Retinal Microvascular Signs, Cognitive Function, and Dementia in Older Persons
The Cardiovascular Health Study

Michelle L. Baker, MD; Emily K. Marino Larsen, MS; Lewis H. Kuller, MD, DrPH; Ronald Klein, MD, MPH; Barbara E.K. Klein, MD, MPH; David S. Siscovick, MD, MPH; Charles Bernick, MD; Teri A. Manolio, MD, PhD; Tien Yin Wong, MD, PhD

Background and Purpose—Cerebral microvascular disease may be a risk factor for the development of dementia in elderly persons. We describe the association of retinal microvascular signs with cognitive function and dementia among older individuals.

Methods—In the population-based Cardiovascular Health Study, 2211 persons aged 69 to 97 years at recruitment had retinal photography. Photographs were evaluated for retinopathy (eg, microaneurysms, retinal hemorrhages), focal arteriolar narrowing, arteriovenous nicking, and retinal arteriolar and venular caliber. Cognitive status was determined from the Digit–Symbol Substitution Test and Modified Mini-Mental State Examination. Participants were also further evaluated for the presence of dementia with detailed neuropsychological testing. Persons with a prior stroke or taking antipsychotic or antidepressant medications were excluded.

Results—After adjusting for age, gender, race, field center, education level, internal carotid intima-media thickness, body mass index, hypertension, diabetes, and cigarette smoking status, persons with retinopathy had lower mean Digit–Symbol Substitution Test scores but not Modified Mini-Mental State Examination than those without retinopathy (39 versus 41, \(P=0.002\)). In hypertensive persons, retinopathy (multivariable-adjusted OR, 2.10; 95% CI, 1.04 to 4.24) and focal arteriolar narrowing (OR, 3.02; 95% CI, 1.51 to 6.02) were associated with dementia. These associations were not present in individuals without hypertension.

Conclusions—In older persons, our study shows a modest cross-sectional association between retinopathy signs with poorer cognitive function and, in persons with hypertension, with dementia. These data support a possible role of cerebral microvascular disease in the pathogenesis of impaired cognitive function and dementia in older hypertensive persons. (Stroke. 2007;38:000-000.)

Key Words: cognitive impairment ■ dementia ■ hypertension ■ retinal microvascular disease ■ retinopathy

Cerebrovascular disease is an important risk factor for the development of cognitive impairment and dementia as evidenced from studies showing associations of cognitive impairment with clinical stroke,\(^1,2\) MRI-defined silent stroke and white matter lesions,\(^3,4,6,13\) and with cardiovascular risk factors such as hypertension,\(^7,8,10\) diabetes,\(^9,10\) cigarette smoking,\(^11\) and inflammation.\(^12\) The specific role of cerebral small-vessel disease in the pathogenesis of cognitive impairment and dementia, however, is less clear.\(^13,14\) Pathological studies have demonstrated structural cerebral microvascular alterations (eg, narrowing of cerebral arterioles) among the characteristic degenerative changes seen in dementia.\(^15,18\) However, there remains little clinical data available to test the hypothesis that cognitive impairment and dementia have a microvascular basis. The retinal circulation provides a means to investigate cerebral microvascular disease noninvasively because retinal arterioles have similar anatomy, physiology, and embryology as cerebral arterioles.\(^19\)

In the Atherosclerosis Risk in Communities (ARIC) study, a population-based study among middle-aged persons (51 to 70 years), we have previously reported an association of retinal microvascular signs and cognitive impairment that persisted after adjustment of vascular risk factors as defined from a set of standardized tests (Delayed Word Recall Test, Digit Symbol Subtest, and the Word Fluency Test).\(^20\) Attributable to the relatively young age of the ARIC study cohort,
dementia was not investigated. It therefore remains unclear if similar associations are present in older people who have a higher prevalence of cognitive impairment and dementia and a higher frequency of cerebrovascular risk factors.

In the current study, we examined the associations of retinal microvascular abnormalities with cognitive function and dementia in a population-based sample of older people.

**Materials and Methods**

**Study Population**

The Cardiovascular Health Study (CHS) is a population-based longitudinal investigation of coronary heart disease and stroke in adults 65 years of age and older. The study population, study design, and methods are described in detail elsewhere. In brief, recruitment of 5888 eligible persons took place in 1989 to 1993 at 4 field centers. Differences between those recruited and those not recruited have been presented elsewhere. All CHS participants completed up to 10 annual clinic visits. Informed consent was obtained from all participants at entry into the study and at periodic intervals. Institutional Review Board approval was obtained at all sites collecting and analyzing data.

**Retinal Photography and Grading**

Retinal photographs were first offered to participants 10 years after enrollment during the 1997 to 1998 clinic visit, and their interpretation in the CHS has been previously reported in detail. The photographs were evaluated according to a standardized protocol into 4 broad categories for: (1) retinopathy signs (microaneurysms, retinal hemorrhages, cotton wool spots, hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, and vitreous hemorrhage); (2) arteriovenous nicking; (3) focal arteriolar narrowing; and (4) retinal arteriolar and venular caliber. For the evaluation of retinal arteriolar and venular caliber, retinal photographs were digitized and the caliber of all arterioles and venules coursing through an area one half to one disc diameter from the optic disc margin was measured and summarized.
Assessment of Cognitive Function and Dementia
Cognitive function was assessed at baseline (1989 to 1990) using the Mini-Mental State Examination and annually thereafter using the Modified Mini-Mental State Examination (3MSE) and Digit–Symbol Substitution Test (DSST). We used the cognitive function scores from the 1997 to 1998 examination (at the time of retinal photography) for the 2211 participants in this analysis. Overall, there were 3602 participants evaluated for the presence of dementia as part of a CHS cognition study (CHSCS) performed in the 1998 and 1999 on all available subjects who were classified as high risk; in addition, all participants at one study site (Pittsburgh, Pa.) received this testing regardless of dementia risk. Finally, in the third stage of dementia evaluation, those participants who were classified as high risk for dementia but unavailable for in-person evaluation (and self-reported use of insulin or oral hypoglycemic agents. Coronary heart disease, myocardial infarction, and stroke were ascertained and classified by an adjudication process involving medical history, physical examination, and laboratory criteria, including an electrocardiogram. The cumulative history (up to the time of retinal photography) was used to define absence versus presence of these cardiovascular events.

Vascular ultrasound examination of the common and internal carotid arteries was used to determine the intima-media thickness and presence or absence of atherosclerotic plaque. The internal carotid intima-media thickness was defined as the mean value obtained from measurements of right and left sides on 3 different scan planes. Medical history, medication use, and cigarette smoking status were ascertained from questionnaires. Anthropometry was assessed by measurement of body mass index and waist-to-hip ratio. Blood collection, processing, and definitions for fasting glucose and lipids are described elsewhere. All variables defined were based on the 1997 to 1998 examination concurrent with retinal photography, except data on most blood chemistry (1992 to 1993), carotid ultrasonography (1992 to 1993), waist-to-hip ratio (1992 to 1993), body mass index (1996 to 1997 height and 1997 to 1998 weight), and fasting glucose (1996 to 1997).

Statistical Methods
Retinal signs were analyzed as binary (absent, present) or categorical (retinal vascular caliber categorized into quintiles) variables. Cogni-
tive function scores of DSST and 3MSE were analyzed as continuous variables. Dementia was analyzed as a binary variable (absent, present). Analysis of covariance models were used to compare those included and excluded from the analyses adjusting for age, gender, and race when appropriate.

We examined the mean DSST and 3MSE scores in the presence or absence of specific retinal microvascular signs adjusting for age and other factors using analysis of covariance models. We used logistic regression models to determine odds of dementia in association with retinal signs. We constructed 2 models initially adjusting for age and then subsequently for gender, race, field center, education level, internal carotid intima-media thickness, body mass index, hypertension, diabetes status, and cigarette smoking status. We used logistic regression models to determine odds of dementia in association with retinal signs. We constructed 2 models initially adjusting for age and then subsequently for gender, race, field center, education level, internal carotid intima-media thickness, body mass index, hypertension, diabetes status, and cigarette smoking status. We constructed 2 models initially adjusting for age and then subsequently for gender, race, field center, education level, internal carotid intima-media thickness, body mass index, hypertension, diabetes status, and cigarette smoking status. We repeated these analyses in patients with and without hypertension and diabetes. In a separate model, we additionally adjusted for cerebral MRI signs of white matter lesions (absent, present) and cerebral infarcts (absent, present). Finally, we examined associations separately for “pure” Alzheimer-type dementia (AD) and “mixed” AD and “pure” vascular dementia (VaD). All analyses were performed with SPSS (SPSS Inc, Chicago, Ill.).

Results
Of the 2211 participants included in this analysis of cognitive function, 1767 were evaluated for dementia as part of the CHS CS with 159 diagnosed as having dementia. Of those with dementia, 99 were classified with AD, 11 with VaD, 49 with “mixed” AD and VaD, and 5 with other types, including dementia associated with Parkinson disease. A comparison of baseline characteristics of individuals included (n = 2211) and excluded (n = 2038) appear in Table 1. Individuals included were more likely to be white, younger males, and less likely to have hypertension, higher waist-to-hip ratio, coronary heart disease, myocardial infarction, diabetes, or to have a cigarette smoking history.

Table 2 shows the mean DSST and 3MSE scores by presence of retinal microvascular signs. After adjusting for age, mean DSST scores for individuals with any retinopathy were lower than for those without retinopathy and arteriovenous nicking. After further adjustment for gender, race, field center, and other factors, the association between retinopathy and lower DSST persisted but no association was seen for other retinal signs. Further adjustment for cerebral MRI signs of white matter lesions and cerebral infarcts did not change these associations (data not shown). 3MSE scores were not associated with retinal signs. In a separate analysis of retinopathy with DSST and 3MSE in people without diabetes, associations were largely similar (DSST adjusted mean of 39 versus 42 comparing persons with and without diabetes).
Table 3 shows the association of retinal signs with dementia in the whole cohort (n=159) and in persons with and without hypertension. In multivariable models, among persons with hypertension, retinopathy (OR, 2.10; 95% CI, 1.04 to 4.24) and focal arteriolar narrowing (OR, 3.02; 95% CI, 1.51 to 6.02) were associated with dementia. Further adjustment for cerebral MRI signs resulted in similar associations for both retinopathy (OR, 2.10; 95% CI, 0.89 to 4.95) and focal arteriolar narrowing (OR, 3.34; 95% CI, 1.48 to 7.54). These associations were not present in individuals without hypertension. A test for interaction did not demonstrate significant interactions between retinal signs and hypertension status.

In analyses stratified by diabetes status, in people without diabetes (n=1726), retinopathy (OR, 1.96; 95% CI, 0.96 to 4.02) and focal arteriolar narrowing (OR, 2.20; 95% CI, 1.17 to 4.13) were associated with dementia, but in persons with diabetes (n=289), neither retinal sign was associated with dementia (OR, 0.32; 95% CI, 0.07 to 1.44 for retinopathy and OR, 1.49; 95% CI, 0.27 to 8.40 for focal arteriolar narrowing). Other retinal signs were not associated with dementia in people with or without diabetes (data not shown).

Finally, we performed an analysis of subtypes of dementia. There were 99 cases of AD, 11 cases of VaD, and 49 cases of “mixed” AD and VaD. Focal arteriolar narrowing was associated with mixed dementia (multivariable adjusted OR, 3.57; 95% CI, 1.31 to 9.75) but not associated with AD (OR, 1.38; 95% CI, 0.64 to 2.97). There were insufficient cases of VaD for analysis.

**Discussion**

In this population-based, cross-sectional study of older persons, we demonstrated that individuals with retinopathy signs had lower mean DSST but not 3MSE scores and in persons with hypertension, retinopathy signs and focal arteriolar narrowing were associated with dementia. We found stronger associations of focal arteriolar narrowing with “mixed” AD and VaD than for “pure” AD. Our data are consistent with the hypothesis that in persons with hypertension, a larger proportion of dementia is related to microvascular disease than in persons without hypertension.

There are few relevant studies for comparison. In the ARIC study, retinal microvascular signs were assessed using identical retinal grading protocols, and cognitive function was assessed using the Delayed Word Recall Test, DSST, and Word Fluency Test. The ARIC study demonstrated a stronger and more consistent association between most retinal microvascular signs with these 3 cognitive function tests. The differences in results between the ARIC and CHS are likely complex. First, the ARIC study included only middle-aged persons aged 51 to 70 years, whereas the current CHS analysis included older persons aged 69 to 97 years. The frequency of cardiovascular risk factors differed between the 2 populations. In the ARIC study, the prevalence of hypertension and diabetes was 30% and 8%, respectively, whereas in the CHS, the prevalence was 60% and 14%, respectively. Thus, the frequency of cognitive impairment and dementia and their association with microvascular disease are likely to vary between the 2 cohorts. Second, individuals with retinal microvascular signs and cognitive impairment may have died before the retinal photography, which was performed...
6 years from baseline in the ARIC and 10 years from baseline in the CHS. Differential mortality and participation rates may have affected participant selection and thus the observed associations.

Despite these differences, comparison of the ARIC and CHS data provides important insights. The more consistent association of most retinal signs with cognitive impairment in the ARIC cohort is consistent with the hypothesis that cerebral microvascular disease may play a more prominent role in cognitive impairment in younger than older people and in the pathogenesis of dementia in persons with hypertension. However, direct comparison of the associations with DSST, which was assessed in both the ARIC and CHS, showed that the magnitude of the retinopathy association was in fact stronger in the CHS with a mean multivariable-adjusted difference in DSST scores between persons with and without retinopathy of only 1.0 in the ARIC study but 3.0 in the current CHS. However, this small difference is of uncertain clinical significance. Although limited by small numbers, we found stronger associations of focal arteriolar narrowing with “mixed” dementia than for “pure” AD (OR, 3.57 versus 1.38), which supports a microvascular etiology for “mixed” dementia. However, not all our data are consistent with this hypothesis, because other retinal signs were not related to cognitive tests or dementia. Additionally, no association in people with diabetes (in whom the risk dementia from microvascular disease is higher) and the fact that adjustment for MRI white matter lesions (which are manifestations of cerebral microvascular disease) did not attenuate the associations argues against microvascular disease underlying these observations.

Nonetheless, we note that the retinal signs most strongly related to lower cognitive scores and dementia in both studies (eg, microaneurysms and retinal hemorrhages) are indicators of more severe retinal microvascular disease and are usually seen when there is a breakdown of the blood retinal barrier. Additionally, these retinopathy signs have been previously reported to have the strongest associations with incident clinical stroke, MRI-defined cerebral infarcts, white matter lesions, and atrophy and cardiovascular mortality. In contrast, other retinal characteristics such as arteriovenous nicking and focal arteriolar narrowing, which may reflect less severe retinal pathological changes and are less strongly associated with stroke and subclinical cerebrovascular conditions, were not consistently related to cognitive impairment and dementia in either the ARIC study or CHS.

The limitations of this study should be mentioned. First, an important limitation is selection and survival bias. There were a large number of exclusions in this study (see the Figure), which may have influenced some findings. Participants excluded were more likely to be older and black and more likely to have cardiovascular risk factors such as hypertension, diabetes, coronary heart disease, or a cigarette smoking history. Because these factors are related to both dementia and retinopathy, the observed associations could be falsely attenuated. Alternatively, such selection bias may have enhanced other associations. Second, retinal signs in dementia could be related to poor medical care (eg, participants with retinal signs may have poorly controlled hypertension). However, in an analysis adjusting for health insurance status, associations were largely similar (eg, OR for any dementia, 2.21; 95% CI, 1.12 to 4.37 for focal narrowing, data not shown).

From a clinical perspective, this study, in conjunction with other studies, suggests that a retinal examination may provide additional information to assist clinicians and researchers to diagnose different types of cerebrovascular disorders, and possibly even to differentiate between VaD and AD in persons with hypertension. For example, it is possible that some people with dementia could benefit from the addition of retinal photography as part of their dementia workup to evaluate if they have retinal microvascular signs. However, much further research is needed to determine the exact role of retinal photography in clinical neurology.

Summary
In conclusion, our study shows a modest cross-sectional association between retinopathy signs with lower scores on DSST but not 3MSE and, in persons with hypertension, with dementia. The inconsistency of the associations seen in this study, in comparison with the stronger findings in the younger, middle-aged persons in the ARIC study, suggests that microvascular disease may not play as significant a role in the pathogenesis of cognitive changes and dementia in older people. It is also possible that shared risk factors (eg, hypertension) independently cause both microvascular disease and vascular dementia.

Sources of Funding
The research reported in this article was supported by contracts N01-HC-35129, N01-HC-45133, N01-HC-75150, N01-HC-85079 through N01-HC-85086, N01 HC-15103, N01 HC-55222, and U01 HL080295 from the National Heart, Lung, and Blood Institute with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of participating CHS investigators and institutions can be found at www.chs-nhlbi.org. Additional support was provided by NHBLI grant R21-HL077166 and the National Heart Foundation (TYW).

Disclosures
None.

References
Retinal Microvascular Signs, Cognitive Function, and Dementia in Older Persons. The Cardiovascular Health Study
Michelle L. Baker, Emily K. Marino Larsen, Lewis H. Kuller, Ronald Klein, Barbara E.K. Klein, David S. Siscovick, Charles Bernick, Teri A. Manolio and Tien Yin Wong

Stroke. published online May 24, 2007; Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2007/05/24/STROKEAHA.107.483586.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/