045	0.068	0.068	1.22	0.010	1.10	0.165

\* Models were based on logistic regression (odds ratio) or linear regression (regression coefficient). In model 1, age and gender are included. In model 2, hypertension is added to model 1. In model 3, diabetes is added to model 1. In model 4, hypertension and diabetes are added to model 1. The numbers in models 1–3 are the same, because only those without missing values for hypertension and diabetes are included.

photographs that likely reflect small vessel disease. We examined the findings of infarcts and white matter grade on MRI scans done around the time of retinal photographs, as well as changes from MRI scans done 5 years earlier. Retinal photographs were assessed in a standard fashion, including computer-assisted measurements of the caliber of retinal vessels. We found significant associations between the MRI findings and two of the four measures of retinal microvascular abnormalities: arteriovenous nicking and the arteriovenous ratio. In a previous Cardiovascular Health Study paper, consistent associations of these two retinal microvascular abnormalities with clinical and subclinical measures of atherosclerosis were not identified (8). Associations between brain and retinal findings in the current study suggest that small vessels may be similarly affected in both vascular beds, as suggested by others (11–14).

Despite the strong association between hypertension and these retinal microvascular abnormalities reported in previous Cardiovascular Health Study papers (8, 15, 16), the associations between brain and retinal findings were only slightly weakened by adjusting for the presence of hypertension. Perhaps the brain and retinal findings reflect more than simply the effects of concurrent hypertension in two different vascular beds. Alternatively, the definition of hypertension used in this study may not adequately summarize the long-term effects of blood pressure on these vascular beds. Interestingly, arteriovenous nicking and the arteriovenous ratio, the two retinal microvascular abnormalities found to be associated with MRI findings in the current study, were also the only two retinal microvascular abnormalities found to be associated with past blood pressure measured 3–8 years prior to the retinal photographs in both the Cardiovascular Health Study (15) and the Atherosclerosis Risk in Communities (ARIC) Study (17). Thus, these two retinal abnormalities may reflect changes from chronically elevated blood

pressure. In the Cardiovascular Health Study, the presence of diabetes has been associated with retinopathy but not other measures of retinal microvascular abnormalities (16). In the current study, adjustment for the presence of diabetes had even less of an effect on associations than did hypertension. Finally, in one of the stratified analyses with adequate numbers to evaluate for statistical interactions, associations between white matter grade and arteriovenous nicking were stronger for women than men, although this finding may have occurred by chance alone given the number of interactions examined.

We were unable to identify significant associations between MRI findings and retinopathy, as we defined it. Interestingly, consistent associations of retinopathy with clinical and subclinical measures of large vessel disease were identified in previous Cardiovascular Health Study papers even after controlling for several potentially confounding factors including hypertension (8, 16). Retinopathy, but not the other measures of retinal microvascular abnormalities examined in the current study, was associated with the following: prevalent coronary heart disease, myocardial infarction, and stroke; the presence of carotid artery plaque; increased intimal-medial thickness of the common carotid and internal carotid artery; and the ankle-arm index. These findings suggest that, in this population of generally healthy elderly Cardiovascular Health Study participants, retinopathy seems to be associated with manifestations of large vessel disease, while arteriovenous nicking and the arteriovenous ratio seem to be associated with manifestations of small vessel disease of the brain.

The findings in the Cardiovascular Health Study differ somewhat from those described in the ARIC Study using similar methods, where most retinal microvascular abnormalities, especially retinopathy and its components, were associated in cross-sectional analyses with MRI-defined

infarcts (14) and white matter grade (1, 13). The differences in results may be explained by the fact that the 1,717 participants in the Cardiovascular Health Study were older than the 1,684 participants in the ARIC Study, with a mean age of 78 versus 62 years. A survival bias could exist if participants in the Cardiovascular Health Study who had died or were too disabled to attend the 1997 and 1998 study visits had associations more like those described in the ARIC Study. Additionally, pathologic mechanisms and comorbid conditions may differ by age and could help to explain the differences in these large population-based studies. Others have also observed “this ‘age-related’ decrease in the predictive value of retinopathy” (18, p. 1008). Associations between retinal microvascular findings and incident transient ischemic attack or stroke in the Blue Mountains Eye Study, with the mean age of participants being 65.8 years (18), were described as weaker than in the ARIC Study, with the mean age of participants being 53.6 years (19).

Findings in the Cardiovascular Health Study also differ from results from the Rotterdam Study (20). In cross-sectional analyses with a single MRI done on average 3 years after retinal photographs ( $n = 490$ ) and in analyses considering the progression between two MRI scans ( $n = 279$ ), these investigators could not identify significant associations between the smaller arteriovenous ratio and MRI findings. They did find an association between venular dilatation and marked white matter progression. In the current study, associations with white matter grade and worsening were always stronger for smaller arteriolar equivalents than larger venular equivalents. None of the associations with venular equivalents was significant.

This study has its strengths and weaknesses. The strengths include having a large number of well-characterized, generally healthy, elderly participants. Brain and retinal imagings were evaluated in a standard fashion with blinding to any information about the participants. Analyses were cross-sectional but also longitudinal with respect to brain imaging. Nonetheless, better information on the retina may have come from 30-degree stereoscopic retinal photographs of both eyes taken through pharmacologically dilated pupils compared with the 45-degree nonstereoscopic photographs taken of one eye as done in this study. In addition, Cardiovascular Health Study participants who underwent the brain and retinal imaging necessary to be included in these analyses were healthier than those who did not. Perhaps the findings in these other participants would have differed and been more comparable to the results seen in the ARIC Study (1, 13). Finally, given the many comparisons, associations may have occurred by chance.

Four population-based studies in middle-aged (ARIC Study) and elderly (the Rotterdam Study, the Blue Mountains Eye Study, and the current Cardiovascular Health Study) populations have shown associations between the findings on retinal photographs and manifestations of brain vascular disease—either overt with transient ischemic attacks and strokes (18, 19) or covert with white matter abnormalities and infarcts on MRI (13, 20). These observations support the importance of small vessel disease as a cause of brain injury and subsequent disability, which may have implications for prevention and treatment. They further support

the utility of retinal photography as an additional imaging modality in the investigation of brain vascular disease. Longitudinal studies with serial imaging of the brain and retina will be needed to clarify the interplay of small vessel disease in these two vascular beds with aging.

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