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Title: Psychobiological Markers of Allostatic Load in Depressed and Non-Depressed Mothers and Their Adolescent Offspring

Abbreviated Title: Allostatic Load in Depressed Mothers and Their Adolescents

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Abstract

Background: A substantial body of research has emerged suggesting that depression is strongly linked to poor physical health outcomes, which may be partly due to increased allostatic load across stress response systems. Interestingly, health risks associated with depression are also borne by the offspring of depressed persons. Our aim was to investigate whether maternal depression is associated not only with increased allostatic load across cardiac control, inflammation, cellular aging, and behavioral health in mothers, but also if this is transmitted to adolescent children, possibly increasing the risk for early onset of psychiatric conditions and disease in these offspring.

Methods: A pre-registered and case-control study of 180 low-income mothers (50% mothers depressed, 50% mothers non-depressed) and their adolescent offspring was conducted in a laboratory setting in order to determine how depressed mothers and their adolescent offspring systematically differ in terms of autonomic, sympathetic, and parasympathetic cardiac control; inflammation; cellular aging; and behavioral health that are suggestive of higher allostatic load.

Results: Findings indicate that depressed mothers and their adolescent offspring systematically differ in terms of comorbid mental and physical health risk profiles that are suggestive of higher allostatic load. Findings indicate that depressed mothers exhibit elevated resting heart rate and decreased heart-rate variability, while adolescent offspring of depressed mothers also exhibit greater mental health symptoms, elevated heart rate, and accelerated biological aging (shorter telomeres). These effects persisted after controlling for a range of potential covariates, including medication use, sex, age, and adolescents own mental health symptoms.

Conclusions: Findings indicate that maternal depression is associated with indices of increased allostatic load in depressed women and their adolescent children, possibly increasing risk for

early onset of psychiatric conditions and disease in these offspring. Future research is needed to delineate why some systems are more impacted than others in mothers and their offspring.

Key Words: Adolescence, Biomarkers, Health Psychology, Maternal Depression, Parent-Child Relationships

Abbreviations:

BMI- Body Mass Index

CV- coefficient of variation

ECG- electrocardiography

HRV- heart rate variability

ICG- impedance cardiography

PEP- Pre-Ejection Period

RMSSD- Root Mean Square of Successive Differences

sCRP- salivary C-Reactive Protein

SCL- Skin Conductance Level

SNS- Sympathetic Nervous System

Introduction

Individuals experiencing psychiatric disorders such as depression live an average 10 years less than comparison groups (Walker, McGee, & Druss, 2015). Consistent with this finding, a substantial body of research has emerged suggesting that depression is strongly linked to poor physical health outcomes (Bruffaerts et al., 2015; Iacovides & Siamouli, 2008; Mayer et al., 2001; Prince et al., 2007; Scott et al., 2007; Von Korff et al., 2009). This may be partly due to increased allostatic load or the dysregulation of biological stress mechanisms, such as cardiovascular physiology and inflammation (McEwen, 2003; Ulmer-Yaniv, Djalovski, Priel, Zagoory-Sharon, & Feldman, 2018), that may lead to biological "wear and tear" resulting in accelerated biological aging. Importantly, the effect sizes of mental health symptoms on physical health rival those of health behaviors, such as smoking and obesity (Niles & O'Donovan, 2019). These data highlight the need for careful assessment of associations between psychiatric disorders, such as depression, and biological mechanisms associated with the onset and progression of disease.

Health risks associated with depression, moreover, are also borne by the offspring of depressed persons (Ulmer-Yaniv et al., 2018). Depressive disorders disproportionately affect women (Salk, Hyde, & Abramson, 2017), and are experienced by 10-15% of mothers with minor children (Ertel, Rich-Edwards, & Koenen, 2011). Exposure to maternal depression is a particularly potent stressor associated with deleterious emotional and behavioral outcomes, as has been documented in multiple reviews and meta-analyses (Goodman, 2007; Goodman et al., 2011). Recently, research has begun to elucidate the association between maternal depression and poorer physical health in offspring (Casey et al., 2004; Rahman, Iqbal, Bunn, Lovel, & Harrington, 2004; Raposa, Hammen, Brennan, & Najman, 2014). Given evidence of adverse

parenting in women with depressive syndromes, these findings coincide with those of meta-analyses indicating that relationships wield an influence on health outcomes on par with the association between psychopathology and health outcomes as described above, such that relationships have an impact on health in the range of well-known behavioral health variables, such as physical activity, alcohol consumption, and diet (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Holt-Lunstad, Smith, & Layton, 2010).

Most prior research examining the impact of maternal depression on offspring has been limited in one or more of several ways – by focusing on families with young (i.e. prepubescent) children, one domain of function (e.g. psychological, behavioral, or biological), or just one family member (e.g. the parent or child). Recent scientific advances have begun to elucidate that adolescence is a sensitive and dynamic maturational period that is a foundation for future health (Sawyer et al., 2012) and an inflection point for health trajectories across the lifespan (Dahl, Allen, Wilbrecht, & Suleiman, 2018; Patton et al., 2016). Understanding factors that influence adolescent health is vital as adolescents make up a quarter of the world's populations (i.e., 1.8 billion; Sawyer et al., 2012) and adolescent health has historically received little attention (Williams, Holmbeck, & Greenley, 2002), resulting in blunted health gains when compared to other age groups (Patton et al., 2016).

Allostatic Load and Depression

A physically and temporally interconnected array of stress response systems, including the autonomic nervous system and inflammatory system, which have been shown to impact the rate of biological aging (e.g., telomere system), have been proposed to translate stress exposure to negative health outcomes (Hostinar, 2015; Shonkoff et al., 2009). Mechanistically, the autonomic nervous system innervates the inflammatory system (Kemeny & Schedlowski, 2007)

and has been shown to regulate immune activity (Nance & Sanders, 2007) with the sympathetic branch having a pro-inflammatory effect (Jänig, 2014; Nelson et al., 2017) and the parasympathetic branch having an anti-inflammatory effect (Borovikova et al., 2000; Thayer & Sternberg, 2006). Furthermore, heightened levels of inflammation may be particularly detrimental as inflammation is associated with increased cellular turnover, which may shorten telomere length as telomeres shorten with each cell division (Rode et al., 2014) and accelerate biological aging. Visually, this can be depicted through the Cascade Model from Stress to Disease (see Figure 1). Higher levels of allostatic load resulting from the excessive and repeated activation of these stress response systems without the social buffering effects of close and warm relationships (Shonkoff et al., 2012) may partly account for these negative outcomes. This may have later implications for the early onset of disease as repeated activation can compromise these stress response systems (McEwen, 2006) and potentiate the effects of later life stress (Dich et al., 2015). Indeed, human and animal models have established that early life stress is associated with cardiovascular disease, heightened inflammation, and shorter telomere length in adulthood (for reviews see Fagundes & Way, 2014; Murphy et al., 2017; Price, Kao, Burgers, Carpenter, & Tyrka, 2013 Taylor, Lehman, Kiefe, & Seeman, 2006).

Individuals experiencing depression have been shown to have altered functioning across these physically and temporally interconnected stress response systems. Specifically, in terms of alterations to cardiac psychophysiology, those with depression have higher resting heart rates (Allister et al., 2001; Byrne et al., 2010; Fan et al., 2016), which may be due to the lower resting parasympathetic activity (i.e., heart rate variability [HRV]) observed in adolescents and adults with depression (Kemp et al., 2010; Koenig et al., 2016) and possible higher sympathetic activity (Dhar & Barton, 2016). Furthermore, those with depression tend to have higher levels of c-

reactive protein, a measure of inflammation (Slavich & Irwin, 2014; Valkanova et al., 2013), although this is not found in all studies and study quality has been shown to moderate this association in a recent meta-analysis (Horn et al., 2018). Lastly, depression has been shown to be associated with accelerated biological aging as indicated by shorter telomere length (Darrow et al., 2016). In terms of offspring of women with depression, these findings suggest that exposure to maternal depression may upregulate immediate autonomic stress responses, intermediate inflammatory profiles, and long-term cellular aging. In essence, maternal depression may act as a form of social threat that may up-regulate autonomic activation and inflammation (Glaser et al., 2002; Kiecolt-Glaser et al., 2010), shortening telomere length (Nelson et al., 2018), which may lead to a dysregulated phenotype putting offspring at risk for both physical and mental health problems (Slavich & Irwin, 2014).

The Current Study

This case-control study was preregistered on Open Science Framework (https://osf.io/wu4y5/) with open code, and examined cross-sectional differences in biomarkers of allostatic load in mothers with and without depression and their adolescent offspring, as well as indices of mental health in the offspring. The goals of this case-control study were threefold: 1) to identify differences between depressed and non-depressed mothers, 2) to use a multi-method design to index biological markers associated with allostatic load across autonomic-, sympathetic-, parasympathetic-systems, inflammation, and cellular aging; and 3) to examine these same indices, as well as indices of behavioral health in their adolescent offspring to better understand how maternal depression may get under the skin during this understudied developmental period. We hypothesized that mothers in the Depressed Group would have greater mean resting heart rate as a function of both higher resting sympathetic activity (i.e., greater skin

conductance level and shorter pre-ejection period) and lower resting parasympathetic activity (i.e., lower HRV), greater levels of inflammation (c-reactive protein), and shorter telomere length, as compared to non-depressed mothers. We hypothesized that adolescent offspring of depressed mothers (High Risk Group) would demonstrate the same patterning in allostatic load as well as greater behavioral and emotional difficulties.

Methods and Materials

Participants

Participants consisted of 180 low-income women (see Table 1) and their adolescent children, aged 11-14 (see Table 2). Two groups of women were recruited: a Depressed Group, selected for currently elevated depressive symptoms and a history of treatment for depression, and a Non-Depressed Group, selected for no or low levels of current depressive symptomatology, no history of treatment for depression, and no current (i.e., past month) mental health treatment for any mental health disorder. Adolescents of mothers in the Depressed Group were placed in a High Risk Group, while adolescents of mothers in the Non-Depressed Group were placed in the Lower Risk Group (note that we named this "Lower Risk," rather than "Low Risk" as both groups came from a low-income sample). Exclusion criteria for participants of both groups included psychosis, other illness, or cognitive impairment that would interfere with participation (e.g., substance use that would render abstinence for the assessment difficult to tolerate).

Recruitment

In order to recruit a low-income sample, the majority of participants (n = 132) were recruited through the organization that administers the Oregon Health Plan (Medicaid) in the county where data were collected. The remainder of the sample (n = 48) were recruited through

online advertisements; those recruited online were screened to ensure that their incomes would have rendered them eligible for Medicaid. This low-income sample was selected, because mental health problems such as depression are more prevalent in these groups. There were significant group differences in recruitment source, such that more mothers in the Depressed Group were recruited online, X^2 (1) = 12.528, $p < .001$. Mothers and adolescents provided informed consent and assent, respectively prior to assessment. All procedures were approved by Institutional Review Board. Further detail on recruitment procedures can be found in supplemental material.

Assessment Procedures

After the informed-consent procedure, mothers completed a questionnaire, conducted over the phone by research assistants, and then an in home diagnostic interview. Subsequently, mothers and adolescents participated in a laboratory assessment during which adolescents completed a questionnaire, and mothers and their adolescents were outfitted with ambulatory electrocardiography (ECG) and impedance cardiography (ICG) devices to record psychophysiological indices during a 2-minute resting baseline and then participated in two 15-minute interaction tasks (these later tasks were not included in the current study and will not be discussed further here). At the end of the laboratory session, adolescents and mothers provided two saliva samples to index c-reactive protein and telomere length.

Symptom Measures

Self-Report of Mental Health Symptoms. Mothers completed the Patient Health Questionnaire-9 (Kroenke, Spitzer, & Williams, 2001) and adolescents completed the Youth Self Report (Achenbach, 1991).

Diagnostic Measure. Mothers completed the Structured Clinical Interview, non-patient version (First, Spitzer, Gibbon, & Williams, 1996) in order to characterize the sample and ensure

that participants in the Non-Depressed Group did not meet criteria for depressive disorders. Interrater reliability was kappa = .80.

Biological Measures.

Psychophysiological Assessment. ECG and ICG data were acquired using Vrije Universiteit Ambulatory Monitoring System (VU-AMS), which uses a 3-lead ECG and 4-lead ICG. Electrodes were placed in line with the VU-AMS manual instructions (see supplemental material). Data were scored using the Data Analysis and Management Software (DAMS) program (http://www.vu-ams.nl/). To obtain the resting baseline assessment, participants were asked to sit quietly for a 2-minute period. Data were averaged over this 2-minute period.

Autonomic Activity: Heart Rate was calculated based on time (in milliseconds) between successive R waves (R-R intervals) on the ECG to calculate average beats per minute. The root mean square of successive R-R interval differences (RMSSD), which has been shown to reflect HRV or cardiac vagal activity (Kleiger, Stein, & Bigger, 2005; Laborde, Mosley, & Thayer, 2017; Thayer & Lane, 2007), was calculated to measure parasympathetic nervous system activity. Cardiac pre-ejection period (PEP), a marker of sympathetic nervous system (SNS) activity, was automatically calculated for each cardiac cycle as the time interval in msec between the onset of ventricular depolarization (Q wave onset of the ECG) and the opening of the aortic valves (B point in the ICG dZ/dt signal). Skin conductance level (SCL), a second measure of SNS activity, was automatically calculated based on the electrodermal activity of the skin on the pointer and middle fingers, which was measured using direct current utilizing a 16 bit A/D converter and we did not quantify phasic changes. The sampling rate was 10 Hz with a signal range of 0-95 micro Siemens (μS). The SCL signal was pre-processed to remove the noise and power-line interference in the signal. A low-pass filter with cut-off frequency of 2 Hz was used

to filter the signal. In order to avoid shifting of peaks, filtering was done both in forward and reverse directions. The signal was then visually inspected for artifacts and averaged over the 2 minute period.

Inflammation: Saliva samples were collected to capture salivary c-reactive protein (sCRP) according to Salimetrics instructions. Samples were assayed in duplicate by Dr. Elizabeth Shirtcliff's SPIT lab (https://research.hs.iastate.edu/spit-lab/). The inter-assay coefficient of variation (CV) was 3.22% and the intra-assay CV was 1.91%. Samples were log transformed to correct for skew.

Cellular Aging: A saliva sample (DNA Genotek Oragene DISCOVER (OGR-500) collection devices) was collected at the end of the session from a subsample (n = 85) of participants (High Risk Adolescents = 41, Lower Risk Adolescents = 44, Depressed mothers = 44, Non-Depressed mothers = 42) due to financial limitations (see supplemental materials) and assayed by The Blackburn Lab at University of California San Francisco to calculate relative telomere length (T/S ratio). The average CV was 2.18%. There were no differences between the telomere subsample and the full sample on any demographic, adolescent, or maternal variables, except age, such that mothers, $F(1, 178) = 4.34$, $p = .039$, and adolescents, $F(1, 171) = 11.5$, $p < .001$, were older on average in the telomere subsample.

Covariates. We collected the following measures as potential covariates: age, biological sex, ethnicity, race, body mass index (BMI), body temperature to index participant health as this can influence sCRP levels, self-reported gum bleeding and sickness in past 24 hours, and medication use including stimulant, anxiolytic, blood pressure, antibiotic/antiviral, birth control, hormone, NSAIDs, steroids, antihistamines, and adrenergic bronchodilators (see Supplementary Tables for percentage of mothers and adolescents in each group who were on different

medications). Only covariates significantly associated with outcome variables were included in analyses to prevent overfitting.

Statistical Analyses.

All statistical analyses were conducted with R Studio, version 1.1.463. A series of analysis of covariance (ANCOVAs) procedures were performed separately for mothers and adolescents across each of the allostatic load outcome measures using listwise deletion for missing data (see supplementary materials), rather than multiple imputation, because telomere data were collected on less than 50% of the sample due to financial limitations. For each of the adolescent analyses, three separate models were run for each outcome adding more stringent covariates, which included 1) unadjusted model with only the dependent variable, 2) adjusted model with age, biological sex, and medication, and 3) adjusted model with adolescent's own mental health symptoms in addition to prior covariates in order to covary out any influence adolescents' own mental health had on outcome measures. For each of the mother analyses, two separate models were run for each outcome with the second adding more stringent covariates, which included 1) unadjusted model with only the dependent variable and 2) an adjusted model with age and medication use added to the model. Figures show swarmplots to detail raw distribution and effect sizes with bootstrapped 95% confidence intervals (Ho & Tumkaya, 2019). All measures were winsorized to +/- 3 SD. We did not correct for multiple comparisons for heart rate, HRV, inflammation, or telomere length as these were distinct constructs with independent hypotheses, but we did correct for multiple comparisons for the two measures of SNS activity. See supplemental materials for code used for analyses and unadjusted and adjusted results.

Results

Descriptive Statistics. As shown in Tables 1 and 2, there were no significant group differences in adolescent biological sex, adolescent or mother age, race, ethnicity, or maternal education, employment, or income. Figure 2 provides a correlation matrix between both mother and adolescent markers of allostatic load.

Mental Health Symptoms. Adolescents of depressed mothers had significantly higher total mental health symptoms than those of non-depressed mothers, $F(1, 173) = 17.950$, $p < .0001$, controlling for age and sex, $F(1, 171) = 17.904$, $p < .00001$ (see Figure 3a) with Cohen's F = 0.324. Descriptively, 6.67% (n = 6) of adolescents met clinical threshold for total YSR symptoms and 100% of these adolescents had mothers that came from the Depressed Group revealing a significant difference between adolescent groups, $X^2 (1) = 4.256$, $p = .039$. Adolescents of depressed mothers also had significantly higher internalizing mental health symptoms than those of non-depressed mothers, $F(1, 173) = 13.460$, $p = .0003$, controlling for age and sex, $F(1, 171) = 13.404$, $p < .0001$ with Cohen's F = 0.280. Lastly, adolescents of depressed mothers had significantly higher externalizing mental health symptoms than those of non-depressed mothers, $F(1, 174) = 13.390$, $p = .0003$, controlling for age and sex, $F(1, 172) = 13.492$, $p < .0001$ with the same Cohen's F = 0.280 as internalizing symptoms.

Biological Aging. There were no differences between depressed and non-depressed mothers in telomere length, $F(1, 84) = 2.322$, $p = .131$, even after controlling for age, $F(1, 83) = 2.316$, $p = .132$ with Cohen's F = 0.167. In contrast, adolescents of depressed mothers had significantly shorter telomere length compared to those of non-depressed mothers, $F(1, 83) = 6.653$, $p = .012$, even after controlling for age, sex, and adolescents own mental health symptoms, $F(1, 78) = 6.318$, $p = .014$ (see Figure 3b) with Cohen's F = 0.285.

Inflammation. There was no significant difference between depressed and non-depressed mothers on sCRP, $F(1, 135) = 0.606$, $p = .438$, even after controlling for age and BMI, $F(1, 129) = 0.807$, $p = .371$ with Cohen's F = 0.079. There was also no significant difference between adolescent groups on sCRP, $F(1, 151) = 1.812$, $p = .180$, even after controlling for age, sex, BMI and adolescent's own mental health symptoms, $F(1, 140) = 2.202$, $p = .140$ with Cohen's F = 0.125.

Resting Autonomic Activity. Mothers in the Depressed Group had significantly higher heart rates compared to the Non-Depressed Mothers, $F(1, 168) = 5.568$, $p = .019$, even after controlling for age as well as stimulant, anxiolytic, and blood pressure medication use, $F(1, 164) = 5.591$, $p = .091$ (see Figure 4a) with Cohen's F = 0.185. Similarly, adolescents of depressed mothers had significantly higher heart rates compared to those of non-depressed mothers $F(1, 172) = 4.544$, $p = .035$, even after controlling for age, sex, stimulant medication use, and adolescent's own mental health symptoms $F(1, 164) = 5.401$, $p = .021$ (see Figure 3c) with Cohen's F = 0.181.

Resting Parasympathetic Activity. Mothers in the Depressed Group had significantly lower HRV compared to the Non-Depressed Mothers, $F(1, 168) = 6.549$, $p = .011$, even after controlling for age as well as stimulant, anxiolytic, and blood pressure medication use, $F(1, 164) = 6.900$, $p = .009$ (see Figure 4b) with Cohen's F = 0.205. There were no significant difference for HRV between adolescent groups, $F(1, 172) = 0.159$, $p = .691$, even after controlling for age, sex, stimulant medication use, and adolescent's own mental health symptoms $F(1, 164) = 0.319$, $p = .573$ with Cohen's F = 0.044.

Resting Sympathetic Activity. There were no significant differences between depressed and non-depressed mothers for PEP, $F(1, 162) = 0.473$, $p = .493$, even after controlling for age as

well as stimulant, anxiolytic, and blood pressure medication use, $F(1, 158) = 0.475$, $p = .492$ with Cohen's F = 0.055. or SCL, $F(1, 161) = 0.350$, $p = .555$, even after controlling for age as well as stimulant, anxiolytic, and blood pressure medication use, $F(1, 157) = 0.350$, $p = .555$ with Cohen's F = 0.047. There were no significant differences between adolescent groups on PEP, $F(1, 169) = 0.037$, $p = .847$, even after controlling for age, sex, stimulant medication use, and adolescent's own mental health symptoms $F(1, 161) = 0.007$, $p = .932$ with Cohen's F = 0.007, or SCL, $F(1, 158) = 1.704$, $p = .194$, even after controlling for age, sex, stimulant medication use, and adolescent's own mental health symptoms $F(1, 151) = 1.975$, $p = .162$ with Cohen's F = 0.114.

Discussion

Our study examined the association between maternal depression and mother and adolescent patterns of allostatic load across multiple psychobiological systems including indices of autonomic cardiac control, inflammation, and cellular aging. These findings have important implications for understanding the multigenerational linkages between mental and physical health as these biological markers are putative risk factors for subsequent physical and psychiatric health problems. Overall, findings indicate that depressed mothers and their adolescent offspring systematically differ from their non-depressed counterparts in terms of comorbid mental and physical health-risk profiles suggestive of higher allostatic load. These findings are particularly interesting, because both groups came from high-risk (i.e., lower income) backgrounds, which are themselves associated with higher allostatic load (Lupien, King, Meaney, & McEwen, 2000). Moreover, findings indicate that youth of depressed mothers may be at increased risk for developing comorbid mental-physical health complications.

Consistent with numerous previous findings, adolescent offspring of depressed mother showed greater levels of mental health symptoms (Betts, Williams, Najman, & Alati, 2014; Connell & Goodman, 2002; Lyons-Ruth, Easterbrooks, & Cibelli, 1997). Also, depressed mothers and their adolescents showed elevated resting heart rates, an effect that has also been previously observed (Allister, Lester, Carr, & Liu, 2001; Fan et al., 2016).

Depressed mothers also exhibited lower resting HRV, indicating lower baseline parasympathetic activity. This replicates prior literature showing associations between depression and dysregulated parasympathetic activity (Kemp et al., 2010; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). In contrast, this finding was not observed among the adolescent offspring groups. One potential reason for this differential finding between mothers and adolescents may be that mothers have experienced case level depression, while YSR scores indicate that most offspring, even offspring of depressed mothers likely haven't experienced clinical threshold for internalizing disorders. Therefore, one potential interpretation of the currently pattern of findings is that lower HRV may be a unique consequence of experiencing case level depression, rather than a measure of stress exposure *per se* (which characterizes the adolescent offspring sample due to their exposure to living with a mother experiencing depression). Additionally, HRV has been shown to be strongly influenced by developmental age before stabilizing in adulthood (Quintana et al., 2016), and as such developmental processes may be more important than stress exposure in influencing HRV during adolescence. Overall, more research is needed to delineate why HRV effects were observed in depressed mothers, but not their offspring.

Interestingly, adolescents of depressed mothers did exhibit increased cellular aging, while this effect was not observed in depressed mothers. Accelerated cellular aging in adolescents of

depressed mothers is consistent with prior research indicating that the offspring of depressed mothers or with mothers increasing in depressive symptoms have shorter telomere length (Gotlib et al., 2014; Nelson, Allen, & Laurent, 2018), while the null finding for mothers is in contrast to prior research (Darrow et al., 2016; Ridout et al., 2016). One possible explanation for these differential findings between mothers and their adolescents is the fact that the entire sample came from a highly stressed poverty sample, which has been shown to be associated with biological aging (Ridout et al., 2018). This high poverty sample may be relevant to not seeing between group differences in the mothers; that is depression may not add to the effects of poverty on accelerated aging in mothers as prior research has shown that income is associated with telomere length even after controlling for depressive symptoms in adults (Yen & Lung, 2013). In contrast, though the kids are also experiencing poverty, some of the contribution of poverty to distress in kids may be through the effect on parenting; given that there is a strong literature of negative parenting behaviors in depressed mothers (Norcross et al., 2017), which may have accounted for the greater telomere degradation in offspring. Furthermore, a recent meta-analysis found that earlier developmental exposure to adversity, including maternal depression, was associated with shorter telomere length (Ridout et al., 2018) implying that accelerated aging may be more observable in a younger sample when environmental and relational perturbations might have a larger impact on underlying biological systems than experiences of depression later in life (Dahl et al., 2018). This is one explanation for why we found results for offspring, but not their mothers. Needless to say, more research is needed to tease apart why shorter telomere length were observed in offspring, but not their mothers.

Surprisingly, no differences in measures of sympathetic activation between the groups for either mothers or adolescents were found. These findings may indicate that resting sympathetic

activity of the autonomic nervous system may be less determinative of group differences than overall autonomic activity in depressed mothers and their adolescents, as might be expected as resting heart rate is largely parasympathetically controlled as cardiac vagal activity decreases heart rate from its higher intrinsic rate (Jose & Collison, 1970). Indeed, the significant effects observed for heart rate, combined with null effects for sympathetic activity, is consistent with some prior literature (Byrne et al., 2010; Moser et al., 1998), and suggest that heart rate and heart rate variability may be more robust psychobiological markers of vulnerability to depressive disorders than are measures of the sympathetic branch during rest.

One potential interpretation of these findings is that maternal depression may increase not only the mothers' allostatic load, but may also increase the mental health symptoms of their offspring, which may lead to increased allostatic load via upregulated autonomic activation and rate of cellular aging placing these offspring at heightened risk for the early onset of disease (Epel & Prather, 2018). Indeed, data from 17 countries and over 2 million person years shows that depression is associated with various subsequent chronic physical health conditions (odds ration ranging from 1.2 to 2.1; Scott et al., 2016). Conversely, it is possible that living with a depressed parent serves as a source of stress that increases allostatic load and then contributes to the manifestation of mental health difficulties, rather than mental health difficulties increasing allostatic load. Research shows that both mental and physical health conditions can serve as antecedents risk factors for the development of the other (Tegethoff et al., 2016). Future longitudinal studies are necessary to examine these mechanisms as mediators in the link between maternal psychopathology and increased risk for the emergence of disease in offspring. Relatedly, prior research has found that altered autonomic nervous system activity may play a role in the development and onset of psychiatric disorders (Beauchaine, 2001). The current

findings may assist in the understanding of intergenerational mechanisms and the role that altered autonomic cardiac control and other biological markers of allostatic load may play in the development and onset of psychiatric disorders, however future longitudinal studies are required to confirm that these mechanisms are salient mediators in the link between maternal psychopathology and the increased risk for the emergence of disease in offspring.

Limitations and Future Directions

While the present study had significant strengths such as using a multimethod assessment (i.e., mental health, cardiovascular functioning, inflammation, and cellular aging) in both depressed and non-depressed mothers and their adolescent offspring, there are limitations to note. First, this was a cross-sectional study, which precluded the examination of developmental timing effects across adolescence, that is, does maternal depression have differential and shifting influences on adolescent allostatic load over time. Second, this study did not conduct clinical interviews on adolescent offspring limiting the ability to covary differences of allostatic load to symptom level with YSR. Future research should collect clinical interviews on both mothers and offspring. Third, the baseline assessment may not have provided an ecologically valid assessment of physiology as individual differences in response to physiological assessment in a laboratory setting may be artificially inflated or deflated (Jennings, Kamarck, Stewart, Eddy, & Johnson, 2007; Pattyn, Migeotte, Neyt, den Nest, & Cluydts, 2010). As we have argued previously, future studies should utilize ambulatory assessment methods (Nelson et al., Preprint; Nelson & Allen, 2018, 2019), in order to capture ecologically valid resting baselines to bring this type of research out of the lab and into real world contexts (DeJoseph, Finegood, Raver, & Blair, 2017). Fourth, we did not collect data on age of first depressive episode, the duration of the current depressive episode, total number of depressive episodes, or familial history of

depression, which are important variables to consider when investigating the impact depression has on one's own and one's offspring's allostatic load. Future research should make sure to collect these contextual clinical factors in addition to whether or not participants met criteria for depression. Lastly, future research should attempt to integrate information across these distinct psychobiological domains in order to calculate an overall cumulative risk score as has been done in some prior studies using either clinical cutoffs, when possible, or the highest/lowest quartile, depending on construct of interest, when clinical cutoffs are unknown and then summing together dichotomous variables to create a risk score (Seeman et al., 2001; Slopen et al., 2014). Unfortunately, due to only collecting telomere length on a subset of participants we were unable to run these as post-hoc analyses in the current study.

Conclusion

Our study systematically examined the association between maternal depression and a range of cardiovascular, inflammatory, and cellular aging variables in mothers and their offspring. These variables may represent intergenerational risk factors for subsequent physical and psychiatric problems. Findings indicate that both depressed mothers and their adolescent offspring systematically differ in terms of health risk profiles suggestive of higher allostatic load, specifically elevated resting heart rate (mothers and offspring), decreased heart rate variability (mothers), and both accelerated biological aging and increased mental health symptoms (offspring). These findings are particularly noteworthy as all the participants were selected from a population experiencing socioeconomic disadvantage, a well-established risk factor for elevated allostatic load (Lupien et al., 2000). These findings indicate that maternal depression is associated not only with mothers' own allostatic load, but also with increased allostatic load in their offspring, which may place them at risk for psychopathology and the early morbidity.

Key Points and Relevance

- Research suggests that depression is strongly linked to poor physical health outcomes, which may be due to increased allostatic load.
- It is not presently known whether or not indices of allostatic load are transmitted from depressed mothers to adolescent offspring, which may increase risk for psychiatric and physical health conditions.
- This preregistered case-control study of 180 mothers (50% depressed, 50% non-depressed) and their adolescent offspring was conducted to see if depressed mothers and their adolescents exhibit increased allostatic load across cardiac control, inflammation, cellular aging, and behavioral health indices.
- Findings indicate that depressed mothers exhibit elevated resting heart rate and decreased heart-rate variability. Adolescents of depressed mothers exhibited greater mental health symptoms, elevated heart rate, and accelerated biological aging.

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Conflict of Interest

All authors declare no conflicts of interest.

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Table 1. Maternal Characteristics by Group

	Depressed			Non-Depressed			Group Difference
Variable	*N*	Mean (*SD*)	Percentage	*N*	Mean (*SD*)	Percentage	*p*-value
Group	90		100%	90		100%	
Age	90	40.6 (6.5)		90	40.0 (6.4)		.482
Mental Health							
Depressive Symptoms	90	12.32 (5.84)		89	2.57 (2.70)		< .001
Anxiety Symptoms	90	9.69 (5.42)		90	2.34 (2.87)		< .001
Employment							.077
Currently employed	44		48.89%	57		63.33%	
Homemaker	23		25.56%	21		23.33%	
Disabled and unable to work	9		10.00%	1		1.11%	
Underemployed, looking for a job	8		8.89%	8		8.89%	
Currently a student	3		3.33%	1		1.11%	
Other	3		3.33%	2		2.22%	

Education Level					.073
Less than High School	3	3.33%	3	3.33%	
High School Graduate/ GED	8	8.89%	17	18.89%	
Vocational or Professional School Certificate/	7	7.78%	8	8.89%	
Some College	57	63.33%	39	43.33%	
Bachelor's Degree or Higher Degree	15	16.67%	23	25.56%	
Income					.484
<$17,000	25	27.78%	16	18.18%	
$17,000 - $19,999	7	7.78%	13	14.77%	
$20,000 - $24,999	14	15.56%	8	9.09%	
$25,000 - $29,999	11	12.22%	10	11.36%	
$30,000 - $34,999	5	5.56%	6	6.82%	
$35,000 - $39,999	6	6.67%	9	10.23%	
$40,000 - $49,999	8	8.89%	10	11.36%	
>= $50,000	14	15.56%	16	18.18%	
Don’t Know	0	0.00%	2	2.22%	

Table 2. Adolescent Characteristics by Group

	High Risk			Low Risk			Group Difference
Variable	*N*	Mean (*SD*)	Percentage	*N*	Mean (*SD*)	Percentage	*p*-value
Group	90		100%	90		100%	
Age	90	12.90 (1.30)		90	12.90 (1.20)		.455
Adolescent Sex							.968
Male	45		50%	51		56.67%	
Female	45		50%	39		43.33%	
Adolescent Gender							
Male	45		50.00%	52		57.78%	
Female	44		48.89%	36		40.00%	
Other	1		1.11%	2		2.22%	
Race							.294
White or Caucasian	75		83.33%	67		74.44%	
More than One Race	15		16.67%	18		20.00%	

American Indian/ Alaska Native	0	0.00%	1	1.11%	
Native Hawaiian/ Pacific Islander	0	0.00%	1	1.12%	
African American	0	0.00%	1	1.11%	
No Response/ Unknown	0	0.00%	2	2.22%	
Ethnicity					.248
Not Hispanic or Latina	77	85.56%	70	77.78%	
Hispanic or Latina	13	14.44%	20	22.22%	

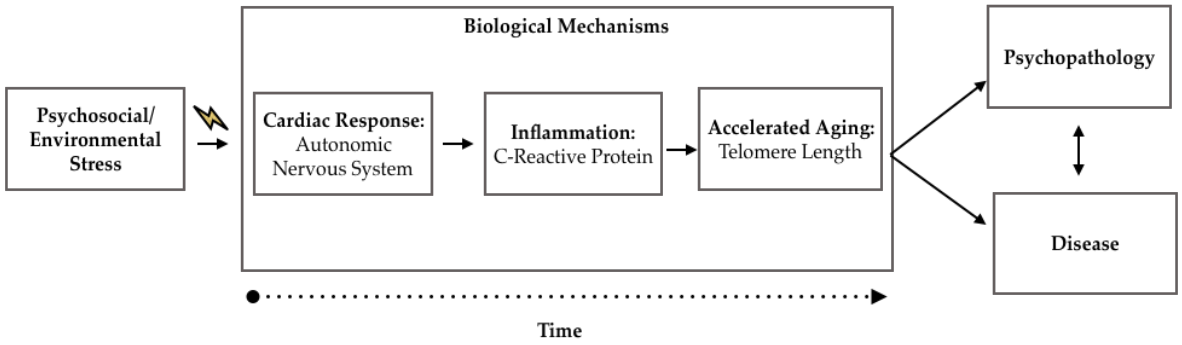

Figure 1. Cascade Model from Stress to Disease.

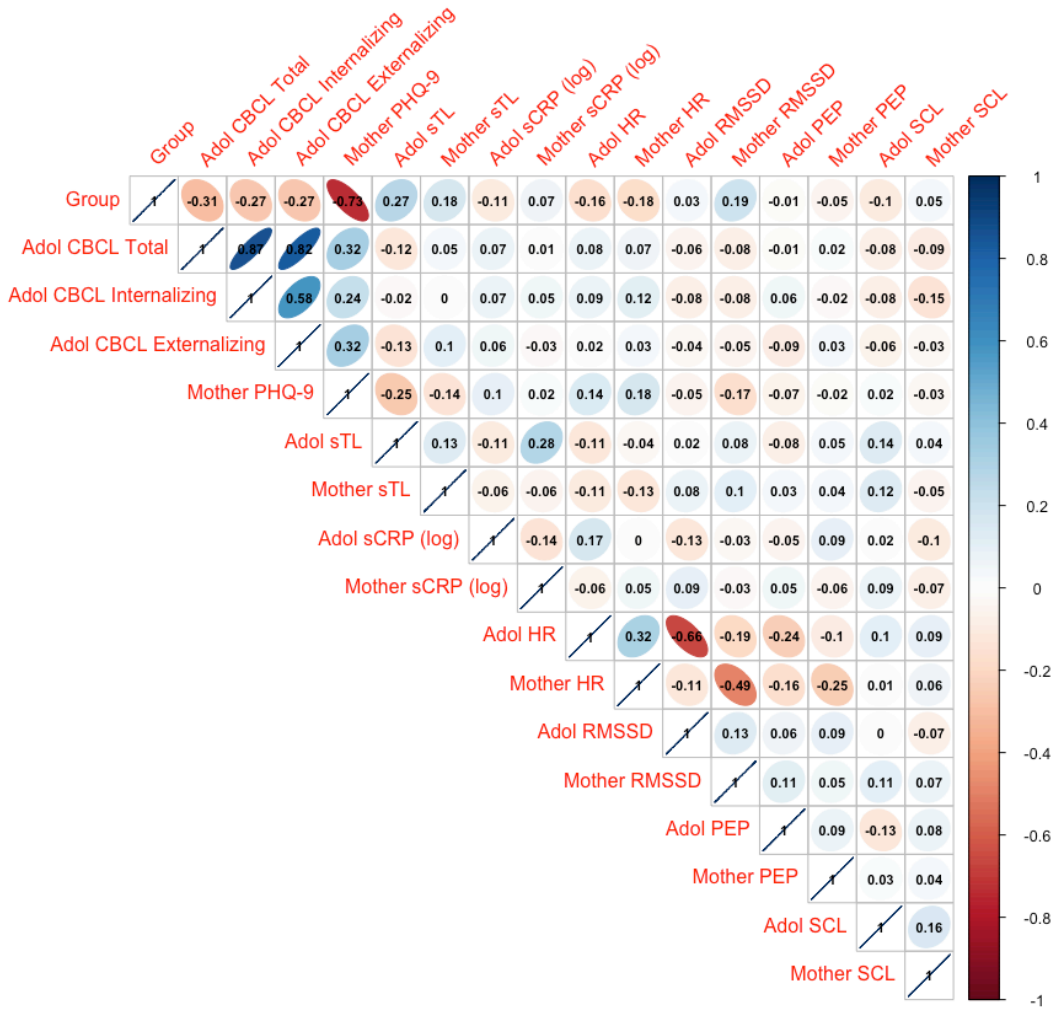

Figure 2. Correlation Matrix Between Group and Both Mother and Adolescent Measures of Allostatic Load. Note: Figure was created with complete observations for each pairwise correlation. Shape and color of circles shows direction and strength of association. Adol = Adolescent; CBCL = Child Behavior Checklist, PHQ-9 = Patient Health Questionnaire 9; sTL = Salivary Telomere Length; sCRP = Salivary C-Reactive Protein; HR = Heart Rate; RMSSD = Root Mean Squared of Successive Differences; PEP = Pre-Ejection Period; SCL = Skin Conductance Level.

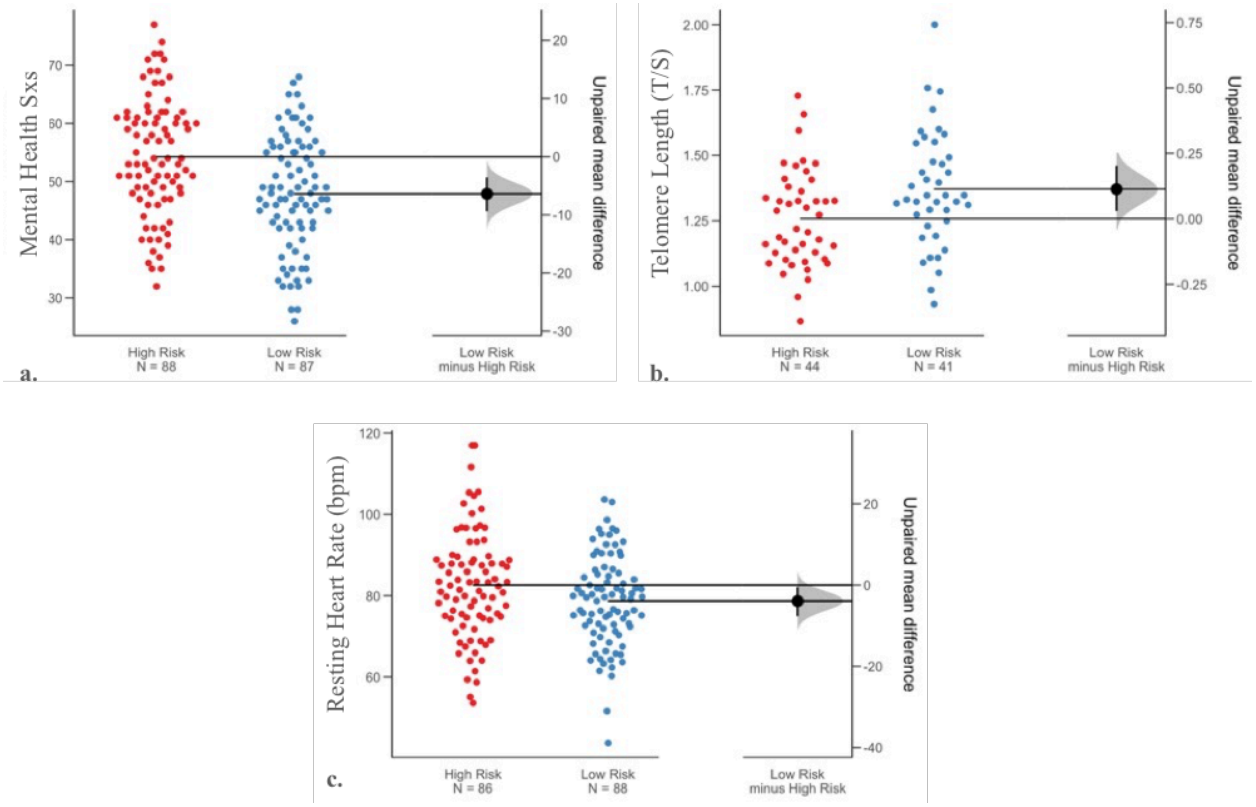

Figure 3. Differences Between High Risk and Lower Risk Adolescents for a. Mental Health Symptoms, b. Telomere Length, and c. Resting Heart Rate.

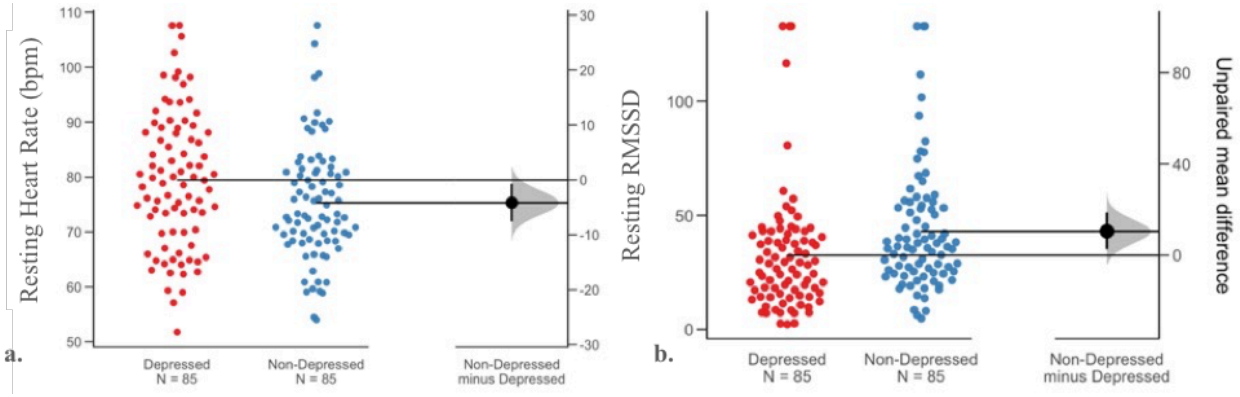

Figure 4. Differences Between Depressed and Non-Depressed Mothers on a. Resting Heart Rate and b. Resting HRV. Note: HRV = heart rate variability; RMSSD = root mean squared of successive differences.