

ONLINE FIRST

Retinal Microvascular Signs and Disability in the Cardiovascular Health Study

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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 mood, which are symptoms of frontal subcortical dysfunction.

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.

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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.^{1,2} These lesions are viewed as the consequence of ischemic injury from vascular risk factors.^{3,4} Moreover, large-vessel lesions, which can be measured by carotid artery intima-media thickness (IMT), are associated with poor cognitive and physical function.^{5,6} 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 patho-

logical changes in retinal microvasculature may reflect similar changes in the brain⁷⁻⁹ and predict incident and progression of cerebral microvascular disease and subcortical atrophy on brain MRI.⁹⁻¹² Retinal signs have been shown to predict cardiovascular events^{13,14} and cognitive decline.¹⁵ 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.¹⁶



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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 mi-

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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.

METHODS

STUDY POPULATION

The Cardiovascular Health Study (CHS) is a population-based cohort study of cardiovascular disease in community-dwelling older adults.¹⁷ In CHS, 5201 adults who were 65 years and older were originally recruited in 1989 and 1990 and an additional 687 eligible African American individuals were recruited in 1992 and 1993.¹⁸ There were 1998 participants who had available data obtained from retinal photography (any of retinal arteriolar and venular caliber, retinopathy, arteriovenous nicking, and focal arteriolar narrowing) during the 1997-1998 visit and from carotid ultrasonography during the 1998-1999 visit. Among those, 1609 who were free of ADL disability at the time of the 1998-1999 visit were eligible for this study. There were 122 with missing information on potential confounders, leaving a total of 1487 for our analysis. Because not all participants had complete data on retinal signs, the sample size varied for the analyses of individual retinal signs.

MEASUREMENT OF RETINAL MICROVASCULAR SIGNS

The details of retinal photography procedures were described previously.^{19,20} 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.^{19,21} 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. Retinal arteriovenous nicking and focal arteriolar narrowing were 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 μ m] of central retinal arteriolar equivalent), generalized venular widening (defined as \geq 90th percentile [213.04 μ m] 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 \geq 2 retinal signs, respectively; $P < .001$) and gait speed (0.93, 0.92, and 0.84 m/s; $P = .047$) in our recent work.¹⁶

MEASUREMENT OF DISABILITY

Participants were followed up annually in the clinic or at home and semiannually by telephone calls through the 1998-1999 visit. Afterwards, telephone follow-ups were continued every 6 months. This study used ADL disability data collected until June 30, 2005. A modified version of the Health Interview Survey Supplement on Aging Questionnaire²² was used to assess disability by asking "Do you have difficulty or are you unable to . . . ?" in the following 6 ADL: bathing, dressing, eating, toileting, walking around the home, and getting out of bed or a chair. In addition, the following instrumental ADL were assessed: walking up 10 steps, doing housework, shopping, preparing meals, paying bills, and using a telephone. Self-reported difficulty or inability to perform any activity without assistance was considered as disability.

ASSESSMENT OF VASCULAR RISK FACTORS AND OTHER COVARIATES

All the measurements performed during the 1997-1998 visit were used, except carotid ultrasonography (1998-1999 visit), anthropometric measurements and blood chemistry results (1996-1997 visit), and brain MRI (1997-1999 visit). The following risk factors were considered: sociodemographic factors, alcohol consumption, cigarette smoking, medical history, medications, body mass index, blood pressure, serum total cholesterol level (milligrams per deciliter), fasting glucose level (milligrams per deciliter; multiply by 0.0555 to convert to millimoles per liter), creatinine level (milligrams per deciliter), and C-reactive protein level (milligrams per liter).¹⁷ Diabetes mellitus was defined as treatment with either oral hypoglycemic agents or insulin in the year before the examination or a fasting glucose level of 126 mg/dL or more in the past year.²³ Advanced carotid atherosclerosis was defined as common carotid artery IMT in the 80th percentile or more (1.23 mm) or internal carotid artery IMT in the 80th percentile or more (2.29 mm) or carotid stenosis of 25% or more.^{24,25} Prevalent cardiovascular disease included ascertained coronary heart disease, myocardial infarction, congestive heart failure, or stroke.²⁶ Functional measures included Digit Symbol Substitution Test scores for executive function, gait speed (meters per second) from a 15-ft walk, and the modified Center for Epidemiologic Studies Depression Scale.²⁷ Ventricular size, white matter lesions, and infarcts were measured from brain MRI.²⁸

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 χ^2 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.²⁹ We examined the interactions with natural logarithm of carotid IMT for individual signs and high burden of retinal signs.

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

Characteristic	%		P Value
	<2 Retinal Signs (n = 819)	≥2 Retinal Signs (n = 61)	
Age, y, mean (SD)	77.5 (4.0)	78.1 (4.2)	.28
Male	39.4	32.8	.30
White	86.1	82.0	.38
Alcohol consumption	43.8	42.6	.85
Current smoking	6.2	14.8	.01
BMI, mean (SD)	26.8 (4.3)	27.4 (4.4)	.27
Cardiovascular disease ^a	25.4	23.0	.67
Systolic blood pressure, mm Hg, mean (SD)	129.8 (18.3)	140.0 (19.7)	<.001
Diabetes mellitus	14.3	19.7	.25
Total cholesterol level, mg/dL, mean (SD)	203.5 (38.1)	207.3 (40.4)	.46
Fasting glucose level, mg/dL, mean (SD)	101.6 (29.9)	107.3 (32.8)	.18
Creatinine level, mg/dL, mean (SD)	1.0 (0.3)	1.0 (0.3)	.49
C-reactive protein level, mg/L, median (25th, 75th percentile)	2.2 (1.1, 5.1)	2.5 (1.0, 5.5)	.85
Internal carotid artery IMT, mm, median (25th, 75th percentile)	1.5 (1.0, 2.1)	1.5 (1.2, 2.5)	.06
Antihypertensive medication use	54.5	52.5	.76
Lipid-lowering medication use	18.1	14.8	.51

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.

^aCardiovascular disease includes prevalent coronary heart disease, myocardial infarction, congestive heart failure, and stroke at the 1997-1998 visit.

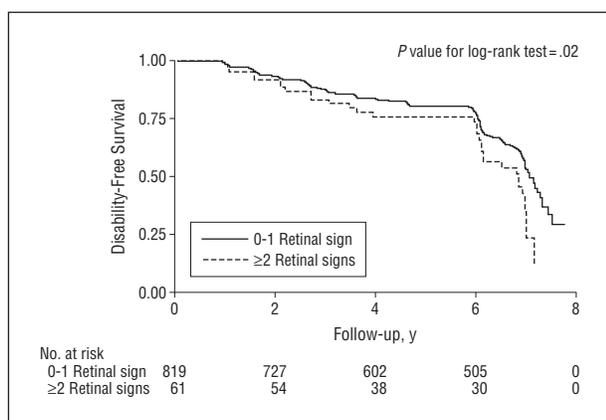


Figure. Kaplan-Meier curve of activities of daily living disability-free survival by the number of retinal signs.

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.^{2,16} 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.

RESULTS

The prevalence of retinal signs was 7.1% (92 of 1294) for retinopathy, 7.5% (85 of 1135) for arteriovenous nick-

ing, 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 (**Table 2**). However, retinal arteriolar caliber (when analyzed as a continuous variable) appeared to be inversely associated with disability (HR, 0.95 per 1-SD increase in central retinal arteriolar equivalent [19.5 μm]; 95% CI, 0.91-1.00; P=.06), whereas retinal venular caliber was not (HR, 1.08 per 1-SD increase in central retinal venular equivalent [17.8 μm]; 95% CI, 0.97-1.22; P=.17). When we examined the interaction with natural logarithm of carotid IMT, none of them were significant for individual retinal signs or 2 or more retinal signs (P>.10 for all; data not shown).

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-

Table 2. Retinal Microvascular Signs and the Rate of Incident Activities of Daily Living Disability

Retinal Sign	Incidence Rate ^a		HR (95% CI) ^b	P Value
	Present	Absence		
Individual retinal sign				
Generalized arteriolar narrowing	53/670 (7.9)	434/5925 (7.3)	1.22 (0.99-1.50)	.07
Generalized venular widening	50/647 (7.7)	437/5948 (7.3)	1.24 (0.96-1.60)	.10
Retinopathy	42/432 (9.7)	446/6208 (7.2)	1.22 (0.82-1.80)	.32
Arteriovenous nicking	31/408 (7.6)	401/5437 (7.4)	1.10 (0.61-1.97)	.75
Focal arteriolar narrowing	47/535 (8.8)	356/4952 (7.2)	1.22 (0.85-1.76)	.28
Total number of retinal signs				
≥2 Retinal signs (vs <2)	30/298 (10.1)	310/4380 (7.1)	1.45 (1.24-1.69)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aIncidence rate is presented as the number of disabilities per total person-years (the number of disabilities per 100 person-years).

^bAdjusted for age, sex, white race, current smoking, body mass index, prevalent cardiovascular disease, systolic blood pressure, diabetes mellitus status, total cholesterol level, natural logarithm of C-reactive protein level, natural logarithm of internal carotid artery intima-media thickness, antihypertensive medication use, lipid-lowering medication use, and self-reported disability in performing instrumental activities of daily living at baseline.

Table 3. Potential Mediation of the Relation Between Retinal Signs and Incident Activities of Daily Living Disability by Executive Function, Gait Speed, and Depressive Symptoms

Model	Adjusted HR (95% CI) ^{a,b}			
	≥2 Retinal Signs (vs <2 Retinal Signs)	DSST Score (per 1-SD Change)	Gait Speed, m/s (per 1-SD Change)	√CES-D Score (per 1-SD Change)
Main model	1.43 (1.13-1.81)
P value	.003			
Further adjusted for				
DSST score	1.34 (1.02-1.76)	0.80 (0.67-0.94)
P value	.04	.009		
Gait speed	1.32 (1.03-1.68)	...	0.77 (0.64-0.92)	...
P value	.03		.005	
√CES-D score	1.36 (1.16-1.59)	1.26 (1.08-1.47)
P value	.001			.004
All 3 measures	1.21 (0.99-1.46)	0.83 (0.70-0.99)	0.81 (0.67-0.99)	1.23 (1.04-1.46)
P value	.06	.04	.04	.02

Abbreviations: CES-D, Center for the Epidemiologic Studies Depression Scale; CI, confidence interval; DSST, Digit Symbol Substitution Test; ellipses, not applicable; HR, hazard ratio.

^aCoefficients for 3 continuous functional measures were standardized. Standard deviation was 13 points for DSST score, 0.22 m/s for gait speed, and 1.09 for √CES-D score.

^bAdjusted for age, sex, white race, current smoking, body mass index, prevalent cardiovascular disease, systolic blood pressure, diabetes mellitus status, total cholesterol level, natural logarithm of C-reactive protein level, natural logarithm of internal carotid artery intima-media thickness, antihypertensive medication use, lipid-lowering medication use, and self-reported disability in performing instrumental activities of daily living at 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 (0.97-1.60) after adjustment. The association between retinal signs and disability was similar by the presence of diabetes or clinical cardiovascular disease at baseline (**Table 4**).

COMMENT

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

Table 4. Stratified Analysis of Retinal Microvascular Signs and the Rate of Incident Activities of Daily Living Disability

Disease Status at Baseline	Incidence Rate by No. of Retinal Signs ^a		HR (95% CI) ^b	P Value
	≥2 Retinal Signs	<2 Retinal Signs		
By diabetes mellitus status				
Absent	24/241 (9.9)	263/3812 (6.9)	1.33 (1.06-1.68)	.02
Present	6/57 (10.6)	47/568 (8.3)	1.54 (0.65-3.68)	.33
By cardiovascular disease status				
Absent	23/231 (10.0)	229/3340 (6.9)	1.35 (1.00-1.82)	.051
Present	7/67 (10.4)	81/1040 (7.8)	1.25 (0.62-2.50)	.53

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aIncidence rate is presented as the number of disabilities per total person-years (the number of disabilities per 100 person-years).

^bAdjusted for age, sex, white race, current smoking, body mass index, systolic blood pressure, total cholesterol level, natural logarithm of C-reactive protein level, natural logarithm of internal carotid artery intima-media thickness, antihypertensive medication use, lipid-lowering medication use, and self-reported disability in performing instrumental activities of daily living at baseline, plus prevalent cardiovascular disease (for diabetes analysis) and diabetes status (for cardiovascular disease analysis).

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.^{7,8,31,32} Microvascular disease in these organs has been implicated in incident cardiovascular and cerebrovascular events,^{13,14} as well as cognitive and physical functional loss,³³⁻³⁶ 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,^{1,2} 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 impairments¹⁶ and others' work on frailty.³⁷ 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.^{16,30,38}

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.¹⁶ 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.^{39,40} 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.^{41,42} 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,⁴³ diabetes,⁴⁴ cardiovascular events,^{13,14} lacunar infarcts,¹¹ and cerebral atrophy.¹² 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.²⁰ 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 in-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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