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Depressive Symptoms and Subclinical Markers of Cardiovascular Disease in Adolescents

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Abstract

Purpose—To examine the association between depressive symptoms and subclinical markers of cardiovascular disease (CVD), specifically arterial stiffness, as indexed by pulse wave velocity (PWV), and carotid artery intima thickening (IMT), in a sample of healthy adolescents, and to explore adolescent hostility as a potential moderator of depression on subclinical markers of CVD.

Methods—One hundred and fifty-seven ($n = 157$) black and white adolescents between the ages of 16–21 completed a follow-up study of psychosocial stress and cardiovascular risk factors that included measures of PWV and carotid IMT. Psychosocial measures included the Center for Epidemiologic Studies Depression Scale (CES-D; divided into tertiles), and the Cook-Medley Hostility Inventory subscales. Linear regression models controlled for sociodemographic variables, health behaviors, blood pressure, body mass index, and heart rate.

Results—Results show that more severe depressive symptoms were associated with higher levels of PWV ($B = 0.17$, $R^2 = 0.30$, $\Delta R^2 = 0.03$, $CI = 2.2 - 47.0$, $p = .03$) but not with higher IMT. Adolescent depression remained a significant predictor of PWV when controlling for adolescent hostility; hostility did not moderate the relationship between adolescent depression and PWV.

Conclusions—Depression may be important in the development of arterial stiffness in adolescence. Further research is needed to delineate the relationship in adolescence and young adulthood between depressive symptoms and the pathogenesis of CVD.

Keywords

depression; adolescents; hostility; pulse wave velocity; cardiovascular disease

Depression is a debilitating and burdensome mental health condition, due to its high prevalence, chronic nature, and associated physical health conditions that contribute to lost productivity and high costs of medical care¹⁻². The relationship between depression and chronic health conditions, such as heart disease, asthma, diabetes, and arthritis, has been highlighted for its public health significance, as depression often develops earlier in the lifespan than do most progressive health conditions³. While the association between depression and chronic physical illness has been firmly documented in the empirical literature, the mechanisms accounting for the association remain unclear⁴. Physiological mechanisms, shared etiological factors, and poor health behaviors have been proposed to account for this relationship⁵.

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The association between depression and cardiovascular disease (CVD) has been well established in adult populations⁶, but has been largely understudied in younger samples. Large epidemiological studies, such as Growth and Health Study and the National Longitudinal Study of Adolescent Health, have found associations between adolescent depressive symptoms and increased physical health problems⁷, greater health care service utilization⁸, and increased risky health behaviors⁹ in young adulthood. Short-term longitudinal studies have found associations between depression in older adolescents (ages 15-21) and chronic illness in early adulthood¹⁰ and depression and self-reported illness in adolescents over a 1-year period¹¹. More recently, Keenan-Miller and colleagues¹² found an association between early-onset depression (prior to age 15) and negative health outcomes in young adulthood (after age 20) in a population based sample of 705 adolescents.

Both arterial stiffness and carotid artery intima media thickening (IMT) are non-invasive measures of subclinical CVD that are strongly associated with future CVD events. Increased arterial stiffness is associated with hypertension, renal failure, and decreased cardiac functioning in adults¹³. Similarly, increased IMT is associated with atherosclerotic lesions in the vasculature, and may be related to increased risk for myocardial infarction (MI)¹⁴. Research on adults indicates associations between depression and subclinical markers of CVD. A population-based study of late life depression¹⁵ found increased arterial stiffness in adults endorsing depressive symptoms, and an even stronger association between arterial stiffness and adults with current DSM-IV diagnoses of depression. Results from the Cardiovascular Health Study suggest that depressive symptoms in adults aged 65 and older are associated with increased risk for the development of carotid artery atherosclerosis, as indexed by greater IMT, over a 3-year period¹⁶. Similarly, Pollitt and colleagues¹⁷ found that hopelessness, a symptom of depression, and hostility, a negative mood state that often accompanies depression¹⁸, were both associated with increased IMT in middle-aged men over a 4-year-period.

A smaller body of empirical research suggests that early indicators and risk factors of CVD are detectable in youths that can predict arterial stiffness and carotid artery IMT in adulthood. Findings from the Bogalusa Heart Study, the longest and most detailed community-based study of black and white children, indicate that the heart disease, atherosclerosis, and coronary heart disease begin in childhood, with some documented anatomic changes between the ages of 5-8¹⁹⁻²⁰. Autopsy studies demonstrate the beginnings of atherosclerosis in children and adolescents, evidenced by atherosclerotic lesions in the aorta and coronary vessels, as well as changes in the kidney vasculature that are strongly associated with risk factors for CVD²¹. In addition, psychosocial risk factors in youths, such as low socioeconomic status (SES), and hostility, have also been associated with increased arterial stiffness over time, and to a lesser degree increased IMT²²⁻²³.

To date, there has been little research on depression in adolescents and subclinical markers of risk for future CVD. The purposes of this study were 1) to investigate the associations between depressive symptoms and subclinical indices of CVD, including arterial stiffness, as indexed by pulse wave velocity (PWV), and carotid artery IMT, while adjusting for important sociodemographic, clinical, and psychological covariates, and 2) to perform exploratory analyses on the potentially moderating effect of hostility on the association between depressive symptoms and these CVD markers. We hypothesized that adolescents with higher self-reported depressive symptoms would have greater arterial stiffness and greater IMT. Given the associations between hostility and depression in adolescents²⁴⁻²⁵, and between hostility and subclinical indices of CVD^{17, 23}, we also explored the relationship between depressive symptoms and hostility in adolescents, and the association between depressive symptoms in relation to hostility and PWV and IMT. We specifically examined whether hostility moderated any associations between depression and PWV and IMT.

Method

Participants

One-hundred fifty-seven adolescents between the ages of 16-21 participated in the present follow-up study of stress and cardiovascular-related health outcomes. They were from a sample of 213 adolescents recruited from two high schools in Pittsburgh, Pennsylvania when they were between the ages of 14-16. Adolescents who expressed interest in the study provided researchers with contact information, and both parents and adolescents were interviewed to determine adolescent eligibility for the study. Adolescents were ineligible for study enrollment if they or their parents reported that they had a history of cardiovascular or renal disease, substance use, or psychiatric illness; parent-reported weight more than 80% of ideal norms for age and gender; an unwillingness to abstain from smoking 12 hours prior to testing; and if they were currently using of prescription medications known to affect the cardiovascular system such as corticosteroids. Both parents and adolescents provided informed consent to participate in this study, which was conducted with approval from the University of Pittsburgh's Institutional Review Board.

Approximately 3.3 years later ($SD = 0.83$; range = 1.5 – 5.9), 157 adolescents (68 blacks and 71 whites; 65 females and 74 males) from the original study participated in a follow-up assessment of laboratory-based cardiovascular functioning and subclinical markers of CVD. Measures of adolescents' weight, height, resting blood pressure, and heart rate (the mean of three seated measurements taken after a 5-minute rest) were also collected at the time of laboratory procedures. Adolescents completed a battery of questionnaires, including a self-report of depressive symptoms, hostility, and physical activity. Of these participants, 18 were excluded from PWV models ($n = 139$) due to missing PWV data ($n = 17$) and missing parent education level data ($n = 1$), and 4 were excluded from IMT models ($n = 153$) due to missing IMT ($n = 1$), missing parent education level ($n = 2$), and missing blood pressure data ($n = 1$). There were no significant differences between those included vs. those not included in the present investigation in regard to demographic data or questionnaire measures.

Measures

Depressive Symptoms—The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item inventory that assesses the frequency of depressive symptoms in the previous week. Symptoms of depression are rated on a 4-point scale (0 – 3), with higher numbers reflecting more frequent depressive symptoms. The CES-D provides a continuous score of depression (range 0 – 60). This instrument has been used in a variety of settings and has demonstrated construct validity in its ability to screen for the presence of depressive disorders²⁶⁻²⁷. Because of strong positive skewness in the present sample, adolescents' CES-D scores were divided into tertiles reflecting depression severity: low (mean = 4.8, $SD = 1.8$, range 0-7), moderate (mean = 10.9, $SD = 1.9$, range 8-14), and high (mean = 21.6, $SD = 7.4$, range 15-47). These categories closely correspond to clinical use of the CES-D, in that scores 16 or greater typically indicate the presence of clinically significant depressive symptoms²⁶⁻²⁷.

Hostility—A subset of items from the Cook and Medley Hostility Inventory²⁸ was used to assess cynicism, hostile affect, and aggressive responding in adolescents. This measure was comprised of 26-items from the Minnesota Multiphasic Personality Inventory that loaded onto factors related to CVD incidence²⁹. The summary score for Total Hostility Scale in this modified version was highly correlated with the Total Hostility Scale of the full scale ($r = 0.93$).

Pulse Wave Velocity—Pulse wave velocity was calculated to measure arterial stiffness, based on the principle that faster time for pressure waves travel from the aorta to a standardized destination point is a marker of stiffer arterial vessels. Blood pressure readings were recorded using an automated device (Dinamap, Critikon Company, Tampa, FL) and subsequently, two nondirectional transcutaneous Doppler flow probes (Model 810-a, 10 Mhz, Parks Medical Electronics, Aloha, OR) were used to obtain simultaneous Doppler flow signals from the right carotid and femoral arteries, respectively. Three data collection runs were obtained, each recording 20 seconds of simultaneous carotid and femoral flow waveforms. Data were collected and scored using software developed by the Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging.

PWV was calculated by dividing the distance traveled by the time differential between simultaneous waveforms from the carotid and femoral arteries (cm/ second), with higher PWV indicating stiffer vessels. Distance traveled between the carotid and femoral sites was measured using a metal tape measure and calculated. The time differential was calculated by averaging the waveforms from the carotid and femoral arteries and determining the time from the R-wave to foot of each waveform. Reliability in calculating PWV using this method within this laboratory is high (intraclass correlation = 0.72-0.86). The average PWV scores obtained on this sample were lower than those reported for obese adolescents³⁰⁻³¹ and lower than those reported for young adults participating in the Bogalusa Heart Study¹⁹.

Intima Media Thickness—Intima media thickness (IMT) was assessed via B-mode ultrasound images from four locations on each of the right and left common carotid arteries. Trained technicians at the University of Pittsburgh Ultrasound Research Laboratory scanned the circumferences of the right and left common carotid arteries from the near and far walls of the distal common carotid artery, far walls of carotid bulbs, and internal carotid artery using a 5.0 MHz linear array transducer and Toshiba SSA-270A scanner (Toshiba American Medical Systems, Tustin, CA). The lumen-intima interface and the media-adventitia interface were traced electronically across a 1-cm segment, and the computer generated a measurement for each pixel over this area using reading software developed for the Cardiovascular Health Study modified in Pittsburgh. Readings were conducted in a setting with careful quality control measures (e.g., temperature control) and with a high level of reliability between technicians (intraclass correlation = 0.91 – 0.99). A single IMT score was obtained by averaging the eight carotid artery readings obtained at the different locations, with higher scores reflecting greater IMT thickness. Mean IMT indices for this sample was consistent with those found in other samples of healthy adolescents³², and were slightly higher than those found in younger samples, comprised of more prepubertal children³³, as expected.

Covariates—*Race* was self-identified, and categorized as Caucasian or African-American. *Body-Mass Index* (BMI) was calculated as body weight (kg) divided by height² (m²). *Smoking status* was ascertained by self-report: 21 adolescents identified as current smokers, 114 adolescents identified as current nonsmokers, and 22 adolescents had unknown smoking status and served as the referent group. *Physical activity* was assessed using three items from the Youth Risk Behavior Survey³⁴ that ask adolescents about the frequency of physical exercise (e.g., aerobic exercise, stretching, strength building) over the past seven days. These items were summed to create a single score of physical activity, with higher numbers indicating more frequent physical activity. *Parent Education* was assessed via parental interview and in the context of quantifying SES. The highest year of education that either parent completed was categorized as low (high school or less), moderate (associates degree/ some college), and high (college degree or more).

Statistical Analysis—Differences in sample characteristics based upon severity of depressive symptoms were examined using one-way Analysis of Variance (ANOVA) and Chi-Square statistics, as appropriate. Relationships between sample characteristics and outcome measures were determined by Pearson's first-order correlations.

The association between depression and subclinical markers of CVD were examined via multiple linear regressions. Based upon previously documented relations with PWV and IMT^{18-23, 30-33}, age, race, sex, BMI, parent education, smoking status (current smoker, current nonsmoker; unknown), physical activity, mean resting systolic blood pressure (SBP), and mean resting heart rate (HR) were included as covariates and entered into Step 1 of each model; depression was entered into Step 2 of each model. Multiple linear regressions were repeated to determine the relationship between depression and PWV or IMT after accounting for concurrent hostility scores. Covariates were entered into Step 1 of each model, hostility scores were entered into Step 2, and depression was entered into Step 3 of each multiple linear regression model. Two dummy coded variables were also created to explore the effects of adolescent depressive severity on subclinical markers of CVD. These dummy coded variables compared the effects of depression for adolescents with either (a) moderate or (b) high depressive symptoms, with adolescents with low depressive symptoms.

Second, exploratory analyses were conducted to determine whether adolescent hostility moderated any association between depressive symptoms and PWV or IMT. Two interaction terms, the products of hostility and the dummy coded variables for depression severity, were entered into Step 3 of each regression model. Adolescent hostility was centered in order to reduce nonessential multicollinearity introduced by the interaction terms.

Results

Participant Characteristics

Sample characteristics for adolescents by strata of depressive symptoms are presented in Table 1. Significant differences between adolescents' PWV and hostility scores based upon severity of depressive symptoms emerged: adolescents with high depressive symptoms had higher PWV and higher hostility scores as compared to adolescents with low depressive symptoms (see Figure 1). As reported elsewhere^{22, 35}, significant associations were found between PWV and race ($r = .21$, $p = .01$), BMI ($r = 0.26$, $p = .001$), parent education level ($r = -0.22$, $p = 0.01$), and SBP ($r = 0.41$, $p = .00$). IMT was significantly correlated with race ($r = .17$, $p = .04$), with African American adolescents having higher IMT than their Caucasian peers, and with SBP ($r = .25$, $p = .001$).

Depression and Subclinical Markers of CVD

A significant relationship between depressive symptoms and PWV was found ($B = 0.17$, $R^2 = 0.30$, $\Delta R^2 = 0.03$, $CI = 2.2 - 47.0$, $p = .03$), after adjusting for age, race, sex, BMI, parent education, smoking status, physical activity, SBP, and HR. More severe depressive symptoms were associated with higher PWV in this sample of adolescents. Results from regressions with dummy coded variables indicated a significant association between the highest depression score group and higher levels of PWV in adolescents ($B = 0.20$, $R^2 = 0.31$, $\Delta R^2 = 0.03$, $CI = 4.3 - 94.1$, $p = .03$) and a nonsignificant relationship between the moderate depression score group and PWV ($B = 0.14$, $R^2 = 0.31$, $\Delta R^2 = 0.03$, $CI = -7.6 - 80.5$, $p = .10$). The relationship between depression and PWV was next examined after accounting for total hostility scores in the same model (see Table 2). Depressive symptoms continued to demonstrate a significant relationship with PWV and accounted for a significant increase in variance explained in predicting PWV.

No significant relationship between depressive symptoms and IMT emerged ($B = -0.02$, $R^2 = 0.13$, $\Delta R^2 = 0.00$, $CI = -0.01 - 0.01$, $p = .83$). Results from regressions using dummy coded variables indicated no significant associations between IMT and depression in adolescents endorsing the highest depression scores ($B = -0.01$, $R^2 = 0.12$, $\Delta R^2 = 0.00$, $CI = -0.02 - 0.01$, $p = .92$) or in adolescents endorsing moderate depression scores ($B = -0.03$, $R^2 = 0.12$, $\Delta R^2 = 0.00$, $CI = -0.02 - 0.01$, $p = .80$).

Hostility as a Moderator of Depression on Subclinical Markers of CVD

Hostility did not significantly moderate the association between adolescent depressive symptoms and PWV, for either moderate severity depressive symptoms ($B = -0.08$, $R^2 = 0.24$, $\Delta R^2 = 0.01$, $CI = -58.7 - 18.1$, $p = .30$) or severe depressive symptoms ($B = -0.07$, $R^2 = 0.24$, $\Delta R^2 = 0.01$, $CI = -45.4 - 16.5$, $p = .36$).

Similarly, there were no significant interactions found between adolescents' moderate depressive symptoms ($B = -0.01$, $R^2 = 0.13$, $\Delta R^2 = 0.00$, $CI = -.01 - .01$, $p = .96$) or severe depressive symptoms ($B = -0.02$, $R^2 = 0.13$, $\Delta R^2 = 0.00$, $CI = -.01 - .01$, $p = .78$) and hostility in predicting IMT.

Discussion

This paper first examined the association between adolescent depressive symptoms and two subclinical markers of CVD, PWV and IMT, while controlling for important sociodemographic, clinical, and psychological covariates. Results suggest that higher depressive symptoms were associated with higher rates of PWV among adolescents. Findings suggest that depressive symptoms may be associated with early changes in the functioning of the cardiovascular system. Elevated depressive symptoms, as with other types of psychosocial risk factors, may increase activity of the sympathetic nervous system, resulting in higher resting systolic blood pressure and heart rate which are known risk factors for arterial stiffness³⁶. However, SBP and HR did not account for the observed relationship between depression and PWV in the current study. Elevated depressive symptoms may also contribute to subclinical CVD through other biologic mechanisms, such as inflammatory processes and enhanced activation of the hypothalamic pituitary adrenal axis, as well as behavioral mechanisms, such as poor diet and poor social support⁵. Although this study cannot inform putative mechanisms by which depression affects arterial stiffness, it provides preliminary support for future investigations of depression and other markers of cardiovascular function.

The second aim of this paper was to explore the potential for adolescent hostility to moderate associations between depressive symptoms and subclinical markers of CVD. Results indicate hostility did not moderate the relationship between depression and PWV, as depressive symptoms accounted for unique variance in predicting PWV. Both depression and hostility may have significant roles in the development of CVD and may cause substantial burden to functioning over time. Subsequent longitudinal research is necessary to explore the co-occurring relationship between hostility and depression across development and their subsequent implications for health outcomes.

Depression was not associated with IMT in adolescents, diverging from what is known about the association between depression and IMT in adults⁸. This finding suggests that an association between depression and structural changes ('thickening') in the carotid artery may be too early to be detected in vasculature of healthy adolescents. Indeed, it has been proposed that arterial stiffness assessed by PWV may begin earlier in life than structural changes in the carotid artery as assessed by IMT³⁷. At the same time, the relationship between depressive symptoms and arterial thickening may be more evident in adolescents

who experience more chronic and severe depressive disorders that contribute to more sedentary activities, disruption of circadian sleep cycles, and/or health risk behaviors. Although the estimates of IMT in this sample mirror those from other healthy samples³³, it is possible that the low variance of IMT scores may have obscured any relationship between depression and arterial thickening in this healthy adolescent sample.

The findings from this study should be interpreted cautiously in light of several methodological limitations. The assessment of depressive symptoms and PWV at one time point limits the inferences that can be made about the relationship between depression and the development of arterial stiffness over time. Repeated measures of PWV over time are necessary to establish antecedent and consequent relationships. In the current study, time of day that PWV and IMT data were collected was not uniform and adolescents' dietary intake was not strictly controlled prior to PWV measurement. Without blood sampling, we did not have measures of adolescents' cholesterol, another risk factor that contributes to CVD, and could not verify the absence of CVD in adolescents outside of self- and parent-reported health history. Because adolescents were not diagnosed with depressive disorders, we cannot presume that the same pattern of findings will generalize to samples of adolescents with psychiatric illness. Given the likelihood that the sample of healthy adolescents in this study is selective, these findings may not generalize to all adolescents.

To date, consistent associations between depression and global indices of health have been found in existing studies on adolescents; however, few studies have examined specific markers of subclinical cardiovascular disease in an adolescent sample. The present study's use of subclinical measures of CVD, which predicts adult clinical CVD, improves upon previous studies that have often relied on adolescent report of health problems or use of health services as outcome measures. Another notable contribution of the present study is its examination of depression and co-occurring psychosocial risk factors in relation to subclinical markers of CVD. Although several studies have assessed the relationship between depressive symptoms, hostility, and health outcomes in adults³⁸⁻³⁹, there is a lack of studies that have investigated the effects of both depressive symptoms and hostility on adolescents' health.

The present study advances research in adolescent health by suggesting increased arterial stiffness as a potential pathway whereby depression may be associated with later CVD. However, future studies are required to examine the specific physiological mechanisms that link depression to increased arterial stiffness. An increased focus on depressive symptoms in adolescents may offer health providers opportunities for early identification of at-risk adolescents. Clinical studies of depressed adolescents are also needed to see if early clinical intervention can reduce potential increases in arterial stiffness⁴⁰.

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Figure 1. Pulse Wave Velocity (cm/sec) by severity of adolescents' depressive symptoms

Table 1
Characteristics of Participants by Severity of Depressive Symptoms

	Low (0-7) (n = 52)	Moderate (8-14) (n = 55)	High (15-47) (n = 50)	p-value
Age (years) -- Mean (SD)	17.7 (1.0)	17.9 (0.8)	17.9 (1.1)	.46
Race -- % (N)	48.1 (25)	54.5 (30)	44.0 (22)	.55
Caucasian				
Sex -- % (N) Male	55.8 (29)	52.7 (29)	48.0 (24)	.73
BMI (kg/m ²) -- Mean (SD)	24.4 (3.8)	24.0 (3.8)	24.5 (4.1)	.82
Parent Education				
Level -- % (N)				.85
Low ($\leq$ high school)	43.1 (22)	37.0 (20)	40.0 (20)	
Medium (Some College)	21.6 (11)	16.7 (9)	18.0 (9)	
High ($\geq$ college)	21.1 (18)	46.3 (25)	42.0 (21)	
Smoking Status				.37
Current Smoker -- % (N)	11.5 (6)	10.9 (6)	18.0 (9)	
Current Nonsmoker -- % (N)	80.8 (42)	70.9 (39)	66.0 (33)	
Unknown -- % (N)	7.7 (4)	18.2 (10)	16.0 (8)	
Physical Activity - Mean (SD)	9.1 (6.8)	8.8 (6.2)	9.9 (5.3)	.66
Total Hostility -- Mean (SD)	13.3 (3.8) ^a	14.9 (3.4)	15.2 (4.4) ^b	.03
SBP prior to PWV (mm Hg) -- Mean (SD)	115.1 (10.4)	115.3 (9.8)	118.7 (14.0)	.25
HR (bpm) -- Mean (SD)	64.8 (14.1)	65.0 (12.0)	69.1 (8.0)	.22
SBP prior to IMT (mm Hg) -- Mean (SD)	115.1 (10.3)	114.1 (8.3)	116.5 (10.6)	.47
PWV (cm/ sec) -- Mean (SD)	516.1 (88.4) ^a	548.2 (120.9)	577.9 (137.7) ^b	.05
IMT (mm) -- Mean (SD)	0.54 (.03)	0.53 (.04)	0.54 (.03)	.86

Note: Means with different superscripts are significantly different (Least Significant Difference); BMI = body mass index; SBP = systolic blood pressure; HR = heart rate; PWV = pulse wave velocity; IMT = intima media thickness

Table 2
Multivariate Linear Regression Model Predicting Pulse Wave Velocity (cm/ sec)

	Standardized B	Confidence Interval (95%)	R ²	ΔR ²	p-value
Step 1:			.28	--	<.001
Age (years)	.08	-9.3 – 27.5			.33
Race (Black= 2 Caucasian = 1)	.07	-24.2 – 55.9			.44
Sex (Female = 2; Male = 1)	.01	-37.1 – 43.5			.88
BMI (kg/ m ²)	.21	1.5 – 10.4			.01
Parent Education Level (low=1, medium=2, high =3)	-.21	-49.2 – -6.2			.01
Current Smoker (unknown as referent)	.02	-64.0 – 79.9			.83
Current Nonsmoker (unknown as referent)	-.00	-53.2 – 51.16			.97
Physical Activity	-.10	-5.0 – 1.2			.22
SBP (mm Hg)	.38	2.2 – 5.7			<.001
HR (bpm)	-.04	-1.7 – 1.0			.63
Step 2:					
Total Hostility	.02	-4.7 – 5.8	.28	.00	.83
Step 3:					
Depression severity (low=1, moderate=2, high =3)	.17	2.1 – 47.7	.30	.03	.03

Note: BMI = Body Mass Index; SBP = systolic blood pressure; HR = heart rate