THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

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

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Objective To evaluate the relationships of depression and anxiety symptoms with cardiovascular disease (CVD) risk factors and measures of vascular health in youth. Major depressive disorder and bipolar disorder are considered CVD risk factors in youth.

Study design Participants (n = 202) were 8- to 18-year-olds from a cross-sectional study evaluating cardiovascular health across a wide range of body mass index 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 for 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 was 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 high-density lipoprotein cholesterol, triglycerides, and metabolic syndrome cluster score; these relationships were attenuated when accounting for percent body fat.

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. *(J Pediatr 2018;■■:■■-■■).*

According to the American Heart Association, pediatric conditions that portend moderate risk for cardiovascular disease (CVD) are those associated with pathologic, physiologic, or subclinical evidence of accelerated atherosclerosis.[1] These conditions include Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease, human immunodeficiency virus, and nephrotic syndrome.[1] The American Heart Association designated major depressive disorder and bipolar disorder as tier II (moderate) CVD 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 pathophysiologic 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 pathophysiologic changes associated with mental health problems may hasten the progression of CVD.[2]

BMI	Body mass index
CES-DC	Center for Epidemiological Studies Depression Scale for Children
CVD	Cardiovascular disease
FMD	Flow-mediated dilation
PWV	Pulse wave velocity
SCARED	Screen for Child Anxiety Related Disorders

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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. The other authors declare no conflicts of interest.

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

https://doi.org10.1016/j.jpeds.2018.03.059

Existing evidence suggests that 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 ages, pubertal maturations, and obesity statuses.

Methods

Participants included in this analysis were children and adolescents 8-18 years of age 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, angiotensin-converting enzyme inhibitors, peroxisome proliferator activated receptor-gamma agonists, or third-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. Body mass index (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 of ≥35 kg/m^2.[9] Total and regional body composition was measured using dual x-ray absorptiometry (GE Healthcare Lunar, Madison, Wisconsin) and analyzed using enCore software (platform version 16.2, GE Healthcare). 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 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 5 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 SD of the RR interval, low frequency, high frequency, and the low frequency to high frequency ratio, all of which are metrics of the overall sympathovagal balance of the autonomic nervous system. Low values of the SD of the RR interval and high values of low frequency to high frequency ratio 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°C-23°C). Artery images were measured by a noninvasive ultrasound examination 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, 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, Iowa).

After 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, California) 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 carotid artery intima-media thickness. 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 the attainment of radiofrequency 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.[10]

Endothelial function was expressed by brachial artery FMD. FMD was measured via standard ultrasound using a 8-15 MHz linear array transducer to obtain B-mode images (Siemens,

FLA 5.5.0 DTD ■ YMPD9908_proof ■ May 10, 2018