Associations Between Depression and Anxiety Symptoms and Retinal Vessel Caliber in Adolescents and Young Adults

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Objective: Previous longitudinal studies suggest that depression and anxiety are associated with risk for cardiovascular disease. The aim of the present study was to test whether an association between depression and anxiety symptoms and retinal vessel caliber, an indicator of subclinical cardiovascular risk, is apparent as early as adolescence and young adulthood. **Methods:** Participants were 865 adolescents and young adults who participated in the Brisbane Longitudinal Twin Study and the Twin Eye Study in Tasmania. Participants completed an assessment of depression/anxiety symptoms (the Somatic and Psychological Health Report) when they were 16.5 years old (mean age), and they underwent retinal imaging, on average, 2.5 years later (range, 2 years before to 7 years after the depression/anxiety assessment). Retinal vessel caliber was assessed using computer software. **Results:** Depression and anxiety symptoms were associated with wider retinal arteriolar caliber in this sample of adolescents and young adults ($\beta = 0.09$, $p = .016$), even after adjusting for other cardiovascular risk factors ($\beta = 0.08$, $p = .025$). Multiple regression analyses revealed that affective symptoms of depression/anxiety were associated with retinal vessel caliber independently of somatic symptoms. **Conclusions:** Depression and anxiety symptoms are associated with measurable signs in the retinal microvasculature in early life, suggesting that pathological microvascular mechanisms linking depression/anxiety and cardiovascular disease may be operative from a young age. **Key words:** depression, anxiety, retinal vessel caliber, cardiovascular, adolescence, young adults.

SPHERE = Somatic and Psychological Health Report; **CRAE** = central retinal arteriolar equivalent; **CRVE** = central retinal venular equivalent; **BMI** = body mass index; **MABP** = mean arterial blood pressure; **MZ** = monozygotic; **DZ** = dizygotic.

INTRODUCTION

Longitudinal studies have shown that individuals with symptoms of depression and anxiety are at increased risk for developing cardiovascular disease, and this association persists after accounting for traditional cardiovascular risk factors (1–7). Depression has even been found to confer risk for coronary events up to 10 years later (2). This finding suggests that the pathophysiological mechanisms linking depression with cardiovascular disease may be operative years before the clinical manifestation of cardiovascular disease, and it highlights the need for studies of depression and anxiety and subclinical markers of cardiovascular disease in early life.

One increasingly recognized marker of early subclinical cardiovascular disease is the caliber of the retinal microvessels (8). Advances in digital retinal photography and retinal image computer analysis now allow for the accurate quantitative assessment of the condition of small retinal blood vessels in large population-based samples (8,9). Retinal microvessels can be used to gauge the health of the microcirculation because the retina shares anatomical and physiological features with other end organs (e.g., heart, brain, and kidneys) (10,11). Research has shown, for example, that retinal vessel caliber predicts risk of coronary heart disease, stroke, cerebral small vessel disease, cognitive impairment, and dementia (8,12–15).

Fewer than a dozen studies have examined associations of depression and anxiety with retinal vessel caliber (16–25) (Table 1). These studies have generally shown that adults with depression and/or anxiety exhibit deviations in retinal vessel caliber, either wider or narrower arterioles or venules, suggesting that microvascular abnormality may underlie the association between depression and anxiety symptoms and cardiovascular disease. However, these studies have primarily focused on older adults. Given mounting evidence that depression, anxiety, and cardiovascular disease have their roots in childhood (26–30), we tested whether an association between depression/anxiety symptoms and retinal vessel caliber is apparent as early as adolescence and young adulthood. In addition, because affective depression and anxiety symptoms often co-occur with somatic symptoms (i.e., fatigue and pain) (31) that may themselves be related to retinal vessel caliber, we differentiated between affective symptoms of depression/anxiety and somatic symptoms.

METHODS

Participants

Participants were members of the population-based Brisbane Longitudinal Twin Study, an ongoing longitudinal study of adolescent and young-adult monozygotic (MZ) and dizygotic (DZ) twin pairs and their siblings (32,33). As described in detail elsewhere (32,33), twins were initially recruited to the study from primary and secondary schools in South East Queensland in 1992, with new twins added at various intervals. All schools in South East Queensland

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TABLE 1. Studies of Depression and Anxiety and Retinal Vessel Caliber

Study	Study Sample	Analysis *N*	Mean Age or Age Range, y	Mental Health Index	Finding
1. Sun et al. (16)	Cardiovascular Health Study	2420	78.5	Short version of the CES-D	No association
2. Kim et al. (17)	Cardiovascular Health Study	1489	78.1	Short version of the CES-D	Depression associated with narrower arterioles
3. Nguyen et al. (18)	Clinic-based study of depressed (n = 34) and nondepressed (n = 27) individuals with Type 2 diabetes and healthy controls (n = 38)	99	56.5	DSM-IV criteria, Hamilton Depression Rating Scale, and Mattis Dementia Rating Scale	Some evidence that depression was associated with wider arterioles and venules.
4. Nguyen et al. (19)	Clinic-based study of depressed (n = 43) and nondepressed (n = 49) individuals with Type 2 diabetes and healthy controls (n = 54)	146	57.8	DSM-IV criteria, Hamilton Depression Rating Scale, Mini Mental State Exam	Depression associated with wider arterioles
5. Cheung et al. (20)	Atherosclerosis Risk in Communities Study	10,339	56.5	Vital exhaustion assessed with the Maastricht questionnaire	Vital exhaustion associated with wider venules
6. Ikram et al. (21)	Rotterdam Study	3605	66.1	Various (CES-D or Hospital Anxiety and Depression Scale, structured interview, general practitioner and pharmacy records)	No association
7. Jensen et al. (22)	Multi-Ethnic Study of Atherosclerosis	>6000	45–84	CES-D, Spielberger trait anxiety	Anxiety (but not depression) associated with narrower arterioles
8. Caspi et al. (23)	Dunedin Multidisciplinary Health and Development Study	1000	38	Structured diagnostic interviews used to create an internalizing latent factor indicated by depression, generalized anxiety disorder, fears/phobias	Internalizing associated with wider venules
9. Meier et al. (24)	Dunedin Multidisciplinary Health and Development Study	Subset of study members with persistent depression (n = 188) versus healthy controls (n = 412)	38	Structured diagnostic interviews used to diagnose persistent depression	Persistent depression associated with wider venules and narrower arterioles
10. Li et al. (25)	Growing Up in Singapore Towards Healthy Outcomes Study & In Vitro Fertilization Study	472–786	30.6 (26 wk of gestation)	Edinburgh Postnatal Depression Scale, State-Trait Anxiety Inventory, Pittsburg Sleeping Quality Index	Depression and poor sleep quality (but not anxiety) associated with wider arterioles

CES-D = Center for Epidemiologic Studies Depression Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
Studies are generally organized by date, with studies using the same sample appearing together. Note that analytic strategy and adjustment for other cardiovascular risks varied considerably across studies.

were approached, and all regions in South East Queensland were represented. Comparisons of this sample with other population-based samples suggest that this sample is representative with respect to a variety of traits, including, for example, personality (34) and retinal vessel caliber (35,36).

Mental health data were collected on up to four occasions between 2000 and 2013 as part of the study of skin mole development (37) as well as the study of cognition (32), and the study of health and well-being (32,33). A subset of participants also completed an extensive eye examination in 2004 to 2008 as part of the Twins Eye Study of Tasmania (38,39). Here we report on 865 participants for whom both mental health data (mean [standard deviation {SD}] age across assessments = 16.52 [2.96]) and eye examination (mean [SD] age = 19.07 [3.53] years) data were available. Although the eye examination was conducted, on average, 2.55 (SD = 1.57) years after the mental health assessment, the eye examination took place anywhere from 2 years before to as many as 7 years after the mental health assessment. The study was approved by the ethics committees of the Royal Victorian Eye and Ear Hospital, the Royal Hobart Hospital, and the QIMR Berghofer Medical Research Institute, as well as the Australian Twin Registry, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all of the participants or their legal guardians, with the participants' assent before examination.

Measures

Depression/Anxiety, Somatization, and Fatigue

The Somatic and Psychological Health Report (SPHERE) questionnaire is a 34-item self-report questionnaire that assesses common symptoms of depression, anxiety, and somatic distress (40–42). In addition to yielding a total score indexing overall mental health and well-being, the SPHERE yields subscale scores indexing primarily affective symptoms of depression/anxiety (14 items; e.g., "feeling irritable or cranky," "feeling unhappy and depressed," and "everything getting on top of you"), somatization (10 items; e.g., "joint pain" and "weak muscles"), and fatigue (9 items; e.g., "poor sleep," "prolonged tiredness after activity," and "poor concentration"). Participants indicated if they had been troubled by symptoms over the past few weeks.

The SPHERE has been shown to have adequate reliability and validity (33,40,41). Internal consistency reliability for the SPHERE and the depression/anxiety, somatization, and fatigue subscales was 0.89, 0.84, 0.70, and 0.75, respectively (40). A prior study showed that the SPHERE accurately identified 93% of individuals with current Diagnostic and Statistical Manual of Mental Disorder depression, anxiety, or somatoform disorders (41). Moreover, the depression/anxiety subscale shows substantial heritability (40%) and correlates strongly with the personality trait of neuroticism ($r = 0.64$) (40).

Item response theory analysis of the SPHERE items was implemented in WINBUGS2 (43) to estimate latent liability scores reflecting a) liability to depression/anxiety (based on the 14 items of the SPHERE depression/anxiety subscale; 1 item overlaps with somatization, and 3 items overlap with fatigue), b) liability to somatization (based on the 10 items of the SPHERE somatization subscale; 1 item overlaps with fatigue), c) liability to fatigue (based on the 9 items of the SPHERE fatigue subscale), and d) poor overall mental health and well-being (based on all 34 items of the SPHERE). High scores on the latent liability indexes reflect that participants endorsed many symptoms. Liability to depression/anxiety was significantly correlated with liability to somatization ($r = 0.54$) and fatigue ($r = 0.70$), and liability to somatization and fatigue were also significantly correlated ($r = 0.63$). Each subscale was significantly correlated with poor overall mental health (0.90, 0.69, and 0.87, respectively).

More than half of the participants ($n = 479$) had completed the SPHERE on more than one occasion as part of different studies (details published previously (40)). Data were collected only once for 386 participants (45%), twice for 152 (17%), three times for 233 (27%), and four times for 94 participants (11%). For participants who had completed the SPHERE on multiple occasions, we averaged the latent liability scores over occasions and took an "average age" at assessment. Our rationale for aggregating the SPHERE data was that an aggregate estimate would be more reliable and accurate than an estimate from any single occasion.

Retinal Vessel Caliber

As described elsewhere (39,44), all of the twins had 10° stereoscopic optic disk–centered photographs using a Nidek 3-Dx/F fundus camera (Nidek) after dilatation of the pupils with tropicamide 1% or cyclopentolate 1%. Photographs were digitalized, and retinal vessel caliber was measured with computer-assisted software (IVAN; University of Wisconsin, Madison, WI) according to a standardized protocol (45). Two trained graders, masked to participant characteristics, performed the vessel measurements on the optic disk–centered image for both eyes for all of the participants. The largest six arterioles and venules coursing through a zone between half to 1 disk diameter from the optic disk margin were measured. Estimates were summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), representing the average caliber (diameter) of arterioles and venules of the eye, respectively, using a revised Knudtson-Parr-Hubbard formula (46). Reliability of the retinal vessel measurement has been published elsewhere (44). Intragrader variation was assessed in 67 randomly selected retinal photographs. The intragrader intraclass correlation coefficient was 0.95 for CRAE and 0.99 for CRVE. Intergrader reliability was assessed in 52 randomly selected retinal images, and the interclass correlation coefficient was 0.93 for CRAE and 0.98 for CRVE. The correlation between CRAE and CRVE was 0.51 ($p < .001$).

Covariates

Smoking status and body mass index (BMI) were included as covariates, as they are associated with both retinal vessel caliber and mental health, in this sample and in others (8,9,47–50). Spherical equivalent and axial length were included as covariates to adjust for any potential effects of these parameters on retinal vessel caliber (45,51). Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A167) shows correlations of these covariates with vessel caliber and mental health. All analyses also controlled for age and sex. Covariates were assessed at the time of the eye examination.

BMI was calculated as kilograms per meter squared. For participants who were missing either height or weight data or both (12%; $n = 102$), we imputed the missing data using the multiple imputation procedure in SAS (SAS Institute, Inc, Cary, NC). Axial length was measured using the IOL Master, and refractive errors were measured using a Humphrey-598 automatic refractor (Carl Zeiss Meditec, Inc, Miami, FL). Spherical equivalent was calculated using the standard formula of the algebraic sum of the dioptric powers of the sphere and half of the cylinder (38).

Statistical Analysis

To examine associations between mental health and retinal arteriolar caliber, we conducted separate linear regressions predicting arteriolar caliber from each mental health risk factor (i.e., we considered each predictor [depression/anxiety, somatization, fatigue, and overall mental health] individually). Associations between each predictor and retinal arteriolar caliber were initially adjusted for the effects of age and sex (Model 1) and then further adjusted for the effects of smoking status, BMI, sphericity, and axial length (Model 2). We then repeated these analyses with venular caliber as the outcome. We report standardized β coefficients from these analyses. To account for participants' familial relatedness (the nonindependence of observations), robust standard errors were computed using the SURVEYREG procedure in SAS (SAS Institute, Inc). This procedure downwardly adjusts the degrees of freedom based on the number of twin pairs in the analysis, taking into account that information obtained about one twin is related to information obtained about the cotwin.

RESULTS

Descriptive statistics for measures of mental health and retinal vessel caliber are presented in Table 2.

Table 3 shows associations between each mental health predictor and vessel caliber. Liability to depression/anxiety was associated with arteriolar ($\beta = 0.09$, $p = .016$) but not venular caliber ($\beta = 0.00$, $p = .90$) (Table 3, Model 1). Specifically, adolescents and young adults with a greater number of depression/anxiety symptoms showed wider arteriolar caliber (Fig. 1). A similar pattern of associations was observed for somatization, fatigue, and overall mental health, although effects for somatization and fatigue did not reach statistical significance. Notably, associations were unchanged after controlling for smoking status, BMI, sphericity, and axial length (Table 3, Model 2).

As an additional check of these associations, we reran Model 2 analyses while also controlling for mean arterial blood pressure (MABP; calculated as 2/3 diastolic + 1/3 systolic blood pressure) in a subset of participants ($n = 291$) who had their blood pressure taken as part of an earlier study (mean age = 14.27 years). MABP was associated with narrower arterioles ($r = -0.18$, $p = .004$), consistent with previous research, but was not associated with depression/anxiety ($r = -0.01$), somatization ($r = -0.01$), or fatigue ($r = 0.03$). As such, associations between mental health measures and arteriolar caliber were unchanged from before to after controlling for MABP. For example, the association between depression/anxiety and arteriolar caliber was $\beta = 0.08$ before and after controlling for MABP.

TABLE 2. Measures of Mental Health and Retinal Vessel Caliber

Measure	Full Sample (n = 865)		Girls (n = 495)		Boys (n = 370)	
	M	SD	M	SD	M	SD
SPHERE (range)						
Depression/Anxiety subscale (0–14)	3.69	3.13	3.76	3.20	3.58	3.03
Somatization subscale (0–10)	1.62	1.59	1.63	1.66	1.61	1.50
Fatigue subscale (0–9)	2.95	1.98	2.83	1.95	3.10	2.01
Overall mental health (0–34)	8.62	5.71	8.61	5.78	8.63	5.61
Retinal vessel caliber, μm						
Arterioles	165.27	12.94	165.27	13.69	165.28	11.89
Venules	249.54	17.96	248.81	18.51	250.52	17.17

SPHERE = Somatic and Psychological Health Report; M = mean; SD = standard deviation.
Note that means for SPHERE and retinal vessel caliber match published means for the larger studies from which these participants were drawn (38–40).

Finally, to determine whether affective symptoms of depression/anxiety were associated with arteriolar caliber over and above somatic symptoms, we examined a model including depression/anxiety, somatization, and fatigue as simultaneous predictors of arteriolar caliber. (Smoking status, BMI, sphericity, axial length, age, and sex were included as covariates.) The association between depression/anxiety and arteriolar caliber was unchanged after additionally controlling for somatization and fatigue (β = 0.08), although this association did not reach statistical significance (p = .099).

DISCUSSION

We found that adolescents and young adults with symptoms of depression/anxiety had wider retinal arteriolar caliber. This is the first study, to our knowledge, to demonstrate an association between depression/anxiety and retinal vessel caliber in a young, otherwise healthy population. Our finding is of interest because although depression and anxiety first develop in adolescence (52), cardiovascular diseases are typically not apparent until years later. Our finding, therefore, adds to a small but growing body of literature suggesting that the pathophysiological mechanisms linking depression and anxiety with cardiovascular disease may be operative from a young age (53–56), possibly at the level of the microvasculature.

The specific pathophysiological mechanisms underlying wider arteriolar caliber are not entirely understood, but one hypothesized mechanism is endothelial dysfunction (impairment of nitric oxide–mediated vasodilation). Wider retinal arteriolar caliber is a sign of impaired autoregulation (57) and has been shown to be associated with reduced flicker-induced vasodilation (58). Notably, endothelial dysfunction is seen in individuals with depression and anxiety (5,56,59). For example, a meta-analysis reported a statistically significant overall correlation of 0.19 between depressed mood and reduced flow-mediated dilation in adults (59). Recent studies of children and adolescents have also shown an association between depression and anxiety and impaired endothelial function assessed using the EndoPAT device (54–56). Moreover, a study using arterial spin labeling technology demonstrated that adolescents diagnosed with depression showed altered cerebral perfusion (60), which could be consistent with impaired autoregulation. These findings further strengthen the possibility that abnormal vascular processes linking depression and anxiety to later cardiovascular disease may begin in childhood.

TABLE 3. Associations Between Measures of Mental Health and Retinal Vessel Caliber

SPHERE Liability Score	Arterioles						Venules					
	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Depression/Anxiety	**0.09**	.037	.016	**0.08**	.036	.025	0.00	.037	.90	−0.01	.035	.72
Somatization	0.06	.035	.072	0.06	.035	.090	0.04	.035	.22	0.02	.034	.63
Fatigue	0.06	.035	.099	0.05	.034	.11	0.00	.035	.94	−0.01	.033	.71
Overall mental health	**0.08**	.036	.024	**0.08**	.036	.028	0.00	.038	.99	−0.02	.036	.67

SPHERE = Somatic and Psychological Health Report; β = standardized β coefficients; SE = robust standard error.
Note: Results are from ordinary least squares regressions predicting arteriolar and venular caliber from each SPHERE liability score, with separate regressions conducted for each SPHERE liability score.
Statistically significant associations are bolded.
[a] Model 1 controls for age and sex.
[b] Model 2 controls for age, sex, smoking status, body mass index, sphericity, and axial length.

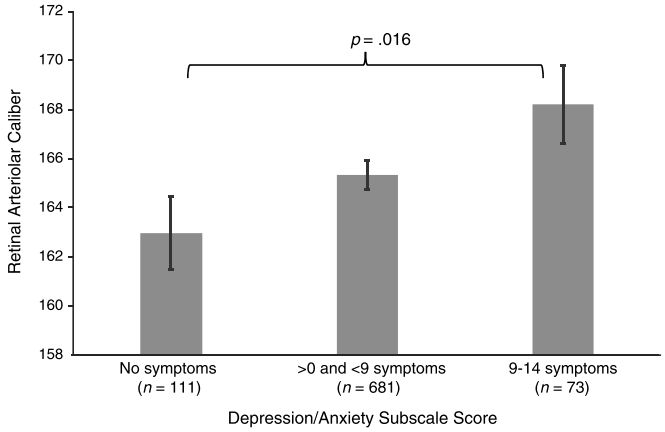

Figure 1. Association between depression/anxiety and retinal arteriolar caliber. Adolescents and young adults with a greater number of depression and anxiety symptoms showed wider arteriolar caliber. Note that depression symptoms were grouped such that the first and third categories roughly correspond to the bottom and top deciles of the sample. Raw means, unadjusted for covariates, are presented. The *p* value indicates the results of a *t* test comparing the group with no symptoms with the group with 9+ symptoms. Error bars = robust standard errors.

Our finding of an association between depression/anxiety and wider arteriolar caliber in adolescents and young adults is generally consistent with three other studies of adults (18,19,25), but findings in adults are inconsistent. A few studies of adults have shown an association between depression and narrower (rather than wider) arteriolar caliber and/or wider venular caliber (Table 1). The reasons for the discrepancies across studies of adults are uncertain, but inconsistent findings may be attributable to methodological differences between studies, such as the age and overall physical health of the sample. Older adults have a higher prevalence of vascular risk factors that exert opposing influences on the microvasculature. For example, hypertension-induced arteriolar narrowing and sclerosis in older adults could obscure the effects of pathological vascular processes that might cause wider arteriolar caliber. The relative healthiness of the adolescents and young adults in the current study reduces the chances of such confounding by other cardiovascular risks. Another possible explanation for the mixed findings is that wider arteriolar caliber might reflect an early emerging microvascular abnormality, whereas wider venular caliber could reflect a more entrenched pathological process. Prospective longitudinal studies are needed to address this question.

A limitation of the current study is that retinal vessel caliber was not assessed concurrently with depression/anxiety symptoms, which may have attenuated their association. We note, however, that the association between depression/anxiety and retinal arteriolar caliber was unchanged when we restricted the analyses to participants ($n = 345$) for whom retinal imaging and depression/anxiety data were collected within 1 year of each other ($\beta = 0.09$ in this subsample compared with the full sample estimate of $\beta = 0.09$). A second limitation is that we only measured retinal vessel caliber at a single time point, and therefore, we cannot determine the temporal ordering of depression/anxiety symptoms and wider arteriolar caliber. The directional and causal nature of the association remains unclear. For example, wider arterioles may be a consequence of depression/anxiety. Conversely, depression/anxiety symptoms may result from wider arterioles or from shared mechanisms that contribute to both. A related limitation is that we did not use the twin design to determine whether common genetic or environmental factors contribute to the association between depression/anxiety and retinal vessel caliber. Studies from this sample (as well as others) have shown that genetic factors play a significant role in retinal vessel caliber (39) and depression/anxiety (40). Moreover, a study of adult twins found a modest genetic correlation between depression and coronary artery disease (61). Thus, a natural question is whether the genetic factors underlying depression/anxiety and retinal vessel caliber overlap. The cross-twin, cross-trait correlations were fairly similar for MZ and DZ twins in this sample (MZ = 0.09, −0.01; DZ = 0.10, 0.12), suggesting a role for shared-environmental influences in the association between depression/anxiety and arteriolar caliber. However, these correlations were too small to reliably parse genetic and environmental influences.

Third, we did not distinguish between depression and anxiety symptoms or assess clinically diagnosable depression and anxiety. Thus, it is unclear whether retinal vessel caliber may show differential associations with depression and anxiety symptoms or whether results will apply to those meeting diagnostic criteria for depression and anxiety disorders. Depression and anxiety disorders tap both affective and somatic symptoms, however, leaving some researchers to question whether somatic symptoms drive the association between depression and anxiety and cardiovascular disease (62,63). A strength of our study is that we were able to distinguish between affective and somatic symptoms, and a multiple regression analysis suggested that affective symptoms of depression/anxiety may be useful indicators of cardiovascular risk. Nonetheless, ongoing data collection in our twins (33) will enable us to examine the association between retinal vessel caliber and clinical indices of depression and anxiety as well as provide a more powerful means of modeling direction of causation.

This study has a number of implications. First, our finding that generally healthy adolescents and young adults with depression/anxiety symptoms have wider arteriolar caliber suggests that depression/anxiety-associated cardiovascular risk may have its roots in childhood. Second, affective symptoms of depression/anxiety may identify youth at risk for cardiovascular disease. Therefore, routine screening for affective symptoms of depression and anxiety may be important for the cardiovascular health of young people as well as older adults (64). Third, retinal imaging is a simple, non-invasive, and cost-effective approach to assessing microvascular health in children, adolescents, and adults. Future research can use retinal imaging to address a variety of important questions. For example, longitudinal studies can address whether increases in depression and anxiety symptoms track with increases in retinal arteriolar caliber, and treatment studies can address whether improvement in depressive and anxiety symptoms is associated with changes in arteriolar caliber. In summary, we provide initial evidence

that adolescents and young adults with depression/anxiety symptoms show microvascular abnormality, a finding that adds to a growing body of research suggesting that the link between depression/anxiety and cardiovascular disease dates back to childhood.

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