Cardiovascular Response to Peer Rejection as a Biomarker for Adolescent Depression Risk

by

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Acknowledgments

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ABSTRACT

Background: This study assessed how cardiovascular measures and cardiovascular reactivity differ between physically healthy adolescent girls diagnosed with major depressive disorder (MDD), those at high risk for MDD (based on parental history of MDD), and control girls with no personal or family history of psychiatric conditions both at baseline and in response to a social exclusion paradigm.

Methods: Eighty-four girls, ages ten to eighteen ($M=13.3$, $SD=2.4$) completed the Yale Interpersonal Stressor-Child version (YIPS-C), a laboratory social exclusion paradigm. Systolic, diastolic, mean arterial blood pressure (SBP, DBP, MAP), and heart rate (HR) were assessed at throughout the stress session during baseline, stress, and recovery periods using an oscillometric device. Reactivity was calculated as percent change in blood pressure or HR from rest to social stressor, by subtracting the mean baseline measurement from the mean stressor measurement (Introduction, Conversation, or Recovery), and then dividing by the mean baseline measurement.

Results: MDD girls showed higher overall mean SBP, DBP, and MAP, as well as lower overall HR throughout the session versus high risk and control girls. MDD girls also showed higher DBP and MAP reactivity versus high risk and control girls, respectively. SBP, DBP, MAP, and HR in high risk girls more closely resembled control girls than girls with MDD throughout the session; cardiovascular reactivity of DBP and MAP of high risk girls was intermediate between control girls and MDD girls. No consistent reactivity trends between groups were present in either systolic blood pressure or heart rate.
Conclusions: It was concluded that high DBP both at baseline and during social stressors as well as high DBP reactivity to social stress may be a mechanism or potential biomarker for adolescent depression risk. Additionally, higher SBP, DBP, and MAP and DBP and MAP reactivity in girls with MDD may signify a potential mechanism linking adolescent MDD to future cardiovascular disease risk.
BACKGROUND

Prevalence of Depression

Major depressive disorder (MDD) is one of the most prevalent mental disorders in the United States. Major depressive disorder diagnosis requires that an individual have at least two major depressive episodes. The DSM-IV classifies a major depressive episode (MDE) as a period of two or more weeks, in which there is a persistent depressed mood or a loss of interest or pleasure throughout daily activities, and at least 5 of the 9 following symptoms present nearly every day: depressed or irritable mood most of the day, decreased interest or pleasure in most activities, significant and unintentional gains or losses in weight or appetite, insomnia or hypersomnia, noticeable psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate and/or indecisiveness, and suicidal ideation or planning. These symptoms must cause significant impairment in necessary functioning to be classified as a major depressive episode (“Diagnostic”, 2000). MDD is currently the leading cause of disability amongst all mental and behavioral disorders (NIMH, 2014). From the years 1990 to 2010, depression accounted for 3.7% of all US disability-adjusted life years, and 8.3% of all US years lived with disability (US Burden of Disease Collaborators, 2013).

Prevalence of Cardiovascular Disease

Cardiovascular disease includes any disease that affects the heart and/or the blood vessels, including heart valve disease, arrhythmia, congenital heart disease, peripheral vascular diseases, orthostatic hypotension, and hypertension, among other diseases. According to the most recent statistical count by the Centers for Disease Control and Prevention, heart disease, especially coronary heart disease, remains the leading cause of death for both men and women
within the United States. Every year, about 610,000 US citizens die from heart disease, accounting for roughly one out of every four deaths (CDC, 2013).

There exists a well-established, bidirectional association between major depressive disorder and cardiovascular disease (CVD). CVD history increases the risk of development of MDD, and the presence of MDD increases the risk of future development of CVD (Braune et al., 2013). It has been shown both that depression in patients with existing CVD has worsens prognosis of future CVD events (Nicholson, Kuper & Hemingway, 2006; Lauzon et al., 2003), and that depression in cardiovascularly healthy patients has been linked to future CVD events (Surtees et al., 2008; Kendler et al, 2009). The present study will examine how the presence of MDD may be associated with future cardiovascular risk.

The association between MDD and CVD is well supported; however, the mechanisms linking the two diseases are not completely clear. Factors such as smoking, a sedentary lifestyle, obesity, and diabetes are consistently observed in those with depression, and are also major cardiovascular risk factors. However, many studies have found depression to be an independent risk factor for CVD after adjustments for such factors are taken into consideration (Skala, Freedland & Carney, 2006). Mechanisms linking the two diseases may include increased levels of proinflammatory cytokines, changes in endothelial function and in arterial elasticity, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Braune et al., 2013).

**Hypertension May Link The Two Diseases**

Hypertension, defined as high blood pressure, is one of the leading risk factors for cardiovascular disease morbidity and mortality. Hypertension results in 50% of the U.S. deaths by cardiovascular disease (CDC, 2011; Chobanian et al., 2003). Research also suggests that there is a bidirectional relationship between depression and hypertension. Hypertensive
individuals are more likely to develop MDD, and depressed individuals are more likely to
develop hypertension (Bogner et al., 2013). Thus, hypertension may serve as a mechanism,
linking MDD and CVD.

Hypertension is largely caused by dysregulations in the autonomic nervous system (ANS)
(Palatini & Julius, 2009). Environmental stress stimulates the adrenal medulla to secrete
norepinephrine. Excessive stimulation of the ANS by environmental stressors can cause
sympathetic overdrive, resulting in higher overall heart rates and blood pressures (Mancia &
Grassi, 2014). Additionally, those with hypertension tend to have insufficient parasympathetic
modulation. Sufficiency of parasympathetic modulation may be measured by heart rate
variability (HRV). HRV measures beat-to-beat fluctuation in heart rate in response to stimuli.
Lower HRV indicated that the vagus nerve, the initiation site of the parasympathetic response, is
insufficient. Such ANS dysregulations are thought to exist even prior to the development of true
hypertension, when blood pressure measurements reach a systolic pressure of greater than
140mmHg and diastolic pressure of greater than 90mmHg in adults (Mancia & Grassi, 2014).
Due to the positive correlation consistently found between depression and hypertension, one
would expect such ANS dysregulation to be present in those with MDD. Increased plasma levels
of noradrenaline and low heart rate variability would be expected to be found in depressed
patients that have not yet classified under essential hypertension constraints.

**MDD Patients Show Markers of Hypertension**

Plasma concentrations of norepinephrine are directly correlated with the level of
sympathetic nervous system activity (Carney, Freedland & Veith, 2005). Furthermore, it has
been known for decades that increased plasma and urinary concentrations of catecholamines,
specifically norepinephrine, is increased in patients with MDD who are otherwise healthy (Roy
et al., 1988). To ensure that elevated norepinephrine concentrations were stemming from increased total body sympathetic activity rather than local sympathetic activity or insufficient norepinephrine clearing, Veith et al. (1994) employed radiolabeling techniques to monitor norepinephrine release and clearance. Results indicate that otherwise healthy patients with MDD do have elevated concentrations of plasma norepinephrine, and that such elevated concentrations of norepinephrine result in total body increases in sympathetic activation.

Heart rate variability (HRV) has been the most common method of assessing ANS functioning. Such heart rate rhythms are controlled by intrinsic cardiac pacemakers, which are modulated by the ANS. The heartbeat is controlled by parasympathetic and sympathetic activities of the ANS. Low HRV is indicative of excess sympathetic modulation, insufficient parasympathetic modulation, or a combination of the aforementioned (“Heart, 1996). Most studies have found lower HRV in depressed individuals than in controls, providing further evidence for association between MDD and hypertension risk (see Review: Shinba, 2004).

Studies Support Depressed are Hypertensive

Findings suggest that otherwise healthy patients with MDD exhibit greater sympathetic tone and lesser parasympathetic tone. There has been found to be an overall positive correlation between MDD and elevated blood pressure. (Mancia & Grassi, 2014). Many studies have examined direct effects of MDD and depressive symptom count on systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (in beats per minute). Studies have shown that depressive symptom count alone may be a sufficient predictor of greater SBP, DBP, and MAP. Specifically, Wu et al. found that higher depressive symptom count and lower levels of social support were associated with higher SBP and DBP in women and girls (Wu, Prosser & Taylor, 2010).
Hypertension May Undermine Reactivity Hypothesis

Excessive sympathetic tone and insufficient parasympathetic tone over time may be expected to increase blood pressure and heart rate response to stressors. This is called the reactivity hypothesis. The reactivity hypothesis was proposed in 1981, and suggests that increased cardiovascular reactivity due to accumulation of acute stressors over time may lead to hypertension along with other CVD risk factors (Obrist).

In support of the reactivity hypothesis, it has been observed in otherwise healthy people that increased cardiovascular reactivity to acute psychological stress shows a positive correlation with increased blood pressure when assessed at future dates (Carroll et al., 2001). Worsening of original CVD or CVD risk factors including atherosclerosis, thickened carotid intima, and hypertrophy of the heart (especially of the left ventricle) have also been associated with increased cardiovascular reactivity to acute psychological stress (Matthews et al., 2006; Treiber et al., 2003). More recent research conducted by Stroud et al. (2009) found that adolescents, relative to children, had increased salivary cortisol, salivary alpha amylase, SBP, DBP, and HR responses when compared to younger children. In addition, SBP response was greater in a peer rejection stressor rather than a performance stressor, suggesting that SBP response to peer rejection may be especially involved in mediating depression and CVD risk among adolescents.

Inconsistent Findings: Suggest Decreased Reactivity to Stressors

While many previous studies suggest that those with MDD exhibit increased cardiovascular reactivity to stressors (see review: Kibler and Ma, 2004), more recent studies suggest otherwise. The West of Scotland Twenty-07 study provides some of the first evidence that decreased cardiovascular reactivity, rather than increased reactivity, may be more closely associated with negative health outcomes. In particular, the Twenty-07 study found that those
with higher levels of life stress exhibited decreased cardiovascular reactivity to stressors (Carroll et al., 2000). Specifically amongst younger adults, the number of personal events was a significant predictor of lower levels of SBP and HR reactivity. More recent studies (eg. Phillips, 2011) also suggest that decreased HR reactivity may also be positively correlated with depressive symptom count in the future. This West of Scotland Twenty-07 study provides the first evidence that low cardiovascular reactivity may lead to negative health outcomes in stressed or depressed populations. Salomon et al. suggest that cardiovascular reactivity may be low or high depending on the mood state of the participant, and that either abnormally low or abnormally high reactivity may negatively contribute to future cardiovascular risk (Salomon et al., 2013). It is therefore the goal of the present study to assess whether higher or lower reactivity to social stressors is evoked in girls with MDD relative to control girls.

**MDD in Relation to Puberty**

Though the average age of onset of depression is roughly 30 years of age, the National Survey on Drug Use and Health estimated that just over ten percent of U.S. children ages 12 to 17 had at least one MDD episode within the past year (NIMH, 2013). Thus, understanding the onset of depression in children and adolescence is of critical importance (NIMH, 2013). Various animal studies have found distinct periods of rapid growth of developing brain pathways followed by a period of pruning during adolescence. This suggests that there is a critical period in brain development when most of the neurological pathway development is taking place (eg. Pine, 2004). These animal studies may also be characteristic of human studies, which show that the pubertal transition is associated with increases in gonadal hormones, which ultimately influence various nervous pathways throughout the body (Spear, 2000). These increases in gonadal hormones influence stress response systems. One of such systems is the autonomic
nervous system (ANS). Upon activation, the autonomic nervous system stimulates the adrenal medulla to release noradrenalin. Excess stimulation of the ANS may result in high levels of sympathetic tone. Increased sympathetic tone is also characteristic of depression (Light et al., 1998). Thus, maladaptive ANS functioning in individuals may provide a mechanism by which depression onset occurs along the pubertal transition.

**Importance of Studying Females**

Research has consistently found that women across the globe are about twice as likely as men to suffer from depression as well as anxiety. Such high ratios of depression and anxiety in women over men begins as early as adolescence. This is because initial onset in females occurs more frequently at younger ages than it does in males (Kessler, 1993). Previous studies that have analyzed the sex differences in depression rates have found that females tend to perceive interpersonal concerns such as affiliative need more stressful, while males tend to perceive intellect and performance as more stressful (Gillespie and Eisler 1992). Considering that dominant stressful events shift more from performance-oriented events to interpersonal relationships over the adolescent transition (Steinberg and Morris, 2001), it would make sense for interpersonal conflict or concerns to be a large factor in the initial onset of MDD episodes beginning in adolescent years.

**Aims and Hypothesis of the Present Study**

The present study is part of a larger study carried out by Stroud et al, which aims to assess biomarkers and risk factors for adolescent depression. Given increased rates of depression in females, the present study focused only on females (NIMH, 2013). In addition, only children and adolescents are included in the present study, as adolescence is a key period for understanding the mechanisms of onset of depression. A social exclusion stressor will be
used, in accordance with the findings that interpersonal stressors have been shown to cause increased biological response compared to performance stressors in adolescent populations. This greater response to interpersonal stress is especially prevalent amongst females (Stroud et al., 2009).

In the present study, three groups of female participants were enrolled: depressed, high-risk, and control. Depressed girls met current criteria for MDD according to psychiatric diagnostic criteria (American Psychiatric Association, 2000), high-risk girls had one or more biological parents with a lifetime history of multiple major depressive episodes (MDE’s) or a chronic MDE, and control girls had no personal or parental history of major psychiatric disorder.

While Dr. Stroud et al. focus on potential neuroendocrine and neural biomarkers of MDD, the present study aims to evaluate potential cardiovascular biomarkers in adolescent girls with MDD. The primary goal of the study is to identify which cardiovascular measures –SBP, DBP, MAP, or heart rate –may be potential biomarkers or mechanisms of risk for adolescent depression. Secondly, the present study aims to help settle literature discrepancies regarding whether adolescent girls exhibit higher or lower cardiovascular reactivity to social stress than control girls, particularly to social exclusion stressors. Finally, an additional high-risk study group will be analyzed to determine whether cardiovascular measures and reactivity patterns of high-risk individuals more closely resemble those of control girls or girls with MDD.

Due to suggested ANS dysregulation in favor of sympathetic tone in adolescents with MDD as well as a large body of supporting research in adults with MDD, one would expect adolescent individuals with MDD to exhibit greater overall measures of heart rate and blood pressures both at rest and in response to the social exclusion stressor. This ANS dysregulation would also suggest that depressed girls should have increased heart rate and blood pressure
reactivity to the social stressor, overall. The hypothesis of this paper is thus that depressed girls, relative to control girls, will exhibit higher overall SBP, DBP, MAP, and HR reactivity to social stressors versus control girls. Due to a paucity in research examining adolescent girls at high risk for MDD, correlations between high risk girls and control and MDD girls, respectively, were left as exploratory and will be addressed.
METHODS

Participants

Participants were recruited from Bradley Hospital, Rhode Island Hospital, Women’s Primary Care Center, pediatric clinics, community and Internet postings, and by community outreach. Interested participants were then screened by telephone to test for eligibility. Three groups of girls were enrolled: depressed, high-risk, and control. Girls were classified as depressed if they met current criteria for MDD, high-risk if they had one or more biological parents with lifetime history of recurrent or chronic MDD but did not themselves meet criteria for MDD, and control if both the participant and parents reported no history of major psychiatric condition. Participants were excluded if there were any personal diagnosis or parental diagnosis of bipolar disorder or other form of psychosis, either past or current. Participants taking oral contraceptives, steroids, or thyroid medications were also excluded. Additional exclusion criteria include pregnancy, regular drug and/or alcohol use, autism or mental retardation, as well as metal implants (including braces) or extreme obesity, as these would prevent the participant from participating in an MRI session outside the scope of the present study. Participants taking psycho-stimulant medications were asked to stop taking such medications for the two days preceding the MRI and interpersonal sessions, and those unwilling or unable to comply were also excluded. One participant had taken psycho-stimulant medications two days prior to the interpersonal session; however, she complied to stop medication one day prior to the interpersonal session, and was included in the study session.

A total of 100 adolescent girls were eligible and enrolled in this study: 32 control girls, 35 high-risk girls, 26 depressed girls, and 7 “other” girls who did not meet criteria for any of the three groups following the initial diagnostic session. Due to blood pressure monitor
malfunctioning (1 participant), a desire not to wear the blood pressure cuff (1 participant), expressed discomfort with the blood pressure cuff (7 participants), or unclear study group categorization (7 participants), 16 girls were excluded from analysis. The remaining participants were a total of 84 participants: 28 control girls, 34 high risk girls, and 22 depressed girls, ages 10 to 18 ($M = 13.3$, $SD = 2.4$ years) on the date of their interpersonal session.

The majority of the girls (54%) were of normal BMI, 21% were underweight, 18% were overweight, and 7% were obese. 70 girls identified as non-Hispanic, while 14 girls identified as Hispanic. Overall, 69% considered themselves White, 1.2% considered themselves Asian, 11% considered themselves Black, 18% considered themselves multiracial, and 1% considered themselves Other. The majority of girls were post-puberty (44%), while 36% were mid-puberty, and 20% were pre-puberty. A majority of households (33%) made $100,000+ dollars per year, and a majority of primary parents completed education with a Bachelor of Arts (BA) or Bachelor of Science (BS) degree (22%); however, household income and primary parental education varied greatly (see Table 1, below).

Table 1

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Cardiovascular Measures & Reactivity as Potential MDD Biomarker

Highest Education of Primary Parent

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<td>2 (9%)</td>
<td>6 (27%)</td>
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<td>High School / GED</td>
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<td>2 (6%)</td>
<td>6 (27%)</td>
<td>14 (17%)</td>
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<td></td>
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<tr>
<td>College</td>
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<td>3 (9%)</td>
<td>5 (23%)</td>
<td>14 (17%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assoc.</td>
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<td>5 (15%)</td>
<td>1 (4.5%)</td>
<td>8 (9%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BA / BS</td>
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<td>5 (23%)</td>
<td>18 (22%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA / MS</td>
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<td>8 (23%)</td>
<td>1 (4.5%)</td>
<td>16 (19%)</td>
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<td></td>
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</tr>
<tr>
<td>PhD / MD</td>
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<td>7 (21%)</td>
<td>2 (9%)</td>
<td>11 (13%)</td>
<td></td>
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<td></td>
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</tbody>
</table>

Procedure

Study Group Determination:

The Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime (K-SADS-PL) was administered to the child at her rest session. This semi-structured interview was used to classify the participant as depressed or non-depressed, according to the DSM-IV Axis I psychiatric diagnosis (Kaufman et al., 1997). An initial screen was performed, followed by supplements covering affective, psychotic, behavioral, and substance abuse disorders to ensure that the participant should not be excluded. Anxiety (in its various forms) was also assessed via the K-SADS-PL (Kaufman et al., 1997).

The Structured Clinical Interview for DSM-IV (SCID) was similarly administered to the parents in a separate interview during the rest session. The SCID administration also followed DSM-IV Axis I psychiatric diagnosis guidelines, and involved an initial screen followed by diagnostic classifications for other mood, psychotic, substance, and anxiety disorders (Lobbestael, Leurgans & Arntz, 2011). K-SADS-PL and SCID diagnosis ultimately determined not only whether or not participants were included or excluded from the study, but also determined the study group into which the participant fell.

YIPS-C Interpersonal Session:
The Yale Interpersonal Stressor – Child Version (YIPS-C) was a modified version of the Yale Interpersonal Stressor (YIPS) created by Dr. Stroud et al. (2000, 2009). At the start of the interpersonal session, the examiner directed the child into a room where she initially sat alone, connected the participant to the blood pressure machine, and asked the participant to select a G-rated movie, which the proctor then played prior to leaving the room for thirty minutes to acquaint the participant with the laboratory setting. After fifteen minutes of television viewing, the examiner re-entered the room and marked a line on the blood pressure strip. This line marked where baseline measurements began to be recorded.

Baseline readings were taken for the remaining fifteen minutes of television viewing, then the examiner re-entered the room alongside two confederate actors. These confederate actors were of the same sex and of similar age to the participant, and had been extensively trained prior to the session on how to subtly exclude the participant from conversation. Prior to the interpersonal session, each actress received a list of the participant’s interests and activities. These actresses adjusted their personas prior to the interpersonal session so that their interests and lifestyles were more in line with one another, rather than the interests and lifestyle of the participant. Once all three girls were seated in their places with the participant hooked up to the blood pressure machine, the proctor led a 5-minute introduction where the girls were asked simple ice-breaker questions to get acquainted with one another. This 5-minute introduction period marked where introduction readings were recorded.

Following this introduction, the examiner informed the girls that they would be “getting to know one another” by partaking in three, 5-minute conversations. The three conversation topics included weekend activities, family, and friends, respectively. The actresses slowly excluded the participant from conversation using a variety of verbal and non-verbal gestures.
intended to leave the girl out as the two actresses got along better with one another. To ensure that participants did not notice the deception, social exclusion was kept minimal in the first conversation, gradually building toward the third conversation. Conversation readings were recorded only when participants were in direct conversation with one another.

Between each conversation, the examiner entered the room and administered an affect sheet, measuring how included or excluded the participant felt, and whether or not the participant would want to be friends with the actresses. These measures were taken to ensure that the exclusion paradigm was successful. A saliva sample was also taken following the affect sheet for cortisol, salivary amylase, and sex hormones, which are outside the scope of the present study. These affect periods between conversations marked periods in which affect readings were recorded. Following the final conversation and affect session, the participant was left alone in the room, watching her G-rated movie. This marked the start of the recovery period.

**Measures**

**Cardiovascular Measures:**

Blood pressure was assessed using a Dinamap automatic, oscillometric blood pressure monitor (Critikon Inc., Tampa, FL). The cuff was placed on the left arm of the participant, and either a child or adult cuff was used, appropriately fit to the size of the participant. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were taken every two minutes during the resting baseline period as well as during the conversation periods. Readings were taken every five minutes during the recovery period.

Lines were drawn in pen when the proctor walked into the room 15 minutes prior to the introductions, as well as prior to the start of, and also at the end of, each of each of the three conversations. The interpersonal session was videotaped (for all but one participant in which the
video camera was not functioning properly) live using a video camera made known to the girls at the start of the introduction period. The video camera was placed so that the mothers could view the session from a neighboring room on a computer screen. It was made clear that the participant or the mother could stop the session at any point if they desired, yet no participant or child chose to do so.

The following protocol was made and used as a guide when entering blood pressure strip data into SPSS. For the purposes of this study, a blood pressure reading was defined to start when the cuff had completed pumping, immediately prior to the observed drop in systolic measurements made on the blood pressure monitor. A reading was defined to end upon the sound of a beep, when the final SBP, DBP, MAP and HR data were displayed on the blood pressure monitor.

Only readings that started after the confederates first entered the room were included in the introduction readings. Any reading that started during the timeframe when only the participant was in the room were included in the baseline readings. Only readings that both started and ended during the actual conversing period of the conversations were counted as conversation readings. Readings that started prior to actual conversation were either counted as introduction readings (if started prior to Conversation 1), or else included as affect readings. Readings that ended after the actual conversation ended were included as either affect readings, or as a recovery reading (if taken after Conversation 3).

**Developmental Measures:**

A nurse pubertal and medical exam was held at a session prior to the interpersonal session. A trained nurse collected the exact height and weight of the girl used to calculate body mass index. Girls were then classified as underweight (BMI <18.5), normal (BMI of 18.5-24.9),
overweight (BMI of 25.0-29.9), or obese (BMI >30.0). Pubertal stage was assessed by the nurse using the Tanner stages of physical development. A trained nurse conducted tanner staging via breast and pubic hair criteria. Pictures depicting each Tanner stage were also presented to the child prior to the interpersonal session, and the child self-reports which picture most closely resembled her physical development (Marshall & Tanner, 1969). Participant self-reports were only used in place of the nurse Tanner staging for analysis when nurse staging was unavailable. Tanner stages were conducted using an average of breast/gonad (BG) and pubic hair (PH) tanner stages. Tanner stages of 1 to 2 were classified as pre-puberty, stages of 2.5 to 3.5 as mid-puberty, and stages 4 to 5 as post-puberty.

Statistical Analysis

Statistical analysis was carried out using RStudio, Version 0.98.1091. First, means were calculated for all of the readings across each of the 8 blood pressure segments: baseline, introduction, first conversation, second conversation, third conversation, 0-2-minute recovery, 2-5-minute recovery, and 5-10-minute recovery. These means were calculated for each of the four measures per reading: SBP, DBP, MAP, and HR. The standard deviations for each of these measures in every section were then calculate, and used to assign outliers. Outliers were defined as any reading measurement that fell outside three standard deviations of the segment mean. These outliers were removed, and means were re-calculated for segments that contained outliers.

Percent change in SBP, DBP, MAP, and HR from baseline to introduction and to each of the three conversations and recovery periods were then calculated. Percent change was calculated by subtracting the mean baseline measure from the mean of the measurement of the segment of interest, and then divided by the mean baseline measure.
ANOVA's were first conducted across the three groups to assess differences in SBP, DBP, MAP, and HR measurements taken for each segment of the session among the three study groups (control, high risk, and depressed [MDD]). T-test analyses were then employed to evaluate two-group comparisons in SBP, DBP, MAP, and HR measurements taken for each of the segments of the session. T-tests were utilized to separately compare control versus high risk, high risk versus depressed, and control versus depressed girls. In all analysis, p<.05 is considered significant, and p<.09 is considered marginally significant, or trending.
RESULTS

Means and standard deviations were first calculated for each of the four measurements (SBP, DBP, MAP, and HR) within each of the eight segments (Baseline, Introduction, Conversation 1, Conversation 2, Conversation 3, Recovery 1, Recovery 2, and Recovery 3). Seven segments contained a participant whose mean measurement (SBP, DBP, MAP or HR) was greater than or less than three standard deviations away from that particular segment’s mean across all participants. These outliers were then removed from the seven participants’ YIPS-C cardiovascular measure data. All results depicted below exclude these seven outlying participant readings, unless specified otherwise.

Mean Cardiovascular Measures Across YIPS-C Session:

Mean SBP, DBP, MAP, and HR measures across the Baseline, Introduction, Conversation and Recovery periods were assessed across study groups using t-tests, and are reported in Tables 2, 3, 4, and 5. Note that in all tables, “Intro” refers to the Introduction period, “Convo1, Convo2, and Convo3” represent the first, second, and third conversations, respectively, and that “Rec1, Rec2, and Rec3” represent the first two minutes of recovery, the second through fifth minutes of recovery, and the fifth through tenth minutes of recovery, respectively.
Table 2

Mean Systolic Blood Pressure (in mmHg) Over The Course Of YIPS-C Laboratory Session

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Baseline</th>
<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>105.7</td>
<td>113.8</td>
<td>116.1</td>
<td>114.4</td>
<td>113.9</td>
<td>115.1</td>
<td>111.8</td>
<td>111.8</td>
</tr>
<tr>
<td></td>
<td>(9.8)</td>
<td>(13.3)</td>
<td>(13.2)</td>
<td>(11.3)</td>
<td>(13.2)</td>
<td>(13.4)</td>
<td>(11.8)</td>
<td>(9.9)</td>
</tr>
<tr>
<td>High-Risk</td>
<td>105.6</td>
<td>112.6</td>
<td>114.8</td>
<td>114.9</td>
<td>113.2</td>
<td>111.5</td>
<td>112.8</td>
<td>109.8</td>
</tr>
<tr>
<td></td>
<td>(11.7)</td>
<td>(12.8)</td>
<td>(11.6)</td>
<td>(14.1)</td>
<td>(13.1)</td>
<td>(12.0)</td>
<td>(10.3)</td>
<td>(12.0)</td>
</tr>
<tr>
<td>MDD</td>
<td>109.2</td>
<td>118.0</td>
<td>118.6</td>
<td>116.2</td>
<td>115.6</td>
<td>115.8</td>
<td>114.7</td>
<td>111.0</td>
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<td>(11.8)</td>
<td>(11.3)</td>
<td>(8.8)</td>
<td>(13.9)</td>
<td>(13.3)</td>
<td>(12.6)</td>
</tr>
</tbody>
</table>

+.05<p<.09 *p<.05

Table 3

Mean Diastolic Blood Pressure (in mmHg) Over The Course Of YIPS-C Laboratory Session

<table>
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<th>Study Group</th>
<th>Baseline</th>
<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
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<tr>
<td>Control</td>
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<td>68.7</td>
<td>69.3</td>
<td>69.2</td>
<td>67.8</td>
<td>66.2</td>
<td>66.7</td>
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<td>(5.1)</td>
<td>(6.3)</td>
<td>(7.0)</td>
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<td>(7.2)</td>
<td>(6.7)</td>
<td>(6.5)</td>
<td>(3.6)</td>
</tr>
<tr>
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<td>66.0</td>
<td>64.4</td>
<td>63.7</td>
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<td>(6.0)</td>
<td>(6.6)</td>
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<td>(6.4)</td>
<td>(6.9)</td>
<td>(6.0)</td>
<td>(5.6)</td>
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<tr>
<td>MDD</td>
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<td>71.3*</td>
<td>69.5</td>
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<td>67.2</td>
<td>65.3</td>
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<tr>
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<td>(6.6)</td>
<td>(6.6)</td>
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<td>(5.9)</td>
<td>(5.9)</td>
<td>(6.8)</td>
<td>(3.6)</td>
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</tbody>
</table>

+.05<p<.09 *p<.05
Table 4

*Average Mean Arterial Blood Pressure (in mmHg) Over The Course Of YIPS-C Laboratory*

<table>
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<tr>
<th>Session</th>
<th>Study Group</th>
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<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
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<td>87.1</td>
<td>86.6</td>
<td>85.8</td>
<td>85.8</td>
<td>84.7</td>
<td>84.3</td>
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<td></td>
<td></td>
<td>(5.4)</td>
<td>(6.4)</td>
<td>(6.9)</td>
<td>(6.6)</td>
<td>(6.6)</td>
<td>(6.3)</td>
<td>(5.8)</td>
<td>(3.9)</td>
</tr>
<tr>
<td></td>
<td>High-Risk</td>
<td>80.5</td>
<td>86.2+</td>
<td>86.4</td>
<td>85.8</td>
<td>85.2</td>
<td>84.0</td>
<td>83.8</td>
<td>82.7</td>
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<td>(7.0)</td>
<td>(6.9)</td>
<td>(5.7)</td>
<td>(6.7)</td>
<td>(6.7)</td>
<td>(6.1)</td>
<td>(5.0)</td>
<td>(6.3)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
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<td>88.5+</td>
<td>89.6</td>
<td>87.6</td>
<td>87.1</td>
<td>86.1</td>
<td>85.3</td>
<td>83.3</td>
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<tr>
<td></td>
<td></td>
<td>(6.6)</td>
<td>(6.9)</td>
<td>(5.9)</td>
<td>(5.2)</td>
<td>(4.6)</td>
<td>(5.4)</td>
<td>(7.3)</td>
<td>(5.8)</td>
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</tbody>
</table>

+.05<p<.05 *p<.05

Table 5

*Mean Heart Rate (in beats per minute) Over The Course Of YIPS-C Laboratory Session*

<table>
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<tr>
<th>Session</th>
<th>Study Group</th>
<th>Baseline</th>
<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>79.3+</td>
<td>84.0</td>
<td>82.4</td>
<td>82.6</td>
<td>82.2</td>
<td>82.6</td>
<td>81.0</td>
<td>82.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9.4)</td>
<td>(10.5)</td>
<td>(10.4)</td>
<td>(11.3)</td>
<td>(11.9)</td>
<td>(9.6)</td>
<td>(12.3)</td>
<td>(11.3)</td>
</tr>
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<td>79.4+</td>
<td>83.6</td>
<td>81.6</td>
<td>81.9</td>
<td>81.7</td>
<td>80.8</td>
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<td>(11.7)</td>
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<td>(12.55)</td>
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<td>(11.9)</td>
<td>(7.5)</td>
<td>(11.0)</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>74.1+</td>
<td>80.3</td>
<td>77.9</td>
<td>77.2</td>
<td>77.0</td>
<td>79.2</td>
<td>75.9</td>
<td>76.9</td>
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<tr>
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<td></td>
<td>(10.6)</td>
<td>(12.3)</td>
<td>(12.9)</td>
<td>(11.3)</td>
<td>(11.7)</td>
<td>(12.0)</td>
<td>(12.9)</td>
<td>(10.6)</td>
</tr>
</tbody>
</table>

+.05<p<.05 *p<.05
Baseline Cardiovascular Measures

Although not significant, girls with MDD had higher mean baseline blood pressures during the pre-stress period across all three blood pressure variables (SBP, DBP, and MAP). Although trending, baseline blood pressure measures were also consistently lower in high-risk girls than in control girls across the three blood pressure measures. Although trending, baseline heart rate was higher in girls with MDD than both control girls as well as in girls at high risk of major depression (see Figure 1).

Figure 1. Mean Baseline Heart Rates (in beats per minute) Across Study Groups

![Figure 1](image)

*Note.* Error bars indicate +/- Standard Error of the Mean (S.E.M.).
Cardiovascular Measures Across Introduction Period and Three Conversations

Girls with MDD tended to have higher overall blood pressure measures (SBP, DBP, and MAP) than both control girls and high-risk girls throughout the introduction and conversation stressor period. Specifically, DBP was significantly higher in depressed girls than control girls during the introduction period and first conversation (see Figure 2), and mean arterial pressure was marginally higher in depressed girls than in control girls during the first conversation (see Figure 3).

Although not significant, heart rate remained lower throughout the session in girls with MDD than both control and high risk girls. Although only trending, high-risk girls had slightly lower overall cardiovascular measures (SBP, DBP, MAP, and HR) than high-risk girls, but more closely resembled control girls than depressed girls across all cardiovascular stressor measures.

Figure 2. Mean Diastolic Blood Pressure Measures During Stressor
Figure 2. During the first conversation, mean diastolic blood pressure was significantly higher in MDD girls (M=72.6, SD=6.6) than in high-risk girls (M=68.8, SD=5.3); t(38.9)=-2.3, p=0.03. Mean diastolic blood pressure was also significantly higher in depressed girls during the second conversation (M=71.3, SD=6.0) than in high-risk girls (M=67.1, SD=6.0); t(40.8)=-2.5, p=0.02. Though only marginally significant, diastolic blood pressure during the introduction was also higher in depressed girls (M=71.3, SD=6.6) than in high-risk girls (M=67.4, SD=6.6); t(42.7)=-1.8, p=0.09.

Note. Error bars indicate +/- Standard Error of the Mean (S.E.M.).

Figure 3. A borderline significant difference in mean arterial pressure was observed during the first conversation between girls at high-risk of MDD (M=86.4, SD=5.7) and those with current MDD (M=89.6, SD=5.9); t(44.5)=-2.0, p=0.056.

Note. Error bars indicate +/- Standard Error of the Mean (S.E.M.).
Percent Change in Cardiovascular Measures Across Stressor

Mean percent change measures were calculated by subtracting the segment of interest (Introduction, Conversation 1, 2, or 3, or Recovery 1, 2, or 3), from the mean baseline reading at rest, and dividing by mean baseline reading. Significance of mean percent change measures in SBP, DBP, MAP, and HR measures across Introduction, Conversation and Recovery periods were assessed via t-tests, and are reported in Tables 6, 7, 8, and 9. Note that in all tables, “Intro” refers to the Introduction period, “Convo1, Convo2, and Convo3” represent the first, second, and third conversations, respectively, and that “Rec1, Rec2, and Rec3” represent the first two minutes of recovery, the second through fifth minutes of recovery, and the fifth through tenth minutes of recovery, respectively.

Table 6

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.2%</td>
<td>9.1%</td>
<td>7.0%</td>
<td>6.6%</td>
<td>8.1%</td>
<td>6.5%</td>
<td>7.3%*</td>
</tr>
<tr>
<td></td>
<td>(8.2%)</td>
<td>(6.7%)</td>
<td>(5.9%)</td>
<td>(7.9%)</td>
<td>(7.2%)</td>
<td>(7.2%)</td>
<td>(5.4%)</td>
</tr>
<tr>
<td>High-Risk</td>
<td>6.4%</td>
<td>9.3%</td>
<td>9.3%</td>
<td>7.8%</td>
<td>5.9%</td>
<td>6.7%</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>(6.7%)</td>
<td>(8.5%)</td>
<td>(9.9%)</td>
<td>(8.6%)</td>
<td>(8.6%)</td>
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</tr>
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<td>MDD</td>
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<td>8.2%</td>
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<td>5.3%</td>
<td>3.0%*</td>
</tr>
<tr>
<td></td>
<td>(4.8%)</td>
<td>(7.9%)</td>
<td>(7.3%)</td>
<td>(9.1%)</td>
<td>(10.4%)</td>
<td>(7.8%)</td>
<td>(4.0%)</td>
</tr>
</tbody>
</table>

+.05<p<.09  *p<.05

Note. Means are given for each study group, above respective standard deviations (in parenthesis).
Cardiovascular Measures & Reactivity as Potential MDD Biomarker

Table 7

*Percent Change In Diastolic Blood Pressure From Baseline To Introduction, Stressors, and Recovery*

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.9%</td>
<td>7.4%</td>
<td>7.0%</td>
<td>4.6%</td>
<td>2.5%</td>
<td>3.7%</td>
<td>0.8%</td>
</tr>
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<td></td>
<td>(5.8%)</td>
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<td>(7.8%)</td>
<td>(7.8%)</td>
<td>(4.8%)</td>
</tr>
<tr>
<td>High-Risk</td>
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<td>10.5%</td>
<td>7.9%</td>
<td>7.4%</td>
<td>6.0%</td>
<td>2.3%</td>
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<td>(8.5%)</td>
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<td>(9.1%)</td>
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</tr>
<tr>
<td>MDD</td>
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<td>12.9%</td>
<td>11.2%</td>
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<td>6.4%</td>
<td>4.9%</td>
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<td>(7.4%)</td>
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<td>(7.0%)</td>
<td>(7.4%)</td>
<td>(7.7%)</td>
<td>(7.1%)</td>
<td>(6.9%)</td>
</tr>
</tbody>
</table>

+.05<p<.09  *p<.05

Note. Means are given for each study group, above respective standard deviations (in parenthesis).

Table 8

*Percent Change In Mean Arterial Pressure From Baseline To Introduction, Stressors, and Recovery*

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Intro</th>
<th>Convo1</th>
<th>Convo2</th>
<th>Convo3</th>
<th>Rec1</th>
<th>Rec2</th>
<th>Rec3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.0%</td>
<td>6.1%</td>
<td>5.1%</td>
<td>4.1%</td>
<td>4.4%</td>
<td>3.8%</td>
<td>3.5%</td>
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<td></td>
<td>(4.6%)</td>
<td>(5.0%)</td>
<td>(4.3%)</td>
<td>(5.0%)</td>
<td>(4.3%)</td>
<td>(4.9%)</td>
<td>(3.5%)</td>
</tr>
<tr>
<td>High-Risk</td>
<td>6.4%</td>
<td>7.9%</td>
<td>7.2%</td>
<td>6.5%</td>
<td>4.8%</td>
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<td>3.1%</td>
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<tr>
<td></td>
<td>(5.3%)</td>
<td>(5.6%)</td>
<td>(6.0%)</td>
<td>(6.4%)</td>
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<td>(6.2%)</td>
</tr>
<tr>
<td>MDD</td>
<td>7.1%</td>
<td>8.9%</td>
<td>7.1%</td>
<td>7.0%</td>
<td>5.2%</td>
<td>3.6%</td>
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<tr>
<td></td>
<td>(4.5%)</td>
<td>(5.9%)</td>
<td>(5.2%)</td>
<td>(5.7%)</td>
<td>(4.8%)</td>
<td>(4.8%)</td>
<td>(3.7%)</td>
</tr>
</tbody>
</table>

+.05<p<.09  *p<.05

Note. Means are given for each study group, above respective standard deviations (in parenthesis).
Mean Percent Change from Baseline to Introduction Period and Conversations

Although not always statistically significant, percent change from baseline to stressor period for both DBP and MAP were consistently greater in girls with MDD than high risk girls, and higher in high risk girls than control girls. Specifically, percent change in diastolic blood pressure was significantly greater in depressed girls than control girls during the introduction period and first conversation (weekend activities), and marginally greater in girls with MDD than control girls during the second conversation (family) (see Figure 4). Percent change in mean arterial pressure was marginally larger in girls with MDD than control girls during the first and third conversations (weekend activities and friends) (see Figure 5). No consistent trends in percent change in either SBP or HR measures across study groups were found (p’s>.05.)
Figure 4. Percent Change in Diastolic Blood Pressure During Introduction and First and Second Conversations

*Figure 4.* During the introduction period, mean diastolic blood pressure was significantly higher in depressed girls (M=10.1%, SD=7.4%) than in control girls (M=5.9%, SD=5.8%); t(37.3)=−2.2, p=0.04. Mean diastolic blood pressure was also significantly higher in depressed girls (M=12.9%, SD=7.9%) than in control girls during the first conversation (M=7.4%, SD=8.1%); t(45.4)=−2.4, p=0.02. Though only marginally significant, diastolic blood pressure during the second conversation was also higher in depressed girls (M=11.2%, SD=7.0%) than in control girls (M=7.0%, SD=8.2%); t(423.5)=−1.9, p=0.07.

*Note.* Error bars indicate +/- Standard Error of the Mean (S.E.M.).
Figure 5. Mean Percent Change in Mean Arterial Pressure During First and Third Conversation

(Upon Removal of Outliers)

Figure 5. Depressed girls had significantly higher mean arterial pressure during the third conversation (M=7.7%, SD=6.2%) than control girls (M=4.1%, SD=5.0%); t(36.3)= -2.1, p=0.045. This significant difference between groups was lost upon removal of a segment outlier. Depressed girls had marginally higher mean arterial pressure during the third conversation (M=7.1%, SD=5.7%) than control girls (M=4.1%, SD=5.0%; t(35.8)= -1.8, p=0.08. Depressed girls also have marginally higher mean arterial pressure (M=8.9%, SD=5.9%) during the first conversation than control girls (M=6.1%, SD=5.0%); t(41.5)= -1.8, p=0.09.

Note. Error bars indicate +/- Standard Error of the Mean (S.E.M.).
Percent Change from Baseline to Recovery

Percent change from Baseline to the 5th to 10th minutes of recovery was lower in the depressed group than in the control group (see Figure 6). No other significant differences between study groups were observed in any other measure for any of the three recovery segments.

Figure 6. Mean Percent Change in SBP During 5th to 10th Minutes of Recovery

Figure 6. Depressed girls had a significantly lower percent changes in mean systolic blood pressure during the last 5th to 10th minutes of recovery (M=3.0%, SD=4.0%) than control girls (M=7.3%, SD=5.4%); t(27.18)=2.64, p=0.01.

Note. Error bars indicate +/- Standard Error of the Mean (S.E.M.).
DISCUSSION

Potential Biomarkers of MDD in Adolescents

The present study yielded many statistically and clinically significant findings. As expected, depressed girls had higher overall systolic, diastolic, and mean arterial pressures both at rest and in response to social exclusion than control girls and high risk girls. Specifically, diastolic blood pressure was significantly higher in girls with MDD than control girls, suggesting that DBP may be a potential biomarker of depression in adolescents. Although not significant, mean baseline resting heart rate of girls with MDD was marginally lower than resting heart rates of both control and high-risk girls. Interestingly, heart rate consistently remained lower in girls with MDD throughout the entire YIPS-C session.

Reactivity to stressors, defined as increases in percent change from baseline to introduction and conversation periods, was also significantly greater in girls with MDD than control girls. Reactivity was significantly greater in girls with MDD than control girls during the introduction period and the first conversation, and remained marginally higher in MDD girls than control girls during the second conversation. These findings further suggest that DBP may be a potential biomarker of depression. Specifically, especially high DBP reactivity during ice-breaker-like activities (introduction period) or during initial periods of social exclusion stressors (conversation one) may serve as a biomarker of adolescent depression. MAP reactivity was also significantly greater in girls with MDD than control girls prior to the removal of segment outliers, and remained marginally higher in girls with MDD than control girls during the first and third conversations after outliers were removed. Heart rate reactivity was also greater in the depressed group than the control and high-risk groups upon initial social exclusion stressors.
Contrary to recent research (Stroud et al., 2009), consistent reactivity trends in systolic blood pressure were not observed.

The finding that all blood pressures were elevated in girls with MDD supports research suggesting that autonomic function in depressed girls is dysregulated. Specifically, the present study suggests that high DBP may be more indicative of depression risk than high SBP, alone.

Interestingly, heart rate was lower both at baseline and in response to the social exclusion paradigm in girls with MDD than control girls. If an ANS mechanism were the primary cause of high blood pressure (SBP, DBP, and MAP), then one would expect heart rate to be similarly elevated in girls with MDD. However, results indicate that this is not the case. Thus, other factors other than the ANS are likely factoring into the cardiovascular response mechanisms of those with MDD. It has been suggested by Baker et al. that antisocial behavior in children and adolescents is inversely correlated with resting heart rate. Thus, the more externalizing behavior problems a child has, the greater likelihood that that child will have a lower resting heart rate. Aggression, a diagnostic symptom of antisocial behavior disorder, is highly co-morbid with depression in some individuals, and may explain the lower resting heart rates throughout the session observed in those with MDD (Baker et al., 2009).

Contrary to more recent literature, high blood pressure and heart rate reactivity to stressors seems to be more indicative of depression risk than low heart rate reactivity. Although consistent differences in reactivity were not found in SBP amongst the study groups, girls with MDD experienced heightened DBP and MAP reactivity throughout the YIPS-C stressor session, as well as heightened heart rate reactivity throughout the introduction and initial conversation period. Salomon et al. (2013) suggest that both high and low reactivity may indicate poor health,
and stress that robust reactivity, as well as diminished reactivity, may place individuals at greater risk of developing future CVD.

**Relation to Future CVD Risk**

Hypertension is a well-established risk factor for CVD, and is considered the leading risk factor for mortality within the US (Kearney et al., 2005). Various studies, including the present study, have consistently shown elevated blood pressures in those with MDD. Many studies to date have focused on hypertension in adults with MDD or in those with MDD who have already experienced a major cardiovascular event (Nicholson, Kuper & Hemingway, 2006; Lauzon et al., 2003; Surtees et al., 2008; Kendler et al, 2009). The present study extends prior literature, as it suggests that such increases in blood pressure are already presenting as early as adolescent years.

Studies carried out long ago similarly hypothesized that DBP, rather than SBP, would be the primary risk factor for later cardiovascular disease. DBP is determined largely by arterial vasoconstriction levels. Increased DBP signifies increased vasoconstriction, which induces peripheral resistance. This peripheral resistance is thought to be a primary factor in the development of future cardiovascular disease. Thus, higher DBP may be a more significant predictor of CVD than SBP, alone (Wiggers, 1932). Contrarily, more recent studies have suggested that high systolic blood pressure is the greatest predictor of cardiovascular disease risk. However, such studies were mainly carried out in older adults. Diastolic blood pressure naturally increases until 50 years of age, and then decreases steadily until the end of life. Thus, higher baseline measures and reactivity measures in SBP may be a higher risk factor in older individuals than DBP. However, in younger populations, it may be possible that DBP is a greater risk factor for future CVD risk.
Limitations and Future Directions

Although the present study had several advantages over other studies—the use of a realistic social stressor rather than a more typical performance-based stressor, strict exclusion criteria including bipolar disorder and psychosomatic medications, and more frequent monitoring of blood pressure throughout the session—there do exist limitations of the present study that should be addressed. Due to the nature of age-matched confederates, different confederate actresses were used throughout sessions of participants in different age groups. It is possible that various confederates may have excluded participants to varying extents. Additionally, due to the high level of co-morbidity between anxiety disorders and MDD, the present study did not exclude for various types of anxiety. Roughly half of the MDD participants presented with a form of anxiety upon K-SADS clinical interviews. Anxiety has known impacts on cardiovascular measures (Vogelzangs et al., 2010), and future, larger-scale studies should assess anxiety and depression independently. The present study population was also majority Caucasian, and future, larger-scale studies may wish to focus on diversifying the study population as much as possible in order to understand differences in cardiovascular affects of depression amongst individuals of more various backgrounds. Finally, the Dinomap, oscillometric blood pressure monitor used in the present study took readings every two minutes during the baseline and stressor periods of the YIPS-C session. Other studies may wish to utilize continuous blood pressure monitors, or less invasive blood pressure monitors, such as finger monitors.

The present study yields important future considerations and implications. In the present study, high-risk girls more closely resembled control girls than girls with MDD across all measured variables. Clear patterns in reactivity were not observed for SBP or HR; however,
high-risk girls were intermediate between control girls and girls with MDD in cardiovascular reactivity to social exclusion. Based on the present findings, it may be hypothesized that high risk girls who later develop MDD should exhibit increases in blood pressure measurements, decreases in resting heart rate, and increases in DBP and MAP reactivity to social exclusion. Future longitudinal studies similar in design to the present study should follow high risk girls to address which measurements change upon the onset of depression in high risk girls who develop initial onset MDD.

Longitudinal studies should also assess future cardiovascular events in each of the three study groups to assess whether potential biomarkers of MDD suggested by the present study may also be potential biomarkers of future CVD risk. Most importantly, the present study emphasizes the importance of monitoring and controlling cardiovascular measures at stages as early as adolescence, to control hypertension that may result from depression, and to avoid future risk of cardiovascular disease.
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