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Original Contribution

Retinal Microvascular Caliber and Incident Depressive Symptoms: The Multi-Ethnic Study of Atherosclerosis

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Cerebral microvascular dysfunction may contribute to depression via disruption of brain structures involved in mood regulation, but evidence is limited. The retina allows for visualization of a microvascular bed that shares similarities with the cerebral microvasculature. We investigated the associations between baseline retinal arteriolar and venular calibers (central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively) and incident depressive symptoms in the Multi-Ethnic Study of Atherosclerosis (MESA). We used longitudinal data on 4,366 participants (mean age = 63.2 years; 48.5% women, 28.4% Black) without baseline depressive symptoms. Depressive symptoms, defined as Center for Epidemiologic Studies Depression Scale score ≥16 and/or use of antidepressant medication, were determined between 2002 and 2004 (baseline; MESA visit 2) and at 3 follow-up examinations conducted every 1.5–2 years thereafter. Fundus photography was performed at baseline. After a mean follow-up period of 6.1 years, 21.9% (n = 958) had incident depressive symptoms. After adjustment for sociodemographic, lifestyle, and cardiovascular factors, a 1–standard-deviation larger baseline CRVE was associated with a higher risk of depressive symptoms (hazard ratio = 1.10, 95% confidence interval: 1.02, 1.17), and a 1–standard-deviation larger baseline CRAE was not statistically significantly associated with incident depressive symptoms (hazard ratio = 1.04, 95% confidence interval: 0.97, 1.11). In this study, larger baseline CRVE, but not CRAE, was associated with a higher incidence of depressive symptoms.

cerebral microcirculation; depression; longitudinal studies; retina; retinal caliber

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging; SD, standard deviation.

Depression is one of the largest contributors to global disability among persons aged ≥65 years (1). However, current antidepressant medications targeting neurotransmitters are less effective (2, 3) and have more side effects (4) in older patients than in younger ones. There is therefore a high need for new preventive and treatment interventions for older individuals, which requires a better understanding of the mechanisms underlying late-life depressive symptoms.

The pathophysiology of depression is multifactorial and complex. The "vascular depression hypothesis" postulates that cerebrovascular damage may predispose people to depression via disruption of frontal and subcortical structures or their connecting pathways involved in mood regulation (5). Cerebral microvascular dysfunction may progressively lead to such damage by inducing increased blood-brain barrier permeability, perfusion defects, hypoxia, and increased angiogenesis (6). In accordance, studies have shown that depression is associated with reduced cerebrovascular reactivity (7) and features of cerebral small-vessel disease (8, 9), and these disturbances may be a result of cerebral microvascular dysfunction. However, data on the association between

direct measures of cerebral microvascular dysfunction and depression are limited.

The retina offers a unique opportunity to study early microvascular changes in the brain, because it allows for direct and reproducible visualization of a microvascular bed that shares embryological, anatomical, and physiological similarities with the cerebral microvasculature (10, 11). Consistent with the hypothesis that retinal microvascular abnormalities are markers of cerebral microvascular dysfunction, previous studies have found that subtle abnormalities of the retinal microvascular network, including central retinal arteriolar and venular calibers or equivalents (central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)), are associated with increased risk of features of cerebral small-vessel disease (12, 13) and cerebral diseases that may, in part, have a microvascular origin, such as stroke (14) and dementia (15). Changes in microvascular caliber reflect both functional and structural mechanisms, including microvascular endothelial-cell dysfunction and remodeling of the vessel wall (16). Most studies have found that smaller CRAE and larger CRVE are associated with features of cerebral small-vessel disease and dementia (13, 14, 17), while some studies have found associations with larger CRAE and these outcomes (13, 14, 17). However, whether CRAE and CRVE are related to incident depressive symptoms is largely unknown. Only 2 studies on measures of the retinal microvasculature and incident depressive symptoms have been published to date, and they provided inconsistent results (18, 19).

Using serial examinations carried out in the Multi-Ethnic Study of Atherosclerosis (MESA), we investigated the association between cerebral microvascular dysfunction, as estimated by baseline CRAE and CRVE, and incident depressive symptoms.

METHODS

Study design

MESA is a longitudinal cohort study of 6,814 men and women aged 45–84 years without clinical cardiovascular disease at study entry from 4 racial/ethnic groups (38% White, 28% Black, 23% Hispanic, and 11% Chinese-American), recruited from 6 US communities. The first examination was conducted between 2000 and 2002, and 5 follow-up examinations have occurred to date. The rationale and methodology of MESA have been described previously (20). The study was approved by the institutional review board at each site, and all participants gave written informed consent. The present analysis used data from MESA visits 2 (2002–2004), 3 (2004–2005), 4 (2005–2007), and 5 (2010–2012).

Retinal microvascular caliber

Fundus photography was performed at visits 2 and 5 according to a standardized protocol with use of a 45-degree digital nonmydriatic camera, as described previously (21). Retinal microvascular caliber was measured using a computer-based program, Interactive Vessel Analyzer (IVAN) (University of Wisconsin, Madison, Wisconsin) (21). All arterioles and venules passing through an area 0.5–1 disc diameter from the optic margin were measured as CRAE and CRVE. In MESA, data from the right eye were selected for measurement of retinal microvascular caliber, but if unavailable, data from the left eye were substituted.

Depressive symptoms

Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (22). Each item is scored from 0 to 3, for a maximum of 60 points, with a higher score representing more depressive symptoms. In addition, use of antidepressant medication (tricyclic agents, nontricyclic agents, and monoamine oxidase inhibitors) was assessed from medication bottles brought to the clinic at each visit. Depressive symptoms were defined as a predefined CES-D cutoff score greater than or equal to 16 (22) and/or use of antidepressant medication at each visit, except for visit 2. At visit 2 only, depressive symptoms were defined solely on the basis of use of antidepressant medication, because the CES-D questionnaire was not administered during that visit.

Covariates

All covariates were measured at visit 2, except for dietary habits, markers of low-grade inflammation (C-reactive protein and interleukin 6), and anxiety, which were measured at visit 1. Educational level (less than high school, high school, or college degree or more), annual income (dollars), smoking status (never, former, or current smoker), current alcohol use (yes/no), physical activity (metabolic equivalent of task–minutes per week spent in moderate-to-vigorous activities), and dietary habits (ideal diet or intermediate/poor diet, as defined by the American Heart Association (23)) were assessed by means of self-administered questionnaires on demographic factors, physical activity, and dietary habits (20). Type 2 diabetes was defined as a fasting blood glucose concentration greater than or equal to 7 mmol/L and/or use of glucose-lowering medication. Hypertension was defined as blood pressure $\geq$140/90 mm Hg and/or use of antihypertensive medication. Pulse pressure was calculated as the difference between systolic and diastolic blood pressures. Anxiety was assessed with the trait subscale of the Spielberger State-Trait Anxiety Inventory (24). Retinopathy signs were defined as described previously (25). Visual impairment was defined as a presenting visual acuity of 20/50 or worse in the better-seeing eye (26). Incident cardiovascular disease was defined as a composite endpoint of myocardial infarction, resuscitated cardiac arrest, stroke, or coronary heart disease (27). Incident dementia was defined as described previously (28).

Statistical analysis

The overarching design of data used in the analysis is summarized in Web Figure 1 (available at https://doi.org/10.1093/aje/kwab255). We used Cox proportional hazards regression

to estimate hazard ratios and 95% confidence intervals for the association between larger baseline CRAE and CRVE (per standard deviation (SD) increment, at visit 2) and incident depressive symptoms among persons who were free of depressive symptoms at baseline and prior to the baseline visit (i.e., CES-D score <16 at visit 1 and no use of antidepressant medication at visits 1 and 2). CRAE and CRVE were evaluated in separate models. Duration of time in the study was used as the time scale. Follow-up time was calculated from visit 2 (2002–2004) to the first incidence of depressive symptoms, death, or the date of the last examination, whichever came first. The linearity assumption was evaluated visually by plotting the incidence rate of depressive symptoms by quartiles of CRAE and CRVE. In addition, we used restricted cubic spline models fitted for Cox proportional hazards models with 4 knots at the 5th, 35th, 65th, and 95th percentiles of CRAE and CRVE, respectively. Although the incidence rate of depressive symptoms did not increase consistently across the quartiles (i.e., the CRAE threshold appeared between the first and second quartiles and the CRVE threshold between the third and fourth quartiles; Web Figure 2), the spline models showed a linear curve for CRVE (Web Figure 3) but not for CRAE (Web Figure 4). The curve for CRAE was in accordance with the nonsignificant finding for CRAE (see Results section).

Results of the analyses were adjusted for the following potential confounders: age, sex, and race/ethnicity (model 1); additionally for educational level, income level, diabetes, body mass index (weight (kg)/height (m)^2), smoking status, current alcohol use, total cholesterol:high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, diet index, physical activity, systolic blood pressure, and use of antihypertensive medication (model 2); and additionally for CES-D score at visit 1 (model 3). These covariates were selected on the basis of their biological plausibility, since they are known to be associated with microvascular dysfunction and depression (29–32).

We examined whether the associations investigated differed by sex, race/ethnicity, diabetes status, or hypertension, but we found no such interaction (all *P*-for-interaction values > 0.10). Therefore, results are reported without stratification for these factors.

The percentage of missing values for covariates was minimal (maximum, 3.6%). We imputed data using multiple imputation by chained equations under the assumption that data were missing at random. We used predictive mean matching to impute 20 data sets with 10 iterations for each data set. For the main analysis, we pooled the results across all imputed data sets using Rubin's rule.

We performed several additional analyses to test the robustness of our findings. First, given that the presence of depressive symptoms was known every 1.5–2 years, on average, at the MESA examination waves (i.e., time to disease onset was interval-censored), we repeated the analysis accounting for interval-censored time-to-event data using a parametric proportional hazards model with a Weibull distribution (33). Second, we repeated the analysis with different definitions of incident depressive symptoms: that is, depression defined only as CES-D score ≥16, irrespective of use of antidepressant medication; depression defined as CES-D score ≥21 instead of CES-D score ≥16; depression defined as new use of antidepressant medication, irrespective of CES-D score; and depression defined as both CES-D score ≥16 and new use of antidepressant medication. A cutoff score of 21 has been considered a clinical cutpoint to indicate probable major depression (34). Third, to minimize potentially confounding effects, we repeated the analysis after excluding the following individuals: persons with prevalent or incident cardiovascular disease; persons with prevalent or incident dementia (i.e., at MESA visit 2 or thereafter); persons with any retinopathy signs at MESA visit 2 or 5; and persons with prevalent visual impairment (i.e., at MESA visit 2). Fourth, we additionally adjusted for study site, markers of low-grade inflammation (i.e., C-reactive protein and interleukin 6), pulse pressure (a surrogate marker for arterial stiffness), and anxiety. Low-grade inflammation, arterial stiffness, and anxiety may act as a confounder, an antecedent, or a mediator. Fifth, we additionally mutually adjusted for CRVE and CRAE, to explore whether the associations (if any) of depressive symptoms with CRAE and CRVE were linked. Sixth, we performed a complete-case analysis without imputation for covariates. Seventh, we evaluated the association between change in CRAE and CRVE between visits 2 and 5 and the presence of depressive symptoms at visit 5 among persons who were free of depressive symptoms before visit 5 (i.e., CES-D score <16 at visits 1, 3, and 4 and no use of antidepressant medication at visits 1–4) using logistic regression analysis. Previous MESA analysis (35) showed that CRVE only minimally decreased in size between visits 2 and 5, with a mean difference in the present study population of −3.0 (SD, 11.2) μm for CRAE (corresponding to a 2.1% decrease in size after visit 2) and −7.1 (SD, 13.9) μm for CRVE (corresponding to a 3.2% decrease in size) (Web Table 1). This analysis was therefore considered explorative only. Eighth, we evaluated the associations of baseline CRAE and CRVE and 7.8-year change in CRAE and CRVE with change in continuous CES-D score between visits 1 and 5 as the outcome using linear regression analysis. Ninth, we repeated the analyses with a composite score of CRAE and CRVE as the determinant, with the composite score calculated as the average of the *z* scores of CRAE and CRVE. Tenth, we evaluated the cross-sectional associations between CRAE and CRVE and prevalent depressive symptoms at MESA visit 5 (the visit with concurrent measurements of retinal microvascular caliber and depressive symptoms).

Statistical analyses were performed with the Statistical Package for the Social Sciences (version 25.0; IBM, Chicago, Illinois) or Stata (version 16.0; StataCorp LLC, College Station, Texas).

RESULTS

The study population included 4,366 participants free of depressive symptoms at baseline who had data on CRAE and CRVE at MESA visit 2 and data on incident depressive symptoms at 1 or more follow-up examinations (Figure 1A). Their mean age was 63.2 (SD, 9.7) years; 48.5% were women, and 28.4% were Black (Table 1). In total, 21.9%

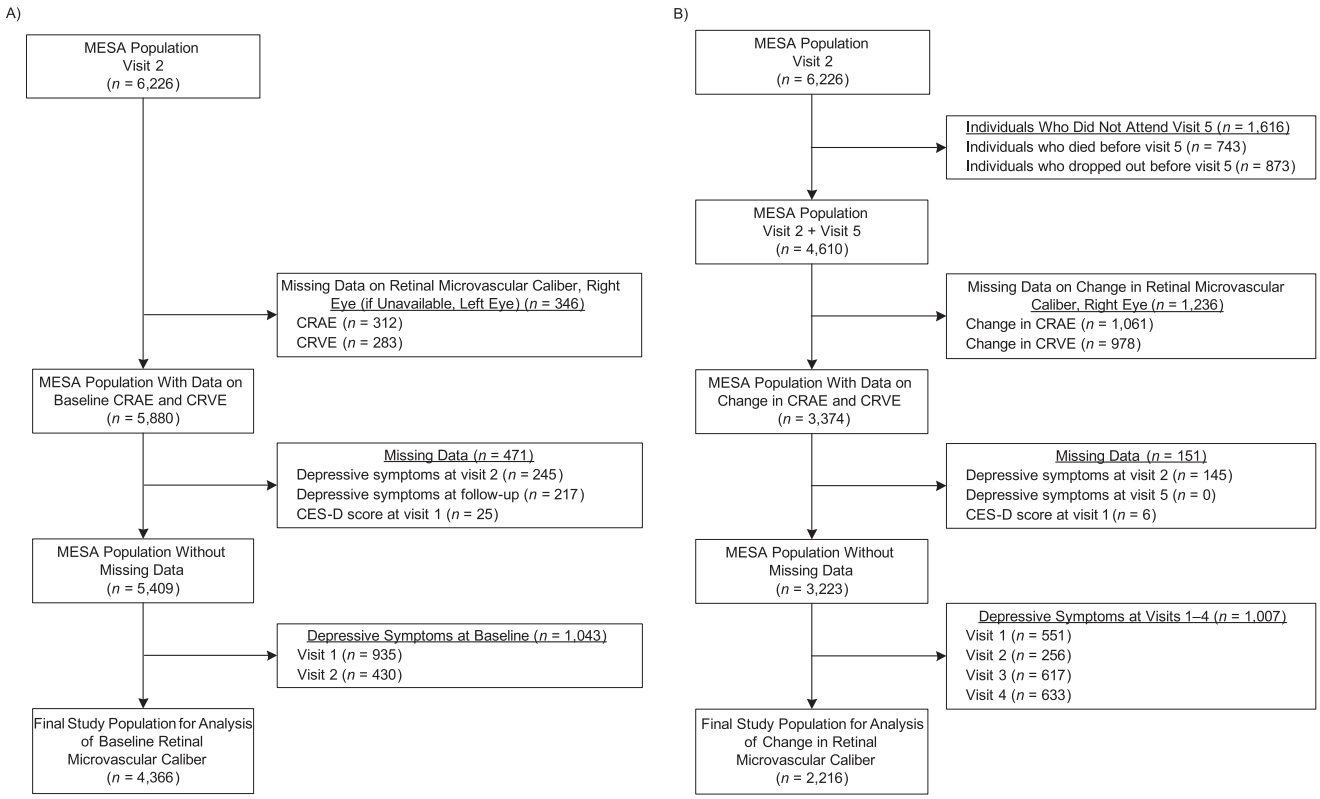

Figure 1. Derivation of the final study populations for analyses of the associations of baseline retinal microvascular caliber (A) and 7.8-year change in retinal microvascular caliber (B) with incident depressive symptoms in the Multi-Ethnic Study of Atherosclerosis (MESA), 2002–2012. Numbers are not mutually exclusive. CES-D, Center for Epidemiologic Studies Depression Scale; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

(n = 958) had incident depressive symptoms after a mean follow-up period of 6.1 (SD, 2.5) years; of those participants, 79.7% (n = 764) had a CES-D score greater than or equal to 16 and 31.5% (n = 302) had started using antidepressant medication. The 1,860 participants excluded from this analysis were more likely to be older, to be less educated, and to have a worse cardiovascular risk profile (Web Table 2).

Results of the Cox regression analysis showed that a 1-SD larger baseline CRAE (14.2 μm) was associated with a higher incidence of depressive symptoms, albeit not statistically significantly (hazard ratio = 1.04, 95% confidence interval: 0.97, 1.11) (Figure 2, model 3). In addition, a 1-SD larger baseline CRVE (22.2 μm) was statistically significantly associated with a higher incidence of depressive symptoms (hazard ratio = 1.10, 95% confidence interval: 1.02, 1.17) (Figure 2, model 3).

Additional analyses

The results of the additional analyses are shown in Figure 3. Results were similar when we repeated the analysis after accounting for interval-censored time-to-event data using a parametric model; when we repeated the analysis using the different definitions of incident depressive symptoms; after we excluded persons with prevalent or incident cardiovascular disease (n = 555); after we excluded persons with prevalent or incident dementia (n = 188); after we excluded persons with any signs of retinopathy at baseline or at visit 5 (n = 685); after we excluded persons with visual impairment at baseline (n = 252); after we additionally adjusted for markers of low-grade inflammation, pulse pressure, anxiety, or study site; and after we mutually adjusted for CRAE and CRVE. Results of the complete-case analysis were consistent with those obtained in the main analysis. Change in retinal microvascular caliber was calculated over a mean follow-up period of 7.8 (SD, 0.4) years among 2,216 participants who were free of depressive symptoms before visit 5 (Figure 1B). In total, 9.3% (n = 206) had incident depressive symptoms at visit 5, of whom 72.3% (n = 149) had a CES-D score greater than or equal to 16 and 33.5% (n = 69) had started using antidepressant medication. The characteristics of persons included in this analysis, compared with those who died (n = 743), dropped out (n = 873), had incomplete data (n = 1,387), or had depressive symptoms before visit 5 (n = 1,007), are shown in Web Table 3. Results of the logistic regression analysis showed that an increase in CRAE or CRVE between visits 2 and 5 was not statistically significantly associated with depressive symptoms at visit 5 after adjustment for all covariates and visit 1 CES-D score (Web Figure 5). Results were similar

Table 1. Baseline (Visit 2) Characteristics of the Study Population, Overall and According to Incident Depressive Symptoms (CES-D Score ≥16 and/or Use of Antidepressant Medication), Multi-Ethnic Study of Atherosclerosis, 2002–2012

Characteristic	Total Study Population (*n* = 4,366)			Depressive Symptom Status					
				No Depressive Symptoms (*n* = 3,408; 78.1%)			Incident Depressive Symptoms (*n* = 958; 21.9%)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Demographic factors									
Age, years			63.2 (9.7)			63.5 (9.7)			62.4 (9.9)
Female sex	2,116	48.5		1,569	46.0		547	57.1	
Race/ethnicity									
White	1,660	38.0		1,301	38.2		359	37.5	
Black	1,241	28.4		1,000	29.3		241	25.2	
Hispanic	880	20.2		636	18.7		244	25.5	
Chinese-American	585	13.4		471	13.8		114	11.9	
Educational level[a]									
Less than high school	666	15.3		471	13.8		195	39.4	
High school	769	17.6		587	17.2		182	19.0	
College or more	2,926	67.1		2,346	68.8		580	60.6	
Annual income, dollars[b]									
<30,000	1,390	33.0		1,026	30.1		364	39.4	
30,000–74,999	1,726	41.0		1,354	41.3		372	40.2	
≥75,000	1,091	25.9		902	27.5		189	20.4	
Lifestyle variables									
Smoking status[c]									
Never smoker	2,054	47.4		1,612	47.6		442	46.5	
Former smoker	1,826	42.1		1,440	42.5		386	40.6	
Current smoker	457	10.5		334	9.9		123	12.9	
Current alcohol use (yes/no)[d]	2,518	57.0		1,979	58.1		539	56.3	
Physical activity, MET-minutes/week[e,f]		3,735 (1,875–6,735)			3,780 (1,920–6,780)			3,544 (1,682–6,623)	
Diet index[g]									
Ideal diet	2,518	59.7		1,966	59.5		552	60.3	
Intermediate or poor diet	1,701	40.3		1,337	40.5		354	39.7	

Table continues

Table 1. Continued

Characteristic	Total Study Population (n = 4,366)			Depressive Symptom Status					
				No Depressive Symptoms (n = 3,408; 78.1%)			Incident Depressive Symptoms (n = 958; 21.9%)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Clinical characteristics									
Type 2 diabetes[h]	594	13.7		445	13.1		149	15.7	
Hypertension[i]	1,957	44.8		1,509	44.3		448	46.9	
Incident cardiovascular disease	555	12.7		406	11.9		149	15.6	
Incident dementia	188	4.3		146	4.3		42	4.4	
Baseline retinopathy	265	10.7		335	10.4		110	1.5	
Incident retinopathy	220	5.0		174	5.1		46	4.8	
Visual impairment	252	5.9		206	6.2		46	4.9	
Body mass index[j]			28.2 (5.4)			28.1 (5.3)			28.6 (5.7)
Blood pressure, mmHg[k]									
Systolic pressure			123.7 (20.4)			123.7 (20.4)			123.6 (20.5)
Diastolic pressure			70.6 (10.1)			70.7 (10.1)			70.3 (9.9)
Pulse pressure, mmHg[k]			53.1 (16.4)			53.1 (16.4)			53.3 (16.3)
Total cholesterol:HDL cholesterol ratio[l]			3.9 (1.2)			4.0 (1.2)			3.9 (1.2)
Use of lipid-modifying medication[m]	964	22.1		749	22.0		215	22.4	
Use of antihypertensive medication[m]	1,770	40.5		1,355	39.8		415	43.3	
Anxiety[f,n]		14 (11–17)			14 (11–16)			16 (13–19)	
Markers of low-grade inflammation									
C-reactive protein, mg/L[f,o]		1.79 (0.80–4.04)			1.78 (0.80–4.01)			1.83 (0.81–4.17)	
Interleukin 6, pg/mL[f,p]		1.13 (0.74–1.79)			1.14 (0.74–1.83)			1.12 (0.74–1.69)	

Table continues

Table 1. Continued

Characteristic	Total Study Population (n = 4,366)			Depressive Symptom Status					
				No Depressive Symptoms (n = 3,408; 78.1%)			Incident Depressive Symptoms (n = 958; 21.9%)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Retinal microvascular caliber, μm									
CRAE			144.2 (14.2)			143.9 (14.2)			145.1 (13.9)
CRVE			214.2 (22.1)			213.7 (21.8)			215.9 (22.7)
Depressive symptoms									
CES-D score[f]		4 (2–8)			4 (1–7)			7 (3–11)	

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent of task; SD, standard deviation.

[a] Data were available for 4,361 persons.
[b] Data were available for 4,207 persons.
[c] Data were available for 4,337 persons.
[d] Data were available for 4,346 persons.
[e] Data were available for 4,360 persons.
[f] Values are expressed as median (interquartile range).
[g] Data were available for 4,219 persons.
[h] Data were available for 4,336 persons.
[i] Data were available for 4,364 persons.
[j] Calculated as weight (kg)/height $(m)^2$. Data were available for 4,365 persons.
[k] Data were available for 4,364 persons.
[l] Data were available for 4,335 persons.
[m] Data were available for 4,365 persons.
[n] Data were available for 4,358 persons. Anxiety was assessed using the trait subscale of the Spielberger State-Trait Anxiety Inventory (24).
[o] Data were available for 4,337 persons.
[p] Data were available for 4,243 persons.

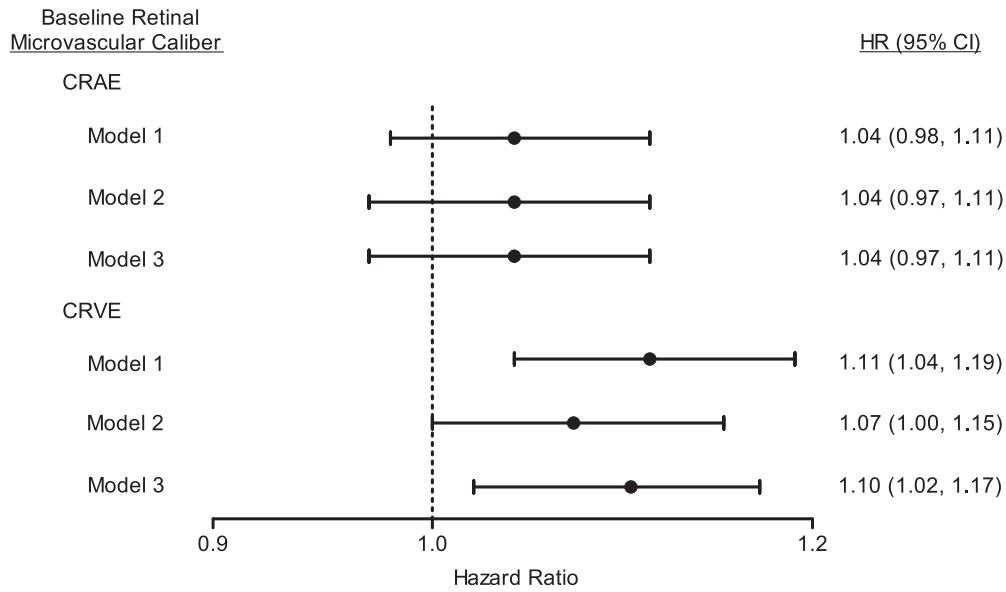

Figure 2. Associations of baseline (visit 2) retinal microvascular caliber (central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)) with incident depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D) score ≥16 and/or use of antidepressant medication) in the Multi-Ethnic Study of Atherosclerosis (MESA), 2002–2012. Results are shown for baseline CRAE and CRVE expressed per 1–standard-deviation increment at MESA visit 2. Model 1 adjusted for age, sex, and race/ethnicity. Model 2 additionally adjusted for educational level, income level, diabetes, body mass index, smoking status, current alcohol use, total cholesterol:high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, diet index, physical activity, systolic blood pressure, and use of antihypertensive medication. Model 3 additionally adjusted for CES-D score at visit 1. Bars, 95% confidence intervals (CIs). HR, hazard ratio.

when we repeated the analyses using change in CES-D score between visits 1 and 5 as the outcome (Web Table 4). When we evaluated the association between a composite score of CRAE and CRVE and incident depressive symptoms, results were similar to those obtained in the analysis with CRVE only (Web Table 5). Results of the cross-sectional analysis were consistent with those obtained in the analysis on incident depressive symptoms (Web Table 6).

DISCUSSION

In this study, a larger baseline CRVE was associated with a higher incidence of depressive symptoms. This association was independent of sociodemographic, lifestyle, and cardiovascular factors. However, baseline CRAE was not associated with incident depressive symptoms.

Comparison with other studies

Previous studies have found associations between indirect measures of cerebral microvascular dysfunction and damage, including blood biomarkers of microvascular endothelial-cell function (9) and magnetic resonance imaging (MRI) features of cerebral small-vessel disease (8, 9), and depressive symptoms. MRI features of cerebral small-vessel disease are indirect or "end-stage" markers of small-vessel abnormalities, because they reflect brain parenchymal damage potentially related to various functional and structural small-vessel changes, including microvascular dysfunction (6). However, only 2 previous studies evaluated the association between measures of the retinal microvasculature and incident depressive symptoms, and these studies had inconsistent findings. In the Maastricht Study, Geraets et al. (18) found that a reduced flicker light-induced retinal arteriolar dilation response, a functional measure of retinal microvascular function (11), was associated with a higher incidence of depressive symptoms, whereas flicker light-induced retinal venular dilation response was not. In the Rotterdam Study, Ikram et al. (19) evaluated the association between CRAE and CRVE and incident late-life depression but did not find a statistically significant association with incident depressive syndromes or depressive symptoms. We extend the results of these previous studies on the retinal microvasculature and depression from Europe with persons of mainly White ethnicity in a multiethnic population from the United States. Importantly, the present study had greater precision (n = 958 events vs. 166 events in the Maastricht Study and 555 in the Rotterdam Study) to estimate associations, possibly because of a larger sample size (n = 4,366 participants vs. 1,865 participants in the Maastricht Study and 3,605 in the Rotterdam Study), and a higher number of follow-up examinations or a longer follow-up duration in which to detect incident depressive symptoms (3 examinations over a mean follow-up period of 6.1 years vs. 4 examinations over a mean follow-up period of only 3.9 years in the Maastricht Study and only 2 examinations over a mean follow-up period of 9.0 years in the Rotterdam Study).

The association between larger baseline CRVE and a higher risk of depressive symptoms is consistent with the

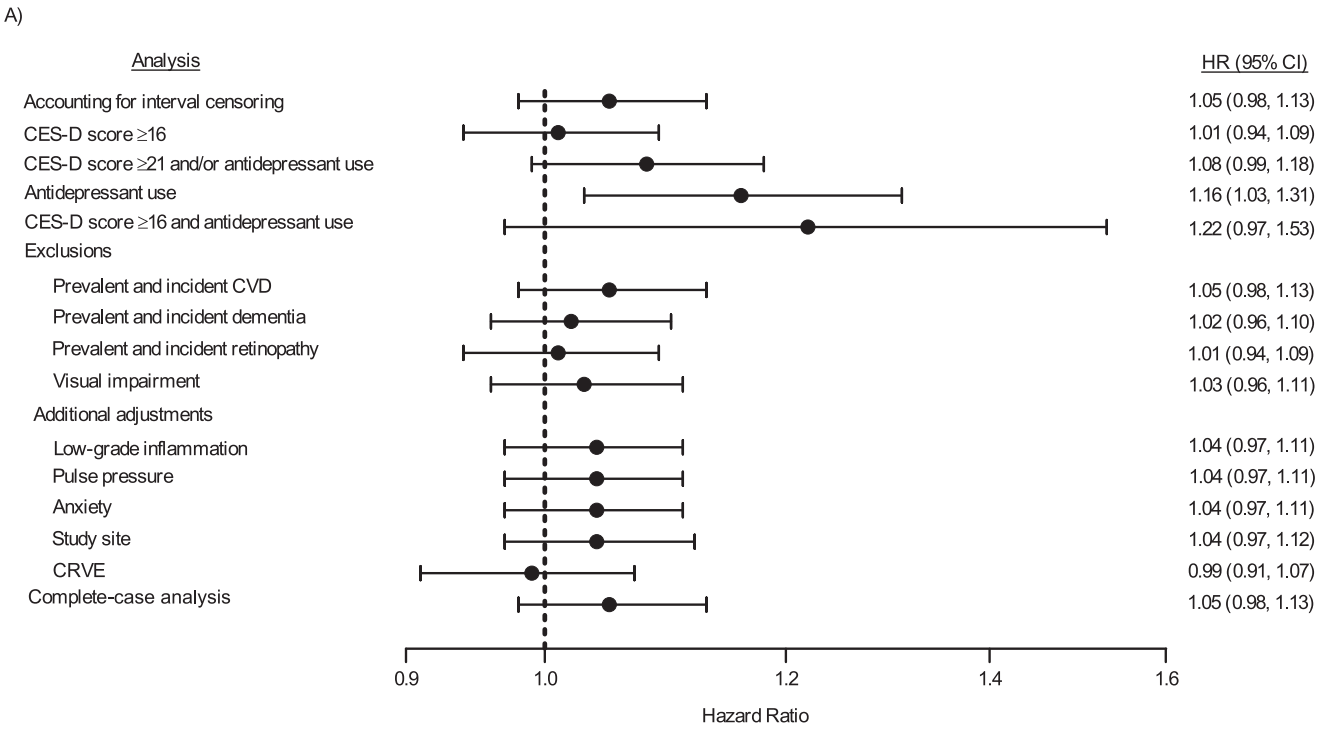

Figure 3 Continues

vascular depression hypothesis. This hypothesis postulates that cerebrovascular damage may predispose people to depression via disruption of frontal and subcortical structures or their connecting pathways involved in mood regulation (5). Retinal venular widening is related to cerebral microvascular hypoperfusion and hypoxia (14), and this may damage structures involved in mood regulation. The risk of depressive symptoms did not increase consistently across quartiles of CRVE, suggesting that the association between CRVE and depression started at a higher level of the exposure. However, to our knowledge, we are the first to report the linearity of this association; therefore, this issue requires further study.

Implications

These findings suggest that cerebral microvascular dysfunction might be a target for prevention and treatment of depression. Evidence suggest that lifestyle modifications, such as weight loss (36, 37), and medications (38, 39), such as renin-angiotensin-aldosterone system inhibitors, might favorably influence both microvascular function and depression.

Depressive symptoms frequently co-occur with other syndromes or diseases that may share a microvascular origin, including cognitive dysfunction, dementia, and cardiovascular disease (40). The mechanisms explaining the link between depressive symptoms and these conditions are incompletely understood and are probably multifactorial. It has been suggested that this link may be explained partially by microvascular dysfunction as a common underlying cause (41–43). The present study is in accordance with that hypothesis.

Other underlying mechanisms may, however, explain the observed association between CRVE and incident depressive symptoms. First, other factors may be independently associated with both microvascular dysfunction and damage and depressive symptoms, such as unhealthy lifestyle, cardiovascular disease, low-grade inflammation, arterial stiffness, and anxiety (29). However, the association between CRVE and incident depressive symptoms was independent of socioeconomic status, lifestyle, cardiovascular risk factors, anxiety, and markers of low-grade inflammation and arterial stiffness. In addition, results were similar when we repeated the analyses after excluding persons with incident cardiovascular disease. Nevertheless, we cannot exclude the possibility of residual confounding. For instance, no data on early-life exposures were available, and this issue requires further study. Second, the association between microvascular dysfunction and depressive symptoms may exist because late-life depressive symptoms may represent an early manifestation of (vascular) dementia (42). However, results were similar when we repeated the analyses after excluding persons with incident dementia. Third, it has been suggested that the association between cerebrovascular damage and depressive symptoms may be (partially) attributable to apathy (44). Apathy overlaps with depression, but it may be a distinct syndrome (45). We did not evaluate apathy, and this issue requires further study.

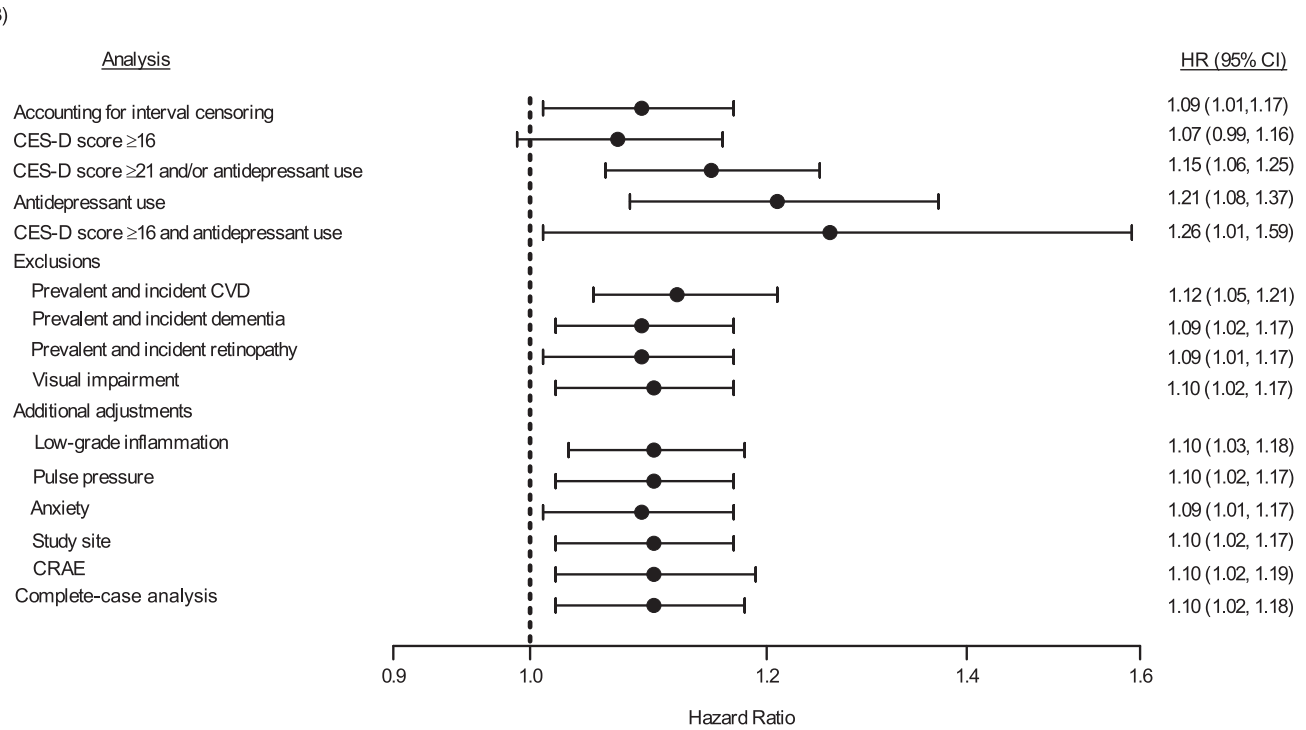

Figure 3. Additional analyses of the associations of baseline (visit 2) central retinal arteriolar equivalent (CRAE) (A) and central retinal venular equivalent (CRVE) (B) with incident depressive symptoms in the Multi-Ethnic Study of Atherosclerosis (MESA), 2002–2012. Results are reported for baseline CRAE and CRVE expressed per 1–standard-deviation increment at MESA visit 2. Additional analyses: 1) accounting for interval-censored time-to-event data using a parametric model; 2) depressive symptoms defined as Center for Epidemiologic Studies Depression Scale (CES-D) score ≥16, irrespective of use of antidepressant medication; 3) depressive symptoms defined as CES-D score ≥21 and/or new use of antidepressant medication; 4) depressive symptoms defined as new use of antidepressant medication, irrespective of CES-D score; 5) depressive symptoms defined as both CES-D score ≥16 and new use of antidepressant medication; 6) exclusion of persons with cardiovascular disease (CVD) at baseline or during follow-up (n = 555); 7) exclusion of persons with dementia at baseline or during follow-up (n = 188); 8) exclusion of persons with any signs of retinopathy at baseline or at visit 5 (n = 685); 9) exclusion of persons with visual impairment at baseline (n = 252); 10) additional adjustment for markers of low-grade inflammation; 11) additional adjustment for pulse pressure; 12) additional adjustment for anxiety; 13) additional adjustment for study site; 14) mutual adjustment for CRVE and CRAE; and 15) complete-case analysis (n = 3,999). All results were adjusted for age, sex, race/ethnicity, educational level, income level, diabetes, body mass index, smoking status, current alcohol use, total cholesterol:high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, diet index, physical activity, systolic blood pressure, use of antihypertensive medication, and CES-D score at visit 1. Bars, 95% confidence intervals (CIs). HR, hazard ratio.

In this study, there was a trend suggesting that a larger baseline CRAE might increase the risk of depressive symptoms, although these results should be interpreted with caution and require replication in other cohort studies. A larger baseline CRAE was borderline not statistically significant in the main analysis and sensitivity analyses. In a previous cross-sectional study, Nguyen et al. (46) found that persons with type 2 diabetes and concurrent depression had larger CRAE than those with type 2 diabetes without depression. In addition, retinal arteriolar widening has been related to a higher risk of the development of MRI features of cerebral small-vessel disease (13, 14, 17). Arteriolar widening might be related to cerebrovascular damage, because it may be accompanied by increased microvascular blood flow. An increased microvascular blood flow is believed to be protective at first, but it may also increase capillary pressure and eventually contribute to cerebrovascular damage (47, 48). However, some previous studies on cerebral diseases other than depression that may, in part, have a microvascular origin (e.g., lacunar and hemorrhagic stroke and dementia (6)) found an association with retinal arteriolar narrowing (25, 49) instead of widening. This issue therefore requires further study.

We did not find an association between change in CRAE and CRVE over a mean follow-up period of 7.8 years and depressive symptoms. However, CRAE and CRVE only minimally decreased in size during this period (mean percentage changes over time were 2.1 and 3.2, respectively), which may have hindered our ability to detect any associations. In addition, participants excluded from the analysis on change in CRAE and CRVE who only had data available on baseline CRAE and CRVE were older and had a worse cardiovascular risk profile than included participants. This may have led to a disproportional loss of people who were

probably at high risk for depression, which may have resulted in underestimation of the associations between change in CRAE and CRVE and depressive symptoms.

Limitations of the study

The present study had several limitations. First, depressive symptoms were assessed by means of a self-administered questionnaire, not a structured interview. Second, misclassification of incident depressive symptoms may have occurred, because antidepressant medication can also be prescribed for conditions other than depression. In addition, the CES-D questionnaire was not administered during the baseline visit of the present study (MESA visit 2). However, we excluded persons who had a CES-D score greater than or equal to 16 at MESA visit 1 and/or used antidepressant medication at MESA visit 1 or 2, and we adjusted for CES-D score prior to the baseline visit (MESA visit 1 in the present study) (50). Furthermore, the correlation between CES-D scores at the consecutive MESA study visits 3, 4, and 5 was relatively high (mean correlation coefficient across the visits = 0.53), which suggests that CES-D scores at visit 1 correlated with depressive symptoms at visit 2. This is consistent with findings from a previous review (51) which showed that middle-aged and older individuals commonly have a trajectory of persistent depressive symptoms, instead of the relapsing-remitting depressive symptoms trajectory that is more common in younger persons. Furthermore, when we defined the outcome by new use of antidepressant medication only (i.e., irrespective of CES-D scores, and with similar definition of the outcome at baseline and follow-up), results were consistent with the main analysis. Third, we had no information on the presence of depressive symptoms in the intervals between visits. The exact date of incident depressive symptoms was therefore not ascertained, which may have led to misclassification of time to incident depressive symptoms. However, results were similar when we repeated the analyses accounting for interval-censored time-to-event data. Fourth, the MESA study population consists mostly of middle-aged participants without prior cardiovascular disease whose cardiovascular risk factors are relatively well-controlled. In addition, participants excluded from the present analysis were older and had a lower educational level and a worse cardiovascular risk profile than those included. This may have led to underestimation of the reported findings due to lower variation in microvascular dysfunction and depressive symptoms. Fifth, a relatively large number of statistical tests were done. The aim of the present study was to investigate the associations between measures of cerebral microvascular dysfunction (CRAE and CRVE) and incident depressive symptoms, which, as a consequence, involves carrying out multiple tests. Sixth, no data were available on direct measures of cerebral microvascular function in the present study. Although retinal microvascular measures are considered a valid proxy for microvascular changes in the brain (10), we cannot exclude the possibility of measurement error bias, which may have led to underestimation of the association between cerebral microvascular dysfunction and incident depressive symptoms.

Conclusion

The present study showed that larger baseline CRVE, but not CRAE, is associated with a higher incidence of depressive symptoms.

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