Retinal Microvascular Signs and Disability in the Cardiovascular Health Study

Objective: To study the associations of retinal microvascular changes, which are associated with systemic conditions and cognitive decline, with disability in performing activities of daily living (ADL).

Design: Prospective cohort study of 1487 community-dwelling participants in the Cardiovascular Health Study (mean age, 78 years) who were free of ADL disability and had available data on retinal signs and carotid intima-media thickness at the 1998-1999 visit. Main outcome measures were incident ADL disability, defined as self-reported difficulty in performing any ADL, by the presence of retinal signs and advanced carotid atherosclerosis, defined by carotid intima-media thickness in the 80th percentile or more or 25% or more stenosis, and potential mediation by cerebral microvascular disease on brain imaging or by executive dysfunction, slow gait, and depressive symptoms but not by cerebral microvascular disease on brain imaging.

Results: During the median follow-up of 3.1 years (maximum, 7.8 years), participants with 2 or more retinal signs had a higher rate of disability than those with fewer than 2 retinal signs (10.1% vs 7.1%; adjusted hazard ratio, 1.45; 95% confidence interval, 1.24-1.69; P < .001). There was no evidence of interaction by advanced carotid atherosclerosis (P > .10). The association seemed to be partially mediated by executive dysfunction, slow gait, and depressive symptoms but not by cerebral microvascular disease on brain imaging.

Conclusions: These results provide further support for the pathophysiologic and prognostic significance of microvascular disease in age-related disability. However, it remains to be determined how to best use retinal photography in clinical risk prediction.


Author Affiliations are listed at the end of this article.

VASCULAR DISEASE AND ITS risk factors are associated with functional impairment in older adults. Small-vessel lesions in the brain that manifest as white matter disease and lacunar infarcts are associated with executive dysfunction, gait disorder, and urinary incontinence. These lesions are viewed as the consequence of ischemic injury from vascular risk factors. Moreover, large-vessel lesions, which can be measured by carotid artery intima-media thickness (IMT), are associated with poor cognitive and physical function. It is evident that both microvascular and macrovascular disease play important roles in the development of functional impairment, but the importance of each process and their potential interaction are poorly understood.

Many studies have used brain magnetic resonance imaging (MRI) to measure cerebral microvascular disease, but substantial evidence suggests that pathological changes in retinal microvasculature may reflect similar changes in the brain and predict incident and progression of cerebral microvascular disease and subcortical atrophy on brain MRI. Retinal signs have been shown to predict cardiovascular events and cognitive decline. We have recently found that a higher burden of retinal signs was associated with poor executive function and physical function in a cross-sectional analysis.

Based on this evidence, we hypothesized that retinal signs might predict future disability in performing activities of daily living (ADL). Since ADL disability is closely associated with loss of independence, institutionalization, and mortality in older adults, ADL disability may reflect overall clinical consequences of microvascular disease.
crovascular and macrovascular disease. To this end, we examined whether retinal signs were associated with an increased risk of incident ADL disability and whether the risk was modified by the presence of advanced carotid atherosclerosis.

MEASUREMENT OF RETINAL MICROVASCULAR SIGNS

The details of retinal photography procedures were described previously. Briefly, a 45° retinal photograph, centered on the region of the optic disc and the macula, was taken of 1 randomly selected eye after 5 minutes of dark adaptation. Trained and certified graders who were masked to subject characteristics evaluated photographs using a standardized protocol.

For the measurement of retinal vascular calibers, photographs were digitized using a high-resolution scanner and the diameters of all arterioles and venules coursing through an area 1/2 to 1 disc diameter from the optic disc margin were measured and summarized in central retinal arteriolar equivalent and central retinal venular equivalent, respectively. These indices represent the average central arteriolar and venular caliber in that eye after taking into account the branching patterns. Retinopathy was considered present if any of the following findings (definite or probable) were noted: retinal microaneurysms, retinal hemorrhages, soft exudates, hard exudates, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, vitreous hemorrhage, disc swelling, and laser photocoagulation scars. Retinopathy was considered present if any of these signs were present among generalized arteriolar narrowing (defined as present if they were graded definite or probable in any of the 4 quadrants).

Additionally, the overall burden of retinal microvascular changes was estimated using the total number of retinal signs present among generalized arteriolar narrowing (defined as <=10th percentile [142.29 µm] of central retinal arteriolar equivalent), generalized venular widening (defined as >=90th percentile [213.04 µm] of central retinal venular equivalent), retinopathy, arteriovenous nicking, and focal arteriolar narrowing. We used an a priori definition of high burden as 2 or more retinal signs (vs low burden defined as <=2 signs), because this cutoff was associated with a lower Digit Symbol Substitution Test score (42.6, 41.8, and 39.8 points for 0, 1, and >=2 retinal signs, respectively; P < 0.01) and gait speed (0.93, 0.92, and 0.84 m/s; P = .047) in our recent work.

STATISTICAL ANALYSIS

All analyses were performed in Stata SE version 11.2 (StataCorp, College Station, Texas). Baseline characteristics were compared using the 2-sample t test, Wilcoxon rank sum test, and χ² test. The outcome was the time to the first occurrence of ADL disability. Participants were followed up until incident ADL disability or censored at the time of death or date of last known contact. Disability-free survival was compared by the burden of retinal signs, using the Kaplan-Meier product estimator and log-rank test. In the main analysis, race-stratified Cox proportional hazard models were used to compute the hazard ratio (HR) and 95% confidence interval (CI) associated with a high burden of retinal signs and with individual signs, after adjusting for sociodemographic characteristics, lifestyle, vascular risk factors, and instrumental ADL disability. The results did not change when instrumental ADL disability was not adjusted for. This stratified Cox model allows the underlying hazard function to vary by race, while adjusting for race effect. The proportionality assumption was satisfied. A potential correlation within CHS centers was accounted for by using a robust variance estimator. We examined the interactions with natural logarithm of carotid IMT for individual signs and high burden of retinal signs.
RESULTS

The prevalence of retinal signs was 7.1% (92 of 1294) for retinopathy, 7.5% (83 of 1135) for arteriovenous nicking, and 10.4% (111 of 1063) for focal arteriolar narrowing. Participants with 2 or more retinal signs, comprising 6.9% (61 of 880) of those with complete retinal data, were more likely to be current smokers and to have higher systolic blood pressure (Table 1).

During the median follow-up time of 3.1 years (range, 0.4-7.8 years), those with 2 or more retinal signs had a significantly lower disability-free survival than those with a low burden (Figure). After adjusting for potential confounders, the presence of 2 or more retinal signs was associated with a 1.45-fold increased rate of disability, whereas individual retinal signs were not significant for potential confounders, the presence of 2 or more retinal signs was associated with a 1.45-fold increased rate of disability (HR, 1.48; 95% CI, 1.31-1.68; P = .001) compared with having no retinal signs and 1.28 (1.10-1.49; P = .002) for advanced carotid atherosclerosis.

In the post hoc analyses, the presence of 2 or more retinal signs was associated with disability (HR, 1.48; 95% CI, 1.31-1.68; P < .001) compared with having no sign, while having 1 retinal sign was not (HR, 1.08; 95% CI, 0.87-1.33; P = .49). We did not find any particular combinations of retinal signs that conferred a greater risk than others (data not shown). When advanced carotid atherosclerosis was used, the adjusted HR (95% CI) was 1.41 (1.23-1.61; P < .001) for 2 or more retinal signs and 1.28 (1.10-1.49; P = .002) for advanced carotid atherosclerosis.

In the post hoc mediation analysis, the association between retinal signs and disability was attenuated and be-

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Table 1. Characteristics of Participants by the Number of Retinal Signs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0-1 Retinal Sign (n = 819)</th>
<th>≥2 Retinal Signs (n = 61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>77.5 (4.0)</td>
<td>78.1 (4.2)</td>
<td>.28</td>
</tr>
<tr>
<td>Male</td>
<td>39.4</td>
<td>32.8</td>
<td>.30</td>
</tr>
<tr>
<td>White</td>
<td>86.1</td>
<td>82.0</td>
<td>.38</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>43.8</td>
<td>42.6</td>
<td>.85</td>
</tr>
<tr>
<td>Current smoking</td>
<td>6.2</td>
<td>14.8</td>
<td>.01</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.8 (4.3)</td>
<td>27.4 (4.4)</td>
<td>.27</td>
</tr>
<tr>
<td>Cardiovascular diseasea</td>
<td>25.4</td>
<td>23.0</td>
<td>.67</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean (SD)</td>
<td>129.8 (18.3)</td>
<td>140.0 (19.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14.3</td>
<td>19.7</td>
<td>.25</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL, mean (SD)</td>
<td>203.5 (38.1)</td>
<td>207.3 (40.4)</td>
<td>.46</td>
</tr>
<tr>
<td>Fasting glucose level, mg/dL, mean (SD)</td>
<td>106.1 (29.9)</td>
<td>107.3 (32.8)</td>
<td>.18</td>
</tr>
<tr>
<td>Creatinine level, mg/dL, mean (SD)</td>
<td>1.0 (0.3)</td>
<td>1.0 (0.3)</td>
<td>.49</td>
</tr>
<tr>
<td>C-reactive protein level, mg/L, median (25th, 75th percentile)</td>
<td>2.2 (1.1, 5.1)</td>
<td>2.5 (1.0, 5.5)</td>
<td>.85</td>
</tr>
<tr>
<td>Internal carotid artery IMT, mm, median (25th, 75th percentile)</td>
<td>1.5 (1.0, 2.1)</td>
<td>1.5 (1.2, 2.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>54.5</td>
<td>52.5</td>
<td>.76</td>
</tr>
<tr>
<td>Lipid-lowering medication use</td>
<td>18.1</td>
<td>14.8</td>
<td>.51</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IMT, intima-media thickness.

SI conversion factors: To convert serum total cholesterol to millimoles per liter, multiply by 0.0259; fasting glucose to millimoles per liter, multiply by 0.0555; creatinine to micromoles per liter, multiply by 88.4; and C-reactive protein to nanomoles per liter, multiply by 9.524.

*a*Cardiovascular disease includes prevalent coronary heart disease, myocardial infarction, congestive heart failure, and stroke at the 1997-1998 visit.

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Figure. Kaplan-Meier curve of activities of daily living disability-free survival by the number of retinal signs.

In the post hoc analyses, we repeated the analysis using the number of retinal signs (0, 1, or ≥2); explored whether particular combinations of retinal signs conferred a higher risk than others; and used advanced carotid atherosclerosis, as defined earlier, instead of natural logarithm of internal carotid IMT. We also examined whether the association attenuated after further adjusting for Digit Symbol Substitution Test score, gait speed, and Center for Epidemiologic Studies Depression Scale score (after square root transformation) (n = 861). This examines the mediation by executive dysfunction, slow gait, and depressed symptoms that are characteristic of frontal subcortical dysfunction in the brain. A similar analysis was done for cerebral microvascular disease on brain MRI by including ventricular size, white matter grade, and infarcts in the main model (n = 651). Finally, we conducted stratified analyses by diabetes and clinical cardiovascular disease at study baseline.
came nonsignificant when Digit Symbol Substitution Test score, gait speed, and Center for Epidemiologic Studies Depression Scale score were adjusted (Table 3). When ventricular size, white matter grade, and infarcts were adjusted for, the adjusted HR (95% CI) for 2 or more retinal signs did not change: 1.25 (0.98-1.59) before and 1.24 (0.96-1.60) after adjustment. The association between retinal signs and disability was similar by the presence of diabetes or clinical cardiovascular disease at baseline (Table 4).

We found that a high burden of retinal signs, defined as having 2 or more retinal signs, was associated with incident ADL disability, independently of vascular risk factors and carotid atherosclerosis, and even among those without diabetes or clinical cardiovascular disease. This association was partially explained by executive dysfunction, slow gait, and depressive symptoms but not by prevalent cerebral microvascular disease on brain MRI. In addition, a high burden of retinal signs appeared to be as important as advanced carotid atherosclerosis in its association with disability. Our study supports the hypothesis that microvascular disease accelerates age-related disability and retinal signs can be useful in understanding mechanisms and predicting outcomes.

In previous research, retinal signs have been linked to major risk factors of disability, including hypertension, diabetes, metabolic syndrome, heart disease, and stroke.30 We recently reported the association of retinal signs with prevalent functional impairment.16 The current study adds to the current literature by showing that retinal signs can predict future ADL disability independently of major risk factors of disability at baseline. We speculate that retinal signs may be a marker of underlying microvascular disease leading to disability rather than...
a direct cause. The presence of microvascular disease in retinal vessels may indicate a similar process in other systemic microvasculature, such as the brain, heart, and kidney. Microvascular disease in these organs has been implicated in incident cardiovascular and cerebrovascular events, as well as cognitive and physical functional loss, all of which contribute to future disability. Although we could not empirically evaluate all these potential links, we found that executive dysfunction, slow gait, and depressive mood, which have been recognized as clinical correlates of hypertensive brain microangiopathy, might partially mediate the association between microvascular disease and disability.

In our study, the rate of disability seemed to rise rapidly when there were 2 or more signs. This refers to a potential threshold effect that clinical phenotypes may not manifest until certain extents of subclinical physiologic derangements accumulate. Such a nonlinear dose-response relationship has been observed in our cross-sectional analysis of retinal signs and functional impairments and others' work on frailty. We also investigated whether certain retinal signs could provide further insights into a particular pathophysiologic process by examining individual signs and their combinations. Although the effect estimates were of a similar magnitude in the same direction for individual signs or their common combinations, our attempt was limited by insufficient power, and therefore, the possibility of differential effects by individual retinal signs remains open. Nonetheless, we do not think that the lack of power for individual signs should underestimate our main findings that the overall burden of retinal signs predicts future disability, because it can be viewed as a composite measure of physiologic changes and cumulative damage in retinal microvasculature from various insults, as evidenced by the distinct association profiles between each sign and vascular risk factors.

In addition, there was no indication that the effect of retinal signs on disability differed by the presence of advanced carotid atherosclerosis. We have previously reported that high carotid IMT was associated with worse executive function when generalized arteriolar narrowing and arteriovenous nicking were present compared with when they were not. The lack of a significant interaction between retinal signs and carotid IMT on ADL disability may reflect the complex process leading to ADL disability that involves both cognitive and physical impairment. We also found that a high burden of retinal signs was more strongly associated with disability than advanced carotid atherosclerosis, although a direct comparison between the arbitrarily defined dichotomous variables is difficult. However, our definition of advanced carotid atherosclerosis has been associated with an increased short-term and long-term risk of cardiovascular events in previous CHS analyses. Our findings imply that microvascular disease seems to have an independent role on the development of functional impairment and disability that is at least as important as yet distinct from macrovascular disease.

Another worthwhile finding is that retinal signs predicted disability among those without diabetes or clinical cardiovascular disease. This finding is important because retinal signs might be a preclinical marker of microvascular disease and endothelial dysfunction that precedes the diagnosis of major risk factors of disability, such as hypertension, diabetes, cardiovascular events, lacunar infarcts, and cerebral atrophy. In multivariable analyses, adjusting for ventricular size, white matter disease, and infarcts on brain MRI did not change our estimates. The evidence from previous research and our results suggest that retinal signs may contain additional prognostic information on the risk of disability that is not readily captured by medical history, laboratory test results, and brain MRI abnormalities at the time of retinal photography.

The strengths of this study are the prospective follow-up (up to 7.8 years); standardized assessments; and consistent findings from several post hoc analyses under different assumptions. A limitation of this study is selection bias, because participants who did not have gradable retinal photographs were more likely than those who did to be older, female, and black and to have more vascular risk factors and diseases. If sicker individuals who did not have retinal photography were more likely to have retinal signs and to develop ADL disability during the follow-up, a selection bias could occur and underestimate...
the association between retinal signs and ADL disability. In CHS, retinal photography, carotid ultrasonography, and brain MRI were taken near the end of person follow-up assessment in 1997-1999. Thus, we used prevalent measures of executive function, gait speed, and depressive mood instead of incident measures. This is an important limitation in interpreting our mediation analysis. In addition, residual confounding cannot be excluded, despite our efforts to adjust for potential confounders that were selected based on biological plausibility. For instance, ankle-arm index, which may be associated with both retinal signs and ADL disability, was not measured at baseline for this analysis. In addition, decreased vision could explain some of the association between retinal signs and disability. Finally, low prevalence of individual retinal signs resulted in 95% CIs that were too wide to exclude a modest association. Despite limited power, we found a significant association of high burden of retinal signs with disability. A larger study with more events is needed to evaluate the effects of individual retinal signs, which will further strengthen our study.

These limitations notwithstanding, our study suggests that the presence of 2 or more retinal signs may be an early marker of microvascular disease that portends an elevated risk for future ADL disability in community-dwelling older adults independently of major risk factors for disability and microvascular disease on brain MRI. These findings lend further support for the role of microvascular disease in age-related functional loss and disability. Given the low prevalence of retinal signs, our results do not justify the use of retinal examination as a routine population-wide screening strategy for disability. However, when retinal examination performed for other indications reveals 2 or more retinal signs, a thorough review and optimization of lifestyle habits and risk factors may be reasonable. Future research should investigate how to best use the information from retinal photography in clinical risk prediction and whether slowing the progression of microvascular disease may prevent disability in high-risk older adults.

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**Author Affiliations:** Division of Gerontology, Beth Israel Deaconess Medical Center (Drs Kim and Lipsitz), Department of Epidemiology, Harvard School of Public Health (Dr Kim), Institute for Aging Research, Hebrew SeniorLife (Drs Kim, Newton, and Lipsitz), and Division of Nephrology, Tufts Medical Center (Dr Sarnak), Boston, Massachusetts; Departments of Medicine and Epidemiology, Johns Hopkins University, Baltimore, Maryland (Dr Chaves); Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania (Drs Newman and Strotmeyer); Department of Ophthalmology, University of Wisconsin School of Medicine and Public Health, Madison (Dr Klein); and Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina (Dr Burke).

**Correspondence:** Dae Hyun Kim, MD, MPH, Department of Medicine/Gerontology, Beth Israel Deaconess Medical Center, 110 Francis St, Ste 1A, Boston, MA 02215 (dkim2@bidmc.harvard.edu).

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**REFERENCES**
