Original Contribution

Psychosocial Risk Factors and Retinal Microvascular Signs

The Multi-Ethnic Study of Atherosclerosis

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The association between psychosocial risk factors and retinal microvascular signs was examined in the Multi-Ethnic Study of Atherosclerosis. Subjects were recruited from Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Levels of depressive symptoms, trait anger, trait anxiety, chronic burdens, emotional support, and cynical distrust were assessed by questionnaire (from July 2000 to July 2002). Digital retinal images (from August 2002 to January 2004) from 6,147 participants were used to evaluate retinopathy and retinal vascular caliber. After controlling for potential confounding factors, the authors found that subjects without access to emotional support (Enriched Social Support Instrument score of <19 vs. ≥19) had 60% greater odds of retinopathy (odds ratio = 1.6, 95% confidence interval (CI): 1.3, 2.0). Subjects with high Spielberger trait-anxiety scale scores (≥22 vs. ≤14) and subjects with high depressive symptoms (Center for Epidemiology Studies Depression Scale score, ≥16 vs. <16) were also more likely to have retinopathy (odds ratio = 1.4, 95% CI: 1.1, 1.9 and odds ratio = 1.5, 95% CI: 1.2, 1.9), respectively. In this cross-sectional study, lack of emotional support, increased trait anxiety, and more depressive symptoms were associated with retinopathy signs, independently of other known risk factors.

anger; anxiety; depression; microvessels; psychology, social; retina; social support

Abbreviations: CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; hsCRP, high-sensitivity C-reactive protein; MESA, Multi-Ethnic Study of Atherosclerosis.

Psychosocial factors, including depressive symptoms, trait anger, trait anxiety, chronic burdens, lack of emotional support, and cynical distrust, have acute as well as chronic effects that may influence cardiovascular disease risk (1–14). Although these psychosocial factors have been associated with clinical cardiovascular disease risk, few studies have examined the associations of psychosocial factors with markers of microvascular disease, such as retinopathy and retinal vascular diameters.

Several hypotheses have been proposed to explain the relation between psychosocial risk factors and clinical cardiovascular disease risk (15). Psychosocial factors may influence the hypothalamic-pituitary-adrenal axis and sympathetic nervous system resulting in acute vascular, hemostatic, and metabolic effects. Alternatively, chronic stress may lead to cardiovascular disease risk by accelerating the atherosclerotic process or increasing adverse health behaviors that in turn increase cardiovascular disease risk. It is likely that stress from psychosocial factors manifests itself through multiple pathways and that the same mechanisms that may lead to cardiovascular disease may also affect the retinal microvasculature. For example, arterial endothelial dysfunction (16, 17) and the disturbances in blood-clotting mechanisms (18, 19) observed with depression may also lead to endothelial dysfunction and increased risk of small thrombotic events in the retina.

Microvascular changes in the retina, including retinopathy and decreased retinal arteriolar and increased retinal venular diameter, are associated with both subclinical and clinical cardiovascular disease. Retinopathy has been shown

to be a predictor of congestive heart failure (20), stroke (21, 22), mortality (23), and coronary artery calcification (24), independently of other common cardiovascular risk factors. Studies suggest that differences in retinal vascular caliber are associated with current (25–29) or past (29, 30) blood pressure, incident hypertension (31–33), carotid atherosclerosis (25, 34), incident coronary heart disease (35), incident stroke (21, 22, 36), cardiovascular mortality (23), magnetic resonance image-detected cerebral lacunar infarcts, and white-matter lesions (37). However, much of the variability in retinal vascular caliber remains to be explained. Generally, retinal arteriolar narrowing is strongly associated with hypertension including past levels of blood pressure. Wider retinal venules are associated with inflammatory markers, diabetes, obesity, and subclinical and clinical stroke.

We hypothesize that stress from psychosocial factors is associated with directly observable retinal microvascular signs, such as retinopathy and decreased retinal arteriole and increased retinal venular caliber.

MATERIALS AND METHODS

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective study of adults aged 45–84 years with no history of clinical cardiovascular disease at baseline (38). Each site recruited equal numbers of men and women and site-specific racial and ethnic proportions. Participants defined themselves as European, African, Hispanic, or Chinese Americans. The baseline examination (from July 2000 to July 2002) included 6,814 participants: 1,086 from Baltimore, Maryland; 1,164 from Chicago, Illinois; 1,077 from Forsyth County, North Carolina; 1,319 from Los Angeles County, California; 1,102 from New York, New York; and 1,066 from St. Paul, Minnesota. Institutional review board approval was granted at each study site, and a written informed consent was obtained from each subject.

Retinal photography and retinal microvascular signs

Fundus photography was performed at examination 2 (from August 2002 to January 2004) by using a standardized protocol (39, 40). Both eyes were photographed by using a nonmydriatic digital fundus camera while patients were seated in a darkened room. Two photographic fields (45°) were taken of each eye. Digital images were evaluated at the University of Wisconsin Ocular Epidemiology Reading Center (Madison, Wisconsin) by graders masked to participant characteristics. Of the 6,237 participants who attended the second examination, 6,147 had retinal photography gradable for signs of retinopathy, and 5,979 were suitable for measurement of retinal vascular caliber.

Retinopathy was considered to be present if any of the following lesions were detected from either field 1 (centered on the optic disc) or field 2 (centered on the fovea) of either eye: microaneurysms, retinal or vitreous hemorrhages, soft or hard exudates, or intraretinal microvascular abnormalities. Retinopathy was graded by using a standardized protocol (41).

Retinal vessel caliber is summarized as the average central retinal arteriolar equivalent (CRAE) and the average central retinal venular equivalent (CRVE) by using formulas developed by Hubbard et al. (42) and modified by Knudtson et al. (43). Retinal vessel size was determined using field 1 images of the right eye unless retinal vascular caliber could not be measured, in which case the left eye was used. All arterioles and venules coursing through an area 0.5–1 disc diameter from the optic disc margin were measured by using a computer-based program (42, 44) (IVAN; University of Wisconsin, Madison, Wisconsin). Previous studies have shown that correlations of measurements between the right and left eyes are high (44). Reproducibility of retinal measurements has been reported, with intra- and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99 (42).

Psychosocial risk factors

Psychosocial risk factors were assessed by using standardized questionnaires written in English, Spanish, or Chinese. All questionnaires were administered at the baseline examination with the exception of cynical distrust, which was given during examination 2.

Depressive symptoms were assessed by using the Center for Epidemiology Studies Depression (CES-D) Scale (45). The scale includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning (46). The response values relate severity in terms of days per week with a score of 0 for "rarely or none of the time (less than 1 day)" to a score of 3 for "most of the time (5–7 days)." The score was dichotomized at ≥ 16, which represents the screening cutoff for depression (47) and corresponds to someone that has reported at least 6 items to be frequently present over the course of the previous week or most of the 20 items to be present for a shorter duration (46).

Spielberger trait anxiety and trait anger were measured by using 10 anxiety-present and anger-present items, respectively. Each item was given a direct score of 1–4 on the basis of 1 ("almost never"), 2 ("sometimes"), 3 ("often"), and 4 ("almost always"). Trait anxiety implies differences between people in their disposition to respond to stressful situations with varying amounts of state anxiety. Trait anger was designed to assess an individual's disposition to feeling angry over time (12, 48). Trait scales were chosen over state scales to better capture the relations that occur over longer periods of time. The Spielberger trait-anger and trait-anxiety scale scores were classified as low (from 10 to 14), moderate (from 15 to 21), and high (from 22 to 40) on the basis of previously published work using these scales (12, 13).

Ongoing difficulties from 5 domains described as very stressful events affecting the lives of subjects for more than 6 months were considered chronic burdens. These included health of self, health of someone close to them, difficulties with a job or ability to work, and financial strains or difficulties in a relationship with someone close to them. The Chronic Burden Scale score was categorized into 3 groups based on scores of 0, 1, or 2 or more ongoing difficulties in any of the 5 domains (47).

Cynical distrust was based on an 8-item subset of the full Cook-Medley Hostility Scale (49). These questions reflect

the subject's negative view of humankind, depicting others as unworthy, deceitful, and selfish (50). Binary responses were scored a "1" each time a subject agreed with the cynical statement. Scores ranged from 0 to 8 and were categorized by quartiles. In order to reduce the participant burden, this questionnaire was administered during examination 2. Thus, there were 600 subjects who were not included and another 47 who were missing 1 or more responses leaving 6,167 available for analysis.

Criteria for low social support are based on the Enhancing Recovery in Coronary Heart Disease Patients Study Social Support Instrument (51). Response categories were modified to follow a consistent format based on the Medical Outcomes Study ranging from 1 ("none of the time") to 5 ("all of the time"). There were 6 items regarding the availability of someone to listen to you, to give advice to you, to show you love and affection, to help with daily chores, to provide emotional support, and to confide in. Scores were dichotomized at ≤18 indicating a highest risk category for lack of social support (51).

Baseline measures

Participants underwent an interview and assessment of cardiovascular risk factors during the course of the study (38, 52). Variables for this analysis were based on data collected at the baseline examination. Demographic variables included age, sex, race/ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, and Chinese), educational level (less than high school, high school/technical school/associates degree, college or more), income (<20,000, 20,000–49,000, ≥50,000 dollars), current occupation (employed, unemployed, retired), and marital status (married, widowed/divorced/separated, never married). Anthropometric measures included height and weight measured with participants wearing light clothing and no shoes, as well as body mass index calculated as weight (kg)/height (m)^2.

Behavior assessment included alcohol use (current, past/never), smoking status (never, former, and current), and physical activity (total metabolic equivalent (MET) minutes/week). Physical activity was measured by using a detailed, semiquantitative questionnaire adapted from the Cross-Cultural Activity Participation Study (38).

Measures of resting blood pressure have been previously described (52). The average of the last 2 measurements was used in analysis. Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or current use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose of ≥7.0 mmol/L (126 mg/dL) or a history of use of insulin or oral hypoglycemic medication. Duration of diabetes was defined as the self-reported number of years since first use of medication to treat diabetes. Undiagnosed diabetes or no diabetes was classified as having no duration. Questions about medication use included use of antipsychotic medications, benzodiazepines, monoamine oxidase inhibitors, peripheral vasodilators (except dipyridamole), tricyclic antidepressants (with or without antipsychotics), and vasodilators (mixed group with or without diuretics).

Serum measures used in this study included plasma total and high density lipoprotein cholesterol, serum glucose, and high-sensitivity C-reactive protein (hsCRP). Fasting (>8 hours) blood samples were drawn from participants, and aliquots were prepared for central analysis and storage at the University of Vermont and the University of Minnesota (38). Standardized protocols, described elsewhere (52), were used for assaying these measures.

Statistical analyses

The percentages of subjects with high levels of psychosocial characteristics across categories of various sociodemographic, behavioral, and health traits are determined and compared by using a χ^2 statistic. Many but not all relations among these sociodemographic, behavioral, and health traits with CRAE/CRVE or retinopathy have been previously studied in this cohort (53), except for education, income, occupation, intentional exercise, marital status, and use of vasodilators or antipsychotic medications. If any of these measures was independently associated with our outcomes after adjustment for known risk factors and associated with our exposures, it was included in the multiple regression analyses described below. Previously established risk factors for CRAE and CRVE include fasting serum glucose, systolic blood pressure, low density lipoprotein cholesterol and high density lipoprotein cholesterol, smoking status, body mass index, and hsCRP (53). Risk factors for retinopathy differ from those listed above for CRAE and CRVE. Risk factors for retinopathy include the presence and duration of diabetes, fasting serum glucose, hypertension status, systolic blood pressure, and low density lipoprotein cholesterol and high density lipoprotein cholesterol (54, 55).

Multiple regression analyses were used to examine our primary aim. In model 1, we evaluated the association of each psychosocial risk factor with each specific retinal microvascular sign, adjusted for age, sex, race/ethnicity, and study site as potential confounders. In model 2, we adjusted for the confounders in model 1, known risk factors for CRAE/CRVE or for retinopathy, and any additional sociodemographic, behavioral, or health measures identified in our preliminary analyses described above. The adjustments included in model 2 vary for retinal vessel caliber and the presence of retinopathy due to their varying risk factors. In multiple regression analyses, an F statistic or χ^2 statistic with a nominal $P < 0.05$ was considered significant. For the associations not judged statistically significant, categorical exposures were treated as continuous, and a test for linear trend was also performed. Additional testing included analyses of model 2 stratified by diabetes status and hypertension status. Analyses were performed by using STATA, release 8, statistical software (StataCorp LP, College Station, Texas).

RESULTS

Table 1 contains baseline characteristics of the MESA cohort showing the associations between selected sociodemographic and behavioral measures and the most severe categories of psychosocial stress. In general, women were

Table 1. Percentage of High Levels of Psychosocial Characteristics by Selected Demographic and Behavioral Measures, the Multi-Ethnic Study of Atherosclerosis Cohort, 2000–2004[a]

	No.	High Trait-Anger[b]		High Trait-Anxiety[c]		Symptoms of Depression[d]		No Emotional Support[e]		High Cynical Distrust[f]		≥2 Chronic Burdens[g]	
		%	P Value	%	P Value	%	P Value	%	P Value	%	P Value	%	P Value
Gender													
Female	3,601	4.9		14.4	<0.001	16.8	<0.001	13.4	<0.05	20.8	<0.001	34.9	<0.001
Male	3,213	4.4		9.1		8.5		11.7		26.0		25.1	
Race													
White	2,622	4.0	<0.001	13.1	<0.001	10.6	<0.001	13.3	<0.01	10.7	<0.001	31.3	<0.001
Chinese	803	4.9		13.6		8.2		11.0		28.8		17.6	
African American	1,893	3.0		8.6		11.8		10.9		25.8		34.5	
Hispanic	1,496	4.6		13.1		20.9		14.5		40.1		30.1	
Age, years													
45–54	1,947	6.5	<0.001	13.9	<0.001	15.6	<0.001	14.5	<0.05	22.0		39.1	<0.001
55–64	1,885	5.1		11.8		11.9		12.7		22.0		32.1	
65–74	2,017	3.8		11.0		11.7		11.3		24.4		24.2	
75–84	965	1.6		10.1		11.9		11.4		26.4		21.3	
Education													
< High school degree	1,225	6.5	<0.001	15.0	<0.001	20.4	<0.001	13.5		49.1	<0.001	26.3	<0.01
High school to associates degree	3,173	4.1		12.3		13.0		12.7		22.6		31.2	
College graduate	2,393	4.4		9.9		8.9		12.0		12.5		31.1	
Income, dollars													
<20,000	1,560	4.7	<0.001	16.6	<0.001	21.0	<0.001	17.7	<0.001	37.7	<0.001	32.1	
20,000–49,000	2,392	5.0		13.2		13.8		14.5		25.7		31.6	
≥50,000	2,589	4.3		7.9		7.5		8.1		12.8		28.8	
Smoking													
Never	3,418	4.0	<0.001	12.6	<0.01	13.3	<0.001	11.8	<0.001	24.5	<0.001	29.4	<0.001
Former	2,487	4.7		10.3		10.9		11.9		19.9		29.3	
Current	887	7.0		14.0		17.0		17.6		28.6		36.6	
Body mass index, kg/m²													
<18.5	1,952	4.3		12.4	<0.05	11.4	<0.001	12.2		21.0	<0.05	25.2	<0.001
18.5–24.99	2,666	4.3		11.3		12.3		12.7		23.0		28.4	
25–29.99	2,945	5.1		11.8		14.3		12.6		25.6		35.2	
≥30	251	7.2		15.3		19.7		15.3		26.4		51.7	
Intentional exercise, MET minutes/week													
<106	1,718	6.9	<0.001	14.6	<0.001	16.6	<0.001	15.2	<0.01	30.5	<0.001	33.0	<0.05
106–825	1,688	4.6		12.8		13.2		12.5		23.1		31.1	
826–2,025	1,691	3.4		10.3		10.0		10.5		20.5		27.8	
≥2,026	1,698	3.7		9.9		11.7		12.2		19.5		29.1	

Abbreviation: CES-D, Center for Epidemiologic Studies Depression; MET, metabolic equivalent.

[a] P values are for the χ^2 statistic of the association between each baseline characteristic and grouped exposure.

[b] High Spielberger trait-anger, ≥22; moderate, 15–21; low, <15.

[c] High Spielberger trait-anxiety, ≥22; moderate, 15–21; low, <15.

[d] Depressive symptoms, CES-D score ≥16; no depressive symptoms, CES-D score <16.

[e] Lack of emotional support, ENRICHD (Enhanced Recovery in Coronary Heart Disease) Social Support Instrument score ≤18; access to emotional support, >18.

[f] High cynical distrust 8-item subset of the full Cook-Medley Hostility Scale, ≥5; moderate, 3 or 4; low, 1 or 2; none, 0.

[g] High burdens, ≥2 ongoing difficulties in the Chronic Burden Scale; moderate, 1; low, 0.

Table 2.   Associations of Demographic and Behavioral Risk Factors with CRAE, CRVE, and Retinopathy, the Multi-Ethnic Study of Atherosclerosis Cohort, 2000–2004

	No.	CRAE[a]		CRVE[a]		Retinopathy[b]	
		Mean (SE)	P Value	Mean (SE)	P Value	Odds Ratio	95% Confidence Interval
Education							
<High school degree	1,225	144.8 (0.53)	<0.001	218.6 (0.80)	<0.001	1.0	
High school to associates degree	3,173	144.9 (0.29)		215.8 (0.44)		1.0	0.80, 1.33
College graduate	2,393	142.1 (0.31)		210.1 (0.47)		0.9	0.65, 1.16
Income, dollars							
<20,000	1,560	144.4 (0.47)	<0.05	217.1 (0.71)	<0.05	1.0	
20,000–49,000	2,392	143.9 (0.33)		214.7 (0.50)		0.9	0.70, 1.13
≥50,000	2,589	143.4 (0.3)		211.5 (0.45)		1.0	0.75, 1.28
Intentional exercise, MET minutes/week							
<106	1,718	144.5 (0.42)		217.8 (0.63)	<0.01	1.0	
106–825	1,688	143.7 (0.4)		213.6 (0.60)		1.1	0.89, 1.45
826–2,025	1,691	143.6 (0.39)		213.4 (0.59)		0.9	0.74, 1.22
≥2,026	1,698	143.4 (0.38)		211.7 (0.57)		1.0	0.79, 1.30
Use of vasodilators							
No	6,493	144 (0.2)	<0.05	214.1 (0.31)		1.0	
Yes	318	139.5 (0.89)		211.5 (1.35)		0.8	0.56, 1.28

Abbreviations: CRAE, central retinal arteriole equivalent; CRVE, central retinal venule equivalent; MET, metabolic equivalent; SE, standard error of the mean.

[a] Adjusted for age, race, sex, study site, systolic blood pressure, serum glucose, smoking status, alcohol use, body mass index, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and high-sensitivity C-reactive protein.

[b] Adjusted for the presence and duration of diabetes, fasting serum glucose, hypertension status, systolic blood pressure, low density lipoprotein cholesterol, and high density lipoprotein cholesterol.

more likely than men to have high levels of psychosocial stress. Negative gradients were seen with level of education, income, age, and physical activity, while positive gradients were seen with body mass index. Current smokers had high levels of stress compared with past and never smokers. We also examined correlations across psychosocial measures (results not shown). Correlations were moderately high ($r = 0.36–0.64$) across 3 of the measures—anxiety, depression, and lack of emotional support. Chronic burden was moderately associated with depression ($r = 0.38$) but not with any of the other measures. Anger showed its strongest association with anxiety ($r = 0.41$). Cynical distrust showed only small correlations with the other measures.

Table 2 identifies potential new demographic and behavioral risk factors for CRAE and CRVE after adjustment for the previously identified risk factors including age, gender, race/ethnicity, systolic blood pressure, cigarette use, fasting serum glucose, current alcohol consumption, body mass index, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and hsCRP. More education and higher income were independently associated with smaller CRAE and smaller CRVE. In addition, use of vasodilators was independently associated with smaller CRAE, and more intentional exercise was independently associated with smaller CRVE. Current occupation, marital status, and the

use of antipsychotic medications were not associated with either CRAE or CRVE and were not included in further analyses. None of these demographic or behavioral measures was associated with the presence of retinopathy after adjustment for traditional risk factors including the presence and duration of diabetes, fasting serum glucose, hypertension status, systolic blood pressure, and low density lipoprotein cholesterol and high density lipoprotein cholesterol.

After adjustment for race/ethnicity, sex, age, and study site (model 1), higher levels of trait anxiety, lack of emotional support, more chronic burdens, and the presence of symptoms of depression were associated with the presence of retinopathy (Table 3). Compared with subjects with high emotional support, those with low support had 60% greater odds of retinopathy (odds ratio = 1.6, 95% confidence interval (CI): 1.25, 1.95). Other high-risk groups included subjects with high trait anxiety compared with low trait anxiety (odds ratio = 1.4, 95% CI: 1.08, 1.81), subjects suffering from depressive symptoms (odds ratio = 1.5, 95% CI: 1.15, 1.83) compared with subjects without depressive symptoms, and those subjects suffering from 2 or more chronic burdens compared with those without any chronic burdens (odds ratio = 1.3, 95% CI: 1.09, 1.62). In addition, the odds of retinopathy increased 10% (odds ratio = 1.1, 95% CI: 1.02, 1.19) per increasing level of cynical distrust.

Table 3.   Odds Ratios of Retinopathy by Categories of Psychosocial Factors, the Multi-Ethnic Study of Atherosclerosis Cohort, 2000–2004

	No.	% Retinopathy	Model 1[a]		Model 2[b]		Goodness-of-Fit Test[c]
			Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	
Trait anger[d]							0.97
Low	3,295	10.8	1.0		1.0		
Moderate	2,492	11.4	1.1	0.95, 1.34	1.1	0.91, 1.32	
High	276	12.0	1.2	0.83, 1.79	1.0	0.69, 1.59	
P_{trend}				0.12		0.45	
Trait anxiety[e]							0.76
Low	2,709	10.6	1.0		1.0		
Moderate	2,646	11.0	1.1	0.93, 1.32	1.1	0.91, 1.33	
High	700	12.9	1.4	1.08, 1.81	1.4	1.11, 1.92	
P_{trend}				0.02		0.01	
Symptoms of depression[f]							0.43
No	5,319	10.7	1.0		1.0		
Yes	742	14.0	1.5	1.15, 1.83	1.5	1.16, 1.91	
P_{trend}				0.002		0.002	
Emotional support[g]							0.82
Yes	5,299	10.5	1.0		1.0		
No	752	14.9	1.6	1.25, 1.95	1.6	1.26, 2.02	
P_{trend}				<0.001		<0.001	
Cynical distrust[h]							0.44
None	1,414	9.3	1.0		1.0		
Little	1,704	9.9	1.0	0.80, 1.30	1.0	0.79, 1.32	
Moderate	1,507	11.8	1.2	0.91, 1.49	1.1	0.84, 1.41	
Severe	1,395	13.6	1.3	1.03, 1.69	1.2	0.89, 1.52	
P_{trend}				0.02		0.22	
Chronic burdens[i]							0.60
0	2,330	10.6	1.0		1.0		
1	1,865	10.0	1.0	0.80, 1.20	1.0	0.78, 1.20	
≥2	1,786	12.6	1.3	1.09, 1.62	1.0	0.87, 1.35	
P_{trend}				0.008		0.49	

Abbreviation: CES-D, Center for Epidemiology Studies Depression.

[a] Adjusted for age, sex, race/ethnicity, and study site.

[b] Adjusted for age, sex, race/ethnicity, and study site in model 1 plus the duration and presence of diabetes, hypertension status, fasting serum glucose, systolic blood pressure, low density lipoprotein cholesterol, and high density lipoprotein cholesterol.

[c] P value for the Hosmer-Lemeshow goodness-of-fit test for model 2.

[d] High Spielberger trait-anger, ≥22; moderate, 15–21; low, <15.

[e] High Spielberger trait-anxiety, ≥22; moderate, 15–21; low, <15.

[f] Depressive symptoms, CES-D score ≥16; no depressive symptoms, CES-D score <16.

[g] Lack of emotional support, ENRICHD (Enhanced Recovery in Coronary Heart Disease) Social Support Instrument score ≤18; access to emotional support, >18.

[h] High cynical distrust 8-item subset of the full Cook-Medley Hostility Scale, ≥5; moderate, 3 or 4; low, 1 or 2; none, 0.

[i] High burdens, ≥2 ongoing difficulties in the Chronic Burden Scale; moderate, 1; low, 0.

In model 2, we adjusted for additional independent predictors of retinopathy including duration of diabetes, presence of diabetes, hypertension or both, systolic blood pressure, fasting serum glucose, low density lipoprotein cholesterol, and high density lipoprotein cholesterol. Subjects with high trait anxiety compared with low trait anxiety, subjects with symptoms of depression versus those without, and subjects without emotional support compared with those with emotional support remained at greater odds for retinopathy (odds ratio = 1.4, 95% CI: 1.11, 1.92; odds

ratio = 1.5, 95% CI: 1.16, 1.91; and odds ratio = 1.6, 95% CI: 1.26, 2.02, respectively). Chronic burdens and cynical distrust were no longer associated with retinopathy after further adjustment.

We also conducted stratified analyses, first by diabetes status and then by hypertension status. The prevalence of retinopathy ranged from 5.8% for subjects with no diabetes or hypertension to 9.6% for subjects with only hypertension. Retinopathy was much more common for subjects with diabetes; the prevalence of retinopathy was 18.4% for those with only diabetes and 24.3% if they also had hypertension. In stratified analyses, associations of depressive symptoms with the odds of retinopathy were stronger in subjects without diabetes than in those with diabetes (odds ratio = 1.6, 95% CI: 1.17, 2.22 vs. odds ratio = 1.2, 95% CI: 0.84, 1.79, respectively), or if they had a lack of emotional support (odds ratio = 1.8, 95% CI: 1.35, 2.46 vs. odds ratio = 1.3, 95% CI: 0.87, 1.84). However, the odds of retinopathy were greater for subjects with hypertension than those without, if they had greater symptoms of depression (odds ratio = 1.6, 95% CI: 1.15, 2.19 vs. odds ratio = 1.3, 95% CI: 0.90, 1.92).

There were only a few associations between psychosocial risk factors and retinal vessel caliber, and most of these results have not been included. However, trait anger was associated with CRAE. After adjustment for age, sex, race/ethnicity, and study site, the mean CRAE was smaller for subjects with higher levels of trait anger, 143.3 μm (standard error, 1.02), compared with subjects with low trait anger, 144.3 μm (standard error, 0.62) (model 1). The difference in the predicted means did increase slightly in the fully adjusted model 2. In addition, these results were most apparent in subjects without diabetes. In this case, the mean CRAE for subjects with high trait anxiety, 141.9 μm (standard error, 1.67), was narrower than for subjects with low trait anxiety, 144.0 μm (standard error, 1.30) (model 2).

Cynical distrust was associated with CRVE. After adjustment for age, race/ethnicity, sex, and study site, subjects with severe cynical distrust had larger CRVE, 217.9 μm (standard error, 1.04), than subjects with no cynical distrust, 211.2 μm (standard error, 1.04). After further adjustment (model 2), this association was no longer statistically significant although the point estimates were relatively unchanged.

DISCUSSION

Retinopathy, which includes microaneurysms, hemorrhages, and exudates, results from a disruption in the retinal-blood-brain barrier, necrosis of smooth muscle and endothelial cells, and retinal ischemia (54, 55). Epidemiologic data suggest that these abnormalities can be found in 2%–14% of the general nondiabetic population and are fairly common even in persons without hypertension (56). This was also true in the MESA cohort where the prevalence of retinopathy was 5.8% for subjects with no diabetes or hypertension, 9.6% for subjects with only hypertension, 18.4% for those with only diabetes, and 24.3% if they had both hypertension and diabetes.

In this study, we have shown that several psychosocial risk factors are independently associated with the presence of retinopathy. After adjustment for potential confounders and known risk factors for retinopathy, a lack of emotional support was associated with a 60% increase in the odds of retinopathy for the entire cohort. In addition, subjects with high trait anxiety compared with low trait anxiety and subjects with depressive symptoms compared with those without had 40% and 50% greater odds of retinopathy, respectively.

We investigated whether associations of psychosocial factors with retinopathy differed in persons with and without diabetes or hypertension, 2 conditions known to be strongly predictive of retinopathy. Heterogeneity in psychosocial effects could result from greater vulnerability of subjects with diabetes and hypertension due to underlying vascular damage associated with these conditions. This appeared to be the case for symptoms of depression, which had a stronger association with retinopathy in subjects with hypertension compared with those without, 60% versus 30% greater odds of retinopathy. It is also possible that psychosocial effects may more easily be detected in persons without the presence of these strong predictors of retinopathy. This was true of less emotional support and symptoms of depression, which had stronger associations with retinopathy in subjects without diabetes than in those with diabetes (80% vs. 30% and 60% vs. 20% greater odds of retinopathy, respectively). However, tests of heterogeneity for these interactions did not reach statistical significance in the entire cohort.

The focus of our study has been to determine if associations exist between measures of psychosocial stress and microvascular signs in the retina. Future studies will be needed to replicate our findings. Because of the correlated nature of some psychosocial measures, it is possible that 1 or 2 of these factors may adequately summarize our findings. Additionally, a better examination of possible effect modifiers in the relation between psychosocial factors and retinopathy is needed to rule out the possibility that results from our stratified analyses represent chance findings.

The association between the psychosocial risk factors including lack of emotional support, high trait anxiety, and symptoms of depression with retinopathy raises questions into possible biologic mechanisms through which these stressors may ultimately lead to retinopathy and possibly other clinical conditions including cardiovascular disease. Because these findings appear independently of diabetes and hypertension status, they may not be operating entirely through these pathways. We hypothesize that enduring effects of psychosocial stress on hemodynamic, vasoconstrictive, and hemostatic forces may lead to endothelial dysfunction or increased risk of small thrombotic events in the retina. Alternatively, these stressors may lead to retinopathy through increased adverse health behaviors for these participants such as noncompliance with taking prescribed blood pressure medication (15).

To our knowledge, this is the most extensive investigation of the relation between psychosocial risk factors and retinal microvascular signs. In one previous paper from the Cardiovascular Health Study (57), no association was found

between retinal microvascular abnormalities and depressive symptoms in people aged 70 years or older. However, the MESA was much larger than the previous study, used the full version of the Center for Epidemiology Studies Depression Scale compared with the modified version in the Cardiovascular Health Study, included photographs of both eyes compared with 1 eye in the Cardiovascular Health Study, and studied a younger cohort.

Although our study has shown several associations with retinopathy but very few associations with retinal vessel caliber, this is not entirely unexpected. Retinopathy is a more severe sign of hypertensive retinal vascular damage, is more reliably measured, is associated pathologically with breakdown of the retinal-blood-brain-barrier and retinal hypoxia, and is a stronger predictor of stroke, cognitive impairment, renal dysfunction, congestive heart failure, and cardiovascular disease mortality than other retinal signs such as blood vessel diameter (54, 55).

Our study does have some limitations. We examined associations between multiple exposures and outcomes increasing the probability of chance findings. This was a cross-sectional analysis, so we could not examine the temporal relations of psychosocial factors with retinal microvascular signs. The MESA population represents a cohort with no history of cardiovascular disease, so our findings may not generalize to the population as a whole. It is likely that model 1 is underadjusted and that model 2 is overadjusted or inappropriately adjusted for our various outcomes. There are likely multiple pathways through which psychosocial risk factors may affect retinal microvasculature, and adjustment for systolic blood pressure, fasting glucose, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and hsCRP may be inappropriate to the extent that these may represent pathways through which psychosocial risk factors may affect retinal microvascular health.

In conclusion, we have shown an association between lack of emotional support, high trait anxiety, and the presence of depressive symptoms with retinopathy. These data suggest that psychosocial factors may have an adverse effect on the microvasculature. It is not known whether retinopathy associated with these psychosocial factors is a marker for similar biologic pathways involving the microvasculature in the development of cardiovascular disease.

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REFERENCES

1. Albert CM, Chae CU, Rexrode KM, et al. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation*. 2005;111(4):480–487.
2. Carney RM, Freedland KE. Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biol Psychiatry*. 2003;54(3):241–247.
3. Chang PP, Ford DE, Meoni LA, et al. Anger in young men and subsequent premature cardiovascular disease: the precursors study. *Arch Intern Med*. 2002;162(8):901–906.
4. Davidson K, Jonas BS, Dixon KE, et al. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA Study? Coronary Artery Risk Development in Young Adults. *Arch Intern Med*. 2000;160(10): 1495–1500.
5. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch Fam Med*. 1997; 6(1):43–49.
6. Kivimäki M, Leino-Arjas P, Luukkonen R, et al. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees [electronic article]. *BMJ*. 2002;325 (7369):857.
7. Matthews KA, Katholi CR, McCreath H, et al. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA Study. *Circulation*. 2004;110(1):74–78.
8. Parkes CM, Benjamin B, Fitzgerald RG. Broken heart: a statistical study of increased mortality among widowers. *BMJ*. 1969;1(5646):740–743.
9. Player MS, King DE, Mainous AG III, et al. Psychosocial factors and progression from prehypertension to hypertension or coronary heart disease. *Ann Fam Med*. 2007;5(5):403–411.
10. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry*. 2003;54(3): 227–240.

11. Williams JE, Nieto FJ, Sanford CP, et al. The association between trait anger and incident stroke risk: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2002;33(1): 13–19.

12. Williams JE, Nieto FJ, Sanford CP, et al. Effects of an angry temperament on coronary heart disease risk: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2001; 154(3):230–235.

13. Williams JE, Paton CC, Siegler IC, et al. Anger proneness predicts coronary heart disease risk: prospective analysis from the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2000;101(17):2034–2039.

14. Yan LL, Liu K, Matthews KA, et al. Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA*. 2003;290(16):2138–2148.

15. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007;370(9592):1089–1100.

16. Broadley AJ, Korszun A, Jones CJ, et al. Arterial endothelial function is impaired in treated depression. *Heart*. 2002;88(5): 521–523.

17. Rajagopalan S, Brook R, Rubenfire M, et al. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Am J Cardiol*. 2001;88(2):196–198.

18. Laghrissi-Thode F, Wagner WR, Pollock BG, et al. Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry*. 1997;42(4):290–295.

19. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. *Am J Psychiatry*. 1996; 153(10):1313–1317.

20. Wong TY, Rosamond W, Chang PP, et al. Retinopathy and risk of congestive heart failure. *JAMA*. 2005;293(1):63–69.

21. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet*. 2001;358(9288):1134–1140.

22. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA*. 2002; 288(1):67–74.

23. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*. 2003;110(5):933–940.

24. Wong TY, Cheung N, Islam FM, et al. Relation of retinopathy to coronary artery calcification: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2008;167(1):51–58.

25. Ikram MK, de Jong FJ, Vingerling JR, et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2004;45(7):2129–2134.

26. Klein R, Klein BE, Moss SE, et al. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. *Arch Ophthalmol*. 1994;112(1):92–98.

27. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150(3): 263–270.

28. Wang JJ, Mitchell P, Leung H, et al. Hypertensive retinal vessel wall signs in a general older population: the Blue Mountains Eye Study. *Hypertension*. 2003;42(4):534–541.

29. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002;86(9):1007–1013.

30. Leung H, Wang JJ, Rochtchina E, et al. Impact of current and past blood pressure on retinal arteriolar diameter in an older population. *J Hypertens*. 2004;22(8):1543–1549.

31. Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. *Hypertension*. 2004;44(4): 442–447.

32. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med*. 2004; 140(4):248–255.

33. Wong TY, Shankar A, Klein R, et al. Prospective cohort study of retinal vessel diameters and risk of hypertension [electronic article]. *BMJ*. 2004;329(7457):79.

34. Liao D, Wong TY, Klein R, et al. Relationship between carotid artery stiffness and retinal arteriolar narrowing in healthy middle-aged persons. *Stroke*. 2004;35(4):837–842.

35. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA*. 2002; 287(9):1153–1159.

36. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. *Neurology*. 2006; 66(9):1339–1343.

37. Ikram MK, De Jong FJ, Van Dijk EJ, et al. Retinal vessel diameters and cerebral small vessel disease: the Rotterdam Scan Study. *Brain*. 2006;129(pt 1):182–188.

38. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002; 156(9):871–881.

39. Klein R, Klein BE, Knudtson MD, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the Multi-Ethnic Study of Atherosclerosis. *Ophthalmology*. 2006; 113(3):373–380.

40. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol*. 2006;141(3):446–455.

41. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5 suppl):786–806.

42. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269–2280.

43. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003; 27(3):143–149.

44. Wong TY, Knudtson MD, Klein R, et al. Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. *Ophthalmology*. 2004;111(6):1183–1190.

45. Radloff L. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977; 1(3):385–401.

46. Eaton W, Muntaner C, Smith C, et al. *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment*. Mahwah, NJ: Lawrence Erlbaum; 2004.

47. Diez Roux AV, Ranjit N, Powell L, et al. Psychosocial factors and coronary calcium in adults without clinical cardiovascular disease. *Ann Intern Med*. 2006;144(11):822–831.

48. Dan AA, Crone C, Wise TN, et al. Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life. *Psychosomatics*. 2007;48(3): 223–229.

49. Ranjit N, Diez-Roux AV, Shea S, et al. Psychosocial factors and inflammation in the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med.* 2007;167(2):174–181.

50. Barefoot JC, Dodge KA, Peterson BL, et al. The Cook-Medley hostility scale: item content and ability to predict survival. *Psychosom Med.* 1989;51(1):46–57.

51. Enhancing recovery in coronary heart disease patients (EN-RICHD): study design and methods. The ENRICHD investigators. *Am Heart J.* 2000;139(1 pt 1):1–9.

52. Center MC. *Multi-Ethnic Study of Atherosclerosis Field Center Manual of Operations*. Seattle, WA: University of Washington; 2001.

53. Wong TY, Islam FM, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the Multi-Ethnic Study of Atherosclerosis (MESA). *Invest Ophthalmol Vis Sci.* 2006;47(6):2341–2350.

54. Klein R. Diabetic retinopathy. *Annu Rev Public Health.* 1996; 17:137–158.

55. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med.* 2004;351(22):2310–2317.

56. Wong TY, Klein R, Klein BE, et al. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol.* 2001; 46(1):59–80.

57. Sun C, Tikellis G, Klein R, et al. Are microvascular abnormalities in the retina associated with depression symptoms? The Cardiovascular Health Study. *Am J Geriatr Psychiatry.* 2007;15(4):335–343.