Published in final edited form as:

J Pediatr. 2018 August ; 199: 85–91. doi:10.1016/j.jpeds.2018.03.059.

Relationships of Anxiety and Depression with Cardiovascular Health in Youth with Normal Weight to Severe Obesity

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Abstract

Objective—To evaluate the relationships of depression and anxiety symptoms with CVD risk factors and measures of vascular health in youth. Major Depressive Disorder and Bipolar Disorder are considered cardiovascular disease (CVD) risk factors in youth.

Study design—Participants (n=202) were 8-18-year-olds from a cross-sectional study evaluating cardiovascular health across a wide range of BMI values (normal weight to severe obesity). CVD risk measurement included blood pressure, fasting lipids, glucose, insulin, carotid artery intima-media thickness, compliance and distensibility, brachial artery flow-mediated dilation, carotid-radial artery pulse wave velocity, body fat percentage, and a metabolic syndrome cluster score. Anxiety and depression symptoms were self-reported on the Screen for Child Anxiety Related Disorders and Center of Epidemiological Studies Depression Scale for Children. Two sets of adjustment variables were used in evaluation of differences between those with and without anxiety or depression symptomatology for the CVD risk factor and vascular outcomes. The first set included adjustment for Tanner stage, sex, and race; the second additionally adjusted for percent body fat.

Results—Anxiety was not significantly associated with CVD risk factors or vascular health in either model. Depression was associated with HDL cholesterol, triglycerides, and metabolic syndrome cluster score; these relationships were attenuated when accounting for percent body fat.

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Portions of this study were presented at Obesity Week 2017, October 29-November 2, 2017, National Harbor, Maryland.

The other authors declare no conflicts of interest.

Conclusions—When accounting for body fat, we found no clear relationship of self-reported depression or anxiety symptoms with CVD risk factors or vascular health in youth.

Keywords

cardiovascular disease; pediatrics; mental health

According to the American Heart Association (AHA), pediatric conditions that portend moderate-risk for cardiovascular disease (CVD) are those associated with pathological, physiologic, or subclinical evidence of accelerated atherosclerosis.(1) These conditions include, Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease, HIV, and nephrotic syndrome.(1) The AHA designated Major Depressive Disorder and Bipolar Disorder as tier II (moderate) cardiovascular disease risk conditions.(2) The recent addition of Major Depressive Disorder and Bipolar Disorder to the moderate-risk classification calls attention to the need for further characterization of the relationship between CVD risk and other forms of depression, as well as other mental health conditions such as anxiety, in children and adolescents.(3)

Several pathophysiological factors may contribute to the association between mental health conditions and CVD risk. Specifically, inflammation,(4) oxidative stress,(5) and autonomic dysfunction(6) have been offered as possible systemic processes that underlie the mental health-CVD association. Inflammation, a key factor in the development of CVD, has been shown to have a bidirectional relationship with depression and childhood adversity.(2, 4) Oxidative stress is often increased in those with mental health disorders, which is notable given the relationship between oxidative stress and CVD progression.(5) Depressed individuals tend to have worse autonomic function compared with those who are not depressed; and as depression increases, autonomic function worsens.(7) Moreover, autonomic dysfunction may lead to many downstream complications such as hypertension in youth.(8) The cumulative effect of these pathophysiological changes associated with mental health problems may hasten the progression of CVD.(2)

Existing evidence suggests the relationship between mental health and CVD risk is strongest among individuals who meet diagnostic criteria for a Major Depressive Disorder and Bipolar Disorder.(2) It is less clear, however, if other forms of depression or other mental health conditions are associated with heightened CVD risk in children and adolescents. The purpose of the current study was to evaluate the relationship between self-reported depression and anxiety symptoms and CVD risk factors, cardiac autonomic function, and vascular structure and function in children and adolescents representing a wide range of age, pubertal maturation, and obesity status.

Methods

Participants included in this analysis were children and adolescents 8-18 years old who had normal weight, overweight/obesity or severe obesity. They were part of a larger cross-sectional study evaluating endothelial health. Participants were recruited from general pediatric clinics at the University of Minnesota, the University of Minnesota Pediatric Weight Management Clinic and the broader community. Exclusion criteria were: obesity

from a known genetic cause, history of bariatric surgery, illness or significant injury in previous 2 weeks, type 1 diabetes mellitus, familial hypercholesterolemia, chronic kidney disease/end-stage renal disease, Kawasaki disease, autoimmune inflammatory diseases, congenital heart disease, or recent (within 3-months) use of medications known to affect endothelial health such as statins, ACE-inhibitors, PPAR-gamma agonists, or 3rd generation beta blockers. All parents/legal guardians and participants provided informed consent and assent, respectively. The University of Minnesota Institutional Review Board approved the protocol and study procedures.

All testing was performed in the morning after the participants had been fasting (including no caffeine consumption) for a minimum of 12 hours. Height and weight were determined using a wall-mounted stadiometer and an electronic scale, respectively. BMI was calculated as the body weight in kilograms divided by the height in meters squared. BMI percentiles were determined using age- and sex-based definitions from the Centers for Disease Control and Prevention. Normal-weight was defined as 5th to <85th percentile, overweight/obesity was defined as 85th to <120% of the 95th percentile, and severe obesity was defined as 120% of the 95th percentile or an absolute BMI $\geq 35 \text{ kg/m}^2$ (11). Total and regional body composition was measured using dual x-ray absorptiometry (iDXA; GE Healthcare Lunar, Madison, WI, USA) and analyzed using enCore software (platform version 16.2, GE Healthcare, Madison, WI). Participants were scanned using standard imaging and positioning protocols while fasting. Tanner stage was determined by a trained pediatrician or registered nurse. Seated blood pressure and heart rate were measured after the participant had been resting quietly without legs crossed for 10 minutes. Three consecutive measurements were taken with an automated brachial cuff at approximately 3-minute intervals and the average of the 3 respective measurements was used for analysis. Lipid, glucose and insulin values were determined with standard methods by the University of Minnesota, Fairview Diagnostic Laboratory.

The SphygmoCor MM3 system (AtCor Medical, Sydney, Australia) was used to measure supine heart rate variability after participants had been at rest for approximately 10 minutes. The electrocardiogram signal was continuously recorded throughout the 15-minute data collection period. Only data collected during the last five minutes were used for analysis, and this segment was reviewed for ectopic heartbeats or arrhythmias. Any portions of the selected segment with abnormal electrocardiogram signals were excluded from analysis. Automated algorithms were used to calculate the standard deviation of the RR interval (SDRR), low frequency, high frequency, and the low frequency to high frequency (LF:HF) ratio, all of which are metrics of the overall sympathovagal balance of the autonomic nervous system. Low values of the SDRR and high values of LF:HF are suggestive of a state of elevated sympathetic tone and/or reduced parasympathetic tone.

All vascular testing was performed in the Vascular Biology Laboratory in the University of Minnesota Clinical and Translational Science Institute in a quiet, temperature-controlled environment (22-23°C). Artery images were measured by a non-invasive ultrasound with participants in the supine position. All images were digitized and stored on a personal computer for later off-line analysis of carotid artery intima-media thickness (cIMT), compliance and distensibility, as well as brachial artery flow-mediated dilation (FMD).

Electronic wall-tracking software was used for the analysis (Vascular Research Tools 5, Medical Imaging Application, LLC, Iowa City, IA, USA).

Following 15 minutes of quiet rest in the supine position, vascular images were obtained of the carotid artery using a conventional ultrasound scanner (Acuson, Sequoia 512, Siemens Medical Solutions USA, Inc, Mountain View, CA, USA) with a 15-8 MHz linear array probe held at a constant distance from the skin and at a fixed point over the imaged artery. The transducer was held at a constant distance from the skin and at a fixed point over the common carotid artery, approximately 1-cm proximal from the carotid bifurcation bulb, to capture the left common carotid artery's lumen diastolic and systolic diameters and cIMT. Depth and gain settings were set to optimize images of the lumen/arterial wall interface. Systolic and diastolic blood pressures were recorded with an automated blood pressure device during the 10-second carotid measurements. The ultrasound scanning system was interfaced with a standard personal computer equipped with a data acquisition card for attainment of radio frequency ultrasound signals from the scanner. Images were collected at 20 frames per second for 10-seconds (200 frames) to ensure the capture of full arterial diameter change during a cardiac cycle. Carotid elasticity properties were calculated using previously published formulas.(12)

Endothelial function was expressed by brachial artery flow-mediated dilation (FMD). FMD was measured via standard ultrasound using a 8-15 MHz linear array transducer to obtain B-mode images (Siemens, Sequoia 512, New York, NY) following current guidelines.(13) An electronic wall-tracking software program (Medical Imaging Applications, Coralville, IA) was used for the measurement of brachial artery diameter and blood flow. Following baseline measurements, a blood pressure cuff was placed on the forearm (distal to the imaged area) and inflated to a supra-systolic level (>200mmHg) for 5 minutes. After 5 minutes, cuff occlusion was released and B-mode ultrasound images were captured for approximately three minutes after release. The maximum diameter recorded following reactive hyperemia was reported relative to baseline vessel diameter ($FMD\% = \frac{\text{peak diameter} - \text{baseline diameter}}{\text{baseline diameter}}$). The same group of sonographers conducted the measurements under the supervision of the same laboratory director throughout. Our laboratory has previously documented satisfactory FMD reproducibility. (14)

Carotid-radial artery pulse wave velocity (PWV) was measured by the SphygmoCor MM3 system. Pulse wave velocity was calculated as distance divided by transit time. Pulse wave transit time increases in stiffer arterial segments; therefore, higher values of PWV represent increased arterial stiffness.

A metabolic syndrome cluster score was calculated as previously reported.(15) The score was determined by using the average of standardized deviates of the primary components of the metabolic syndrome (i.e., the sum of the five sample z scores of waist circumference, triglycerides, inverse HDL-cholesterol, mean arterial pressure, and homeostasis model of insulin resistance (HOMA-IR) divided by 5).(16) A higher sample z-score indicates that the components tend to cluster in the higher sections of the sampling distributions, i.e., represent overall higher risk among the study participants included here.

Anxiety was assessed using the Screen for Child Anxiety Related Disorders (SCARED). The SCARED is a 41-item self-report measure of anxiety symptoms experienced in the prior 3 months, wherein items are answered using a 3-point Likert-type scale.⁽¹⁷⁾ Scores range from 0-82 and, according to the SCARED, a score of at or above 25 is suggestive of anxiety. Missing responses were imputed for those missing four or fewer responses by question subgroup using the mean in the subgroup of the non-missing responses. For those missing more than four responses, anxiety was left as missing.

Depression was assessed using the Center for Epidemiological Studies Depression Scale for Children (CES-DC). The CES-DC is a self-report measure including 20 items that participants rate on 4-point Likert-type scale regarding their symptoms for the prior week.⁽¹⁸⁾ Scores range from 0-60. Based on the CES-DC, a score at or above 16 is suggestive of depression. Missing responses were imputed for those missing fewer than two responses using the mean of their non-missing responses. Responses were left as missing if two or more were missing.

Descriptive characteristics were calculated for the sample overall and separately for those with and without each of anxiety and depression using mean (SD) for continuous variables and N (%) for categorical variables. Two sets of adjustment variables were used to evaluate the mean differences between those with and without anxiety or depression for each of the cardiometabolic outcomes using generalized estimating equations. The first set (Model 1) adjusted for Tanner stage, sex, and race (i.e., white vs. other); the second set (Model 2) additionally adjusted for percent body fat. Although a measure of BMI has clinical utility, it is an estimate of body composition. Therefore, percent body fat was used as a covariate. Confidence intervals and p-values were evaluated based on robust variance estimation. All statistical analyses were performed using R v3.3.1.⁽¹⁹⁾

Results

There were 202 participants (52% male; mean age 12.7 years) who had complete or imputed scores on SCARED or CES-DC (Table 1). Approximately half of the sample was classified as having normal weight and almost one third were in Tanner stage 1 pubertal development. The mean composite score for the 196 participants who had scores for SCARED was 16.5 (± 13.0) and 50 (26%) of these scored at or above the threshold suggestive of anxiety. For the 201 participants who had scores for CES-DC, the mean composite score was 11.2 (± 8.6) and of these 47 (23%) scored at or above the threshold suggestive of depression. Additional information regarding participant demographics as well as cardiovascular and metabolic results are presented in Table I.

When controlling for Tanner stage, sex, and race, there were no significant relationships between anxiety symptomatology and the measures of cardiovascular disease risk ($p > 0.05$, Table 2). In Model 1, depression symptomatology was significantly associated with HDL, triglycerides and the metabolic syndrome cluster score; however, these findings were no longer significantly associated when additionally controlling for percent body fat in Model 2 (Table 3). In fact, when controlling for percent body fat, almost no outcomes were significantly associated with anxiety or depression symptomatology ($p > 0.05$, Model 2,

Tables 2 and 3), the only exception being anxiety symptomatology associated with an increase in carotid artery cross sectional compliance (cCSC; $P = .039$, Model 2, Table 2).

In addition to analyzing these results using a dichotomous cutoff for anxiety and depression symptomatology, the data were analyzed with depression and anxiety as continuous variables using the composite scores with imputation (tables not included). Findings were materially similar with one exception; carotid artery cross sectional distensibility (cCSD) was higher with increased depressive symptoms when measured continuously. We also evaluated the data by separating younger and older participants (ie, 13 years and older vs. under 13). There were no appreciable differences in findings when analyzing the data by age groups (tables not included).

Discussion

In the current study, significant associations were observed between depression symptomatology and two components of the metabolic syndrome score along with the score itself. However, these associations were not significant after controlling for body fat percentage. Further, no relationships were observed between anxiety symptomatology and CVD risk factors or vascular health. These findings suggest that, at least during childhood, the correlation between depression and anxiety symptomatology with CVD risk factors and vascular health may be emerging but that excess adiposity may play a greater role in exacerbating risk.

Although the relationship between mental health and CVD risk in adulthood has been well described,(20) less is known of these associations in children. Similar to adults, the association between severe mental health concerns (e.g., diagnosed disorders, suicide attempts) and CVD events (e.g., CVD-related mortality) in youth is considered more established than milder forms of depression or anxiety and CVD risk.(2) Two population-based studies that included older adolescents and young adults, conducted in the United States and Taiwan, found that diagnoses of depression, bipolar disorder, or anxiety were associated with increased CVD and CVD-related mortality.(21, 22) In a longitudinal study following participants from age 9 to 21 years old, depression diagnoses, depressive symptoms, and number of depressive episodes were associated with C-reactive protein (CRP) levels; however, cumulative depressive episodes were most strongly related with elevated CRP levels even after controlling for other variables (e.g., BMI, nicotine use).(23) In a longitudinal study of self-reported depressive symptoms and endothelial function in 15-19 year old females, current, but not prior, depressive symptoms predicted endothelial function (i.e., pulse-wave amplitude).(24) In cross-sectional research with adolescents, depressive symptoms are associated with some, but not all, measures of CV health and/or endothelial function.(25, 26) Considering prior evidence, it is notable that the current study found associations between depression symptoms over the prior week (as asked on the CES-DC) and some CVD risk factors, even though these were non-significant after controlling for percent body fat.

Less is known about the relationship between anxiety and CVD risk in childhood. In children with anxiety disorders, a more severe anxiety symptom profile was associated with

a greater number of CVD risk factors.(27) Interestingly, in a study using multiple measures of anxiety, increased anxiety symptoms reported on the Pediatric Anxiety Rating Scale was associated with greater waist circumference and percent body fat, yet anxiety symptoms as measured by SCARED were not associated with CVD risk factors.(27) Similarly, in the current study, SCARED results were not significantly associated with CVD risk factors or measures of vascular health.

Most prior studies either used measures of BMI or body fat as an outcome or controlled for these variables in statistical analyses. Those that have included BMI/body fat as an outcome often find a positive association with mental health symptoms; those that control for these variables often find that it at least attenuates relationships between mental health and other CVD risk factors. In the current study, controlling for percent body fat attenuated the relationships between depression symptomatology and components of metabolic syndrome. Inconsistent with prior literature, the current results did not show any clear relationships after controlling for body fatness, even in areas where others had found associations (e.g., depression and PWV).(25) One of the advantages of the current study was our ability to study a wide age-range of children, including those as young as age 8. In contrast, prior research has often focused on adolescents up to young adults when considering the relationship between childhood mental health concerns and CVD risk. The relatively younger age group in the current study may help explain our observations. That is, CVD development is likely occurring long before it can be observed in hard clinical or laboratory signs.(28) However, it should be noted that the results of our study were materially the same when younger children versus adolescents were analyzed separately.

Several strengths and limitations of this study are worth discussing. In addition to the wide age- and BMI-range, this was a well-characterized cohort of participants who underwent a comprehensive panel of cardiovascular measures. Though comprehensive, the current cardiovascular variables included clinical and laboratory measures of risk, rather than end-stage CVD (e.g., heart attack, stroke), which has been more clearly related to mental health concerns than earlier risk factors. Notably, it is quite uncommon for a child to reach the point of end-stage CVD, and therefore, it is not a practical measure to use for this population. Furthermore, the goal is to intervene before the point of end-stage disease. Another limitation of the study was our inability to measure additional variables that potentially contribute to the association between mental health and vascular health, for example, sleep, tobacco use, menstrual cycle, physical activity, diet, inflammation and/or oxidative stress. Given the array of factors measured in the current study, statistical analyses included multiple comparisons, which can increase the likelihood of Type I error. Although the cardiovascular panel was comprehensive, a limitation of the current study was the use of self-report questionnaires of depression and anxiety without a clinical interview or formal diagnosis. Consistent with prior research, symptomatology did not result in significant associations with CVD risk when controlling for percent body fat; these associations are more commonly found in the presence of a formal diagnosis of anxiety or depressive disorders. However, the use of self-report measures in research has practical implications given their clinical utility in gathering information regarding potential diagnoses and determining intervention strategies. In clinical practice, elevations on such measures may warrant close monitoring so that if mental health concerns persist or escalate, both mental

health interventions and preventive guidance related to CVD (e.g., diet and physical activity recommendations) can be provided.

Our study was cross-sectional and did not include follow-up time-points. Furthermore, we observed associations between depression symptomatology and some CVD risk factors before controlling for percent body fat. Therefore, there is a possibility that those with increased mental health symptoms may eventually begin to demonstrate additional clinical or laboratory signs of CVD risk over time. Given the potential plasticity of the cardiovascular system during childhood, our results could be a reflection of physiological compensation for increased stress from depression and/or anxiety symptomatology on the cardiovascular system. Because physiological plasticity may decrease with age, childhood represents a potential window of opportunity for intervention to improve symptoms of depression and/or anxiety before vascular changes emerge and become resistant to change. Longitudinal studies will be required to answer these important questions, as they would allow for the monitoring of disease progression as well as identify opportunities for intervention.

Acknowledgments

Funded by the National Heart, Lung, and Blood Institute/NIH (R01HL110957), the National Center for Advancing Translational Sciences/NIH (UL1TR000114), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/NIH NORC (P30 DK050456). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. A.K. receives research support (drug/placebo) from Astra Zeneca Pharmaceuticals and serves as a consultant for Novo Nordisk, Orexigen, and Vivus Pharmaceuticals but does not accept personal or professional income for these activities. C.F. receives research support from Novo Nordisk.

List of Abbreviations

BMI	Body Mass Index
CES-DC	Center for Epidemiological Studies Depression Scale for Children
CVD	cardiovascular disease
FMD	flow-mediated dilation
SCARED	Screen for Child Anxiety Related Disorders

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Table 1

Participant characteristics.

Covariate	Overall (N=202)	Above Anxiety Threshold (N=49)	Below Anxiety Threshold (N=144)	Above Depression Threshold (N=47)	Below Depression Threshold (N=151)
Race:					
American Indian and Alaskan Native Only	3 (1.5%)*	2 (4.1%)	1 (0.7%)	2 (4.3%)	1 (0.7%)
Asian Only	2 (1.0%)	1 (2.0%)	1 (0.7%)	1 (2.1%)	1 (0.7%)
Black Only	10 (5.0%)	3 (6.1%)	6 (4.2%)	3 (6.4%)	6 (4.0%)
Multiple Races Selected	11 (5.4%)	4 (8.2%)	7 (4.9%)	2 (4.3%)	8 (5.3%)
Other Race Selected Only	4 (2.0%)	0 (0.0%)	3 (2.1%)	1 (2.1%)	3 (2.0%)
White Only	172 (85.1%)	39 (79.6%)	126 (87.5%)	38 (80.9%)	132 (87.4%)
Latino/Hispanic	24 (11.9%) [†]	3 (6.1%)	20 (13.9%) [†]	5 (10.6%)	18 (11.9%) [†]
Male	104 (51.5%)	14 (28.6%)	85 (59.0%)	17 (36.2%)	84 (55.6%)
Tanner Stage:					
1	64 (31.7%)	15 (30.6%)	47 (32.6%)	16 (34.0%)	47 (31.1%)
2	41 (20.3%)	9 (18.4%)	28 (19.4%)	9 (19.1%)	32 (21.2%)
3	33 (16.3%)	9 (18.4%)	21 (14.6%)	7 (14.9%)	26 (17.2%)
4	34 (16.8%)	7 (14.3%)	27 (18.8%)	5 (10.6%)	28 (18.5%)
5	30 (14.9%)	9 (18.4%)	21 (14.6%)	10 (21.3%)	18 (11.9%)
Grouped Tanner Stage:					
1	64 (31.7%)	15 (30.6%)	47 (32.6%)	16 (34.0%)	47 (31.1%)
2-4	108 (53.5%)	25 (51.0%)	76 (52.8%)	21 (44.7%)	86 (57.0%)
5	30 (14.9%)	9 (18.4%)	21 (14.6%)	10 (21.3%)	18 (11.9%)
BMI Classification:					
Normal Weight	101 (50.0%)	19 (38.8%)	80 (55.6%)	15 (31.9%)	86 (57.0%)
Overweight/Obese	53 (26.2%)	12 (24.5%)	36 (25.0%)	15 (31.9%)	37 (24.5%)
Severe Obese	44 (21.8%)	16 (32.7%)	26 (18.1%)	15 (31.9%)	26 (17.2%)
Missing	4 (2.0%)	2 (4.1%)	2 (1.4%)	2 (4.3%)	2 (1.3%)
Age (Yrs)	12.7 (2.64)	12.8 (3.01)	12.7 (2.55)	12.9 (2.96)	12.7 (2.54)
Height (cm)	156 (14.7)	155 (15.8)	156 (14.4)	156 (15.1)	156 (14.6)

Covariate	Overall (N=202)	Above Anxiety Threshold (N=49)	Below Anxiety Threshold (N=144)	Above Depression Threshold (N=47)	Below Depression Threshold (N=151)
Weight (kg)	62.4 (29.7)	68.5 (35.4)	59.8 (27.3)	70.9 (32.5)	59.5 (28.5)
DXA % Body Fat	34.2 (11.7) ^{2,7}	38.1 (9.97)	32.5 (12.0) ²	40.4 (9.74)	32.2 (11.7) ²
BMI	24.7 (8.6)	27.0 (9.67)	23.8 (8.14)	27.9 (9.29)	23.7 (8.23)
BMI Percentile	71.7 (30.0)	80.0 (25.1)	67.6 (31.3)	82.6 (25.1)	67.5 (30.6)
PWV (m/s)	6.54 (1.14) ²	6.49 (0.96)	6.54 (1.18) ²	6.52 (0.95)	6.53 (1.2) ²
LDL (mg/dL)	85.4 (24.7) ⁴	88.5 (22.4) ¹	83.9 (25.7) ³	90.5 (26.0)	83.1 (24.0) ⁴
VLDL (mg/dL)	19.6 (9.58) ^{4,5}	20.9 (8.95) ¹¹	19.2 (9.88) ^{3,2}	21.0 (9.13) ⁸	19.1 (9.73) ^{3,7}
HDL (mg/dL)	50.8 (13.3) ⁴	49.0 (14.5) ¹	51.9 (13.0) ³	46.5 (12.3)	52.4 (13.5) ⁴
Triglycerides (mg/dL)	94.6 (46.2) ⁵	99.5 (43.1) ¹	92.1 (46.3) ⁴	107 (47.5)	90.2 (45.1) ⁵
Cholesterol Ratio	3.38 (0.96) ^{4,5}	3.58 (0.98) ¹¹	3.28 (0.95) ^{3,2}	3.58 (0.87) ⁸	3.28 (0.98) ^{3,7}
NN50	142 (70.6) ¹¹	144 (80.2) ¹	141 (68.5) ⁹	145 (82.3) ²	140 (66.6) ⁹
PNN50	45.3 (23.8) ¹¹	45.4 (26.4) ¹	44.9 (23.4) ⁹	47.8 (27.6) ²	44.2 (22.6) ⁹
HR Mean (ms)	902 (138.2) ¹¹	898 (145.3) ¹	901 (133.5) ⁹	901 (165.8) ²	903 (130.7) ⁹
RMS SDD	95.7 (58.5) ¹¹	94.9 (60.1) ¹	96.5 (59.5) ⁹	113 (75.8) ²	90.1 (51.5) ⁹
LF Max (Hz)	0.09 (0.03) ¹¹	0.09 (0.03) ¹	0.09 (0.03) ⁹	0.08 (0.03) ²	0.09 (0.03) ⁹
HF Max (Hz)	0.27 (0.07) ¹¹	0.27 (0.08) ¹	0.27 (0.06) ⁹	0.26 (0.07) ²	0.27 (0.07) ⁹
LF/HF Ratio	0.88 (0.85) ¹²	0.92 (0.85) ¹	0.85 (0.84) ⁹	0.82 (0.77) ²	0.9 (0.88) ¹⁰
LF Power Normalized	39.1 (18.5) ¹¹	39.8 (20.1) ¹	38.7 (17.9) ⁹	38.2 (17.7) ²	39.5 (18.9) ⁹
HF Power Normalized	60.9 (18.5) ¹¹	60.2 (20.1) ¹	61.3 (17.9) ⁹	61.8 (17.7) ²	60.5 (18.9) ⁹
FMD Max (%)	9.23 (4.06) ^{3,9}	9.57 (4.08) ¹⁰	9.16 (4.13) ^{2,7}	9.39 (3.79) ¹¹	9.17 (4.18) ^{2,6}
FMD Peak Dilation (%)	7.32 (3.87) ^{3,7}	7.56 (3.68) ¹⁰	7.3 (3.96) ^{2,5}	7.59 (3.89) ¹⁰	7.23 (3.91) ^{2,5}
FMD AUC	687 (484.2) ^{3,7}	667 (464.6) ¹⁰	702 (497.9) ^{2,5}	729 (488.4) ¹⁰	672 (486.8) ^{2,5}
Average cIMT	0.54 (0.04) ¹³	0.54 (0.04) ³	0.54 (0.05) ⁹	0.53 (0.04) ³	0.54 (0.05) ¹⁰
Average cDD	14.1 (2.75) ⁶	13.9 (2.75)	14.1 (2.79) ⁵	14.6 (2.87)	13.9 (2.72) ⁶
Average cCSD	30.2 (6.32) ⁶	29.8 (6.29)	30.2 (6.43) ⁵	31.6 (6.59)	29.7 (6.24) ⁶
Average cDC	0.02 (0.0) ⁸	0.02 (0.0)	0.02 (0.0) ⁷	0.02 (0.0) ¹	0.02 (0.0) ⁷
Average cCSC1	0.16 (0.05) ⁶	0.17 (0.04)	0.16 (0.06) ⁵	0.17 (0.08)	0.15 (0.04) ⁶
Average cCSC2	0.01 (0.0) ⁷	0.01 (0.0)	0.01 (0.0) ⁶	0.01 (0.0) ¹	0.01 (0.0) ⁶
Average cIEM	1042 (302.1) ⁶	1054 (333.3)	1041 (295.6) ⁵	1011 (328.4)	1054 (297.2) ⁶

Covariate	Overall (N=202)	Above Anxiety Threshold (N=49)	Below Anxiety Threshold (N=144)	Above Depression Threshold (N=47)	Below Depression Threshold (N=151)
MetS Cluster	-0.16 (0.72) ⁸	-0.06 (0.75) ¹	-0.21 (0.72) ⁷	0.06 (0.68)	-0.24 (0.72) ⁸
Diastolic BP Percentile	34.4 (21.1) ¹	33.7 (18.6)	34.5 (22.1) ¹	33.6 (21.4)	34.6 (21.2) ¹
Systolic BP Percentile	54.4 (28.3) ¹	55.2 (30.1)	53.5 (27.7) ¹	57.5 (28.9)	52.8 (27.8) ¹
Composite Scores without Imputation:					
SCARED	16.2 (12.8) ⁴³	35.3 (9.13) ¹¹	10.3 (6.33) ²³	26.9 (13.9) ¹¹	13.2 (10.7) ²⁹
CES-DC	10.9 (8.44) ¹⁷	16.6 (8.61) ⁶	8.58 (6.42) ¹⁰	23.6 (8.04) ⁷	7.38 (4.07) ⁶
Composite Scores with Imputation:					
SCARED	16.5 (13.1) ¹⁴	35.6 (8.72) ²	10.2 (6.39) ⁴	27.7 (13.7) ⁶	13.2 (11.0) ⁸
CES-DC	11.3 (8.63) ³	16.8 (8.62) ¹	9.02 (6.84) ²	23.6 (7.85)	7.39 (4.04)

* Values expressed are mean (SD) or N (%) where indicated.

[†] Superscripts indicate number of subjects missing a given covariate.

Table 2

Adjusted differences in cardiometabolic outcomes between those with and without anxiety.

Outcome	Model 1*			Model 2		
	Difference	95% CI	P-value	Difference	95% CI	P-value
LDL (mg/dL)	-0.22	(-9.58,9.14)	0.964	-1.37	(-10.59,7.84)	0.770
VLDL (mg/dL)	0.19	(-3.80,4.19)	0.924	-1.87	(-5.61,1.87)	0.326
HDL (mg/dL)	-2.13	(-6.87,2.60)	0.377	0.63	(-3.58,4.84)	0.768
Triglycerides (mg/dL)	2.21	(-13.24,17.65)	0.780	-6.30	(-21.34,8.75)	0.412
Cholesterol Ratio	0.08	(-0.37,0.52)	0.737	-0.14	(-0.51,0.22)	0.440
RMS SDD	-4.02	(-24.72,16.67)	0.703	-1.91	(-22.39,18.57)	0.855
LF/HF Ratio	0.17	(-0.15,0.48)	0.296	0.14	(-0.18,0.46)	0.392
PWV (m/s)	-0.08	(-0.45,0.28)	0.652	-0.03	(-0.39,0.34)	0.888
FMD Peak Dilatation (%)	0.52	(-1.02,2.07)	0.505	-0.01	(-1.52,1.50)	0.991
FMD AUC (%.sec)	31.62	(-165.65,228.89)	0.753	-24.06	(-222.95,174.82)	0.813
Average cIMT (mm)	0.01	(-0.01,0.02)	0.482	0.00	(-0.01,0.02)	0.574
Average cCSD (%)	-0.10	(-2.57,2.36)	0.936	-0.03	(-2.51,2.46)	0.982
Average cCSC (mm ² /mmHg × 10 ⁻³)	0.01	(0.00,0.03)	0.061	0.02	(0.00,0.03)	0.039
Average cIEM (mmHg)	26.84	(-100.55,154.24)	0.680	-8.06	(-128.27,112.14)	0.895
MetS Cluster	0.17	(-0.10,0.44)	0.208	-0.03	(-0.22,0.16)	0.766
Diastolic BP Percentile	0.07	(-7.47,7.62)	0.985	-1.77	(-9.04,5.49)	0.632
Systolic BP Percentile	0.78	(-10.02,11.58)	0.888	-3.10	(-13.04,6.83)	0.541

* Model 1 (adjusted for TANNER grouping, sex, and race) and Model 2 (adjusted for TANNER grouping, sex, race, and percent body fat) using robust variance estimation.

Table 3

Adjusted differences in cardiometabolic outcomes between those with and without depression.

Outcome	Model 1*			Model 2		
	Difference	95% CI	P-value	Difference	95% CI	P-value
LDL (mg/dL)	4.06	(-5.16,13.28)	0.388	2.26	(-7.83,12.36)	0.660
VLDL (mg/dL)	2.00	(-1.56,5.56)	0.271	-0.47	(-3.76,2.81)	0.777
HDL (mg/dL)	-6.64	(-10.63, -2.66)	0.001	-2.47	(-6.05,1.12)	0.177
Triglycerides (mg/dL)	18.04	(2.19,33.89)	0.026	5.06	(-10.87,20.98)	0.534
Cholesterol Ratio	0.27	(-0.11,0.65)	0.167	-0.01	(-0.34,0.33)	0.970
RMS SDD	12.11	(-11.63,35.85)	0.318	17.53	(-6.11,41.16)	0.146
LF/HF Ratio	-0.03	(-0.33,0.27)	0.854	-0.10	(-0.41,0.21)	0.536
PWV (m/s)	0.17	(-0.17,0.51)	0.322	0.24	(-0.12,0.60)	0.184
FMD Peak Dilation (%)	0.36	(-1.14,1.86)	0.638	-0.25	(-1.71,1.21)	0.734
FMD AUC (%.sec)	79.71	(-111.71,271.13)	0.414	27.41	(-157.09,211.91)	0.771
Average cIMT (mm)	0.00	(-0.02,0.01)	0.853	0.00	(-0.02,0.01)	0.815
Average cCSD (%)	1.04	(-1.21,3.28)	0.365	1.39	(-1.09,3.87)	0.273
Average cCSC (mm ² /mmHg × 10 ⁻³)	0.01	(-0.01,0.02)	0.239	0.01	(0.00,0.02)	0.166
Average cIEM (mmHg)	-9.21	(-120.27,101.86)	0.871	-74.32	(-193.49,44.84)	0.222
MetS Cluster	0.33	(0.10,0.56)	0.005	0.01	(-0.15,0.18)	0.881
Diastolic BP Percentile	-1.15	(-8.52,6.21)	0.759	-4.68	(-11.96,2.60)	0.207
Systolic BP Percentile	3.25	(-6.68,13.19)	0.521	-3.65	(-13.29,5.99)	0.458

* Model 1 (adjusted for TANNER grouping, sex, and race) and Model 2 (adjusted for TANNER grouping, sex, race, and percent body fat) using robust variance estimation