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Emerald Yuan March 22, 2023

Depression in Individuals at Clinical High-Risk for Psychosis: The Association with Life Stressors, Stress Sensitivity, and Basal Cortisol Levels

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An abstract of

a thesis submitted to the Faculty of Emory College of Arts and Sciences

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Methods: The study sample included baseline data from North American Prodromal Longitudinal Study-3 (N=806, age 12 to 30). At baseline, the CHR-P group met standard criteria for CHR-P based on SIPS scores on attenuated positive symptom severity ratings. Calgary Depression Scale for Schizophrenia (CDSS) was used to measure current depressive symptom severity over the past two weeks. The modified LES and DSI were administered. Salivary cortisol, LES, DSI, and CDSS were all log-transformed in the analysis. Multiple linear regression was used to predict CDSS.

Results: CHR-P individuals have significantly higher scores in LES, stress sensitivity, DSI, and CDSS compared to controls. However, basal cortisol levels were not significantly higher in the CHR group compared to controls. Life Event Stress total score, CHR, and stress sensitivity together were positively associated with CDSS ($R2=0.42$, $p<0.001$). Stress sensitivity played a partial mediating role in the relationship between LES and CDSS, and there was no significant moderation effect of cortisol in any models.

Conclusion: Our findings suggest that stress sensitivity may be a key factor in the development of depression in CHR individuals, while cortisol levels may not play a significant role. These results underscore the importance of considering life stressors and stress sensitivity in the assessment and treatment of depression in this population and suggest the need for longitudinal follow-ups to further explore the role of cortisol as a potential biomarker.

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Introduction and Scientific Background:

In 2020, Major Depressive Disorder (MDD) affected an estimated 21 million adults in the United States, accounting for 8.4 % of the population (NIMH., 2022.; Proudman et al., 2021). According to the National Institute of Mental Health, young adults aged 18-25 have the highest prevalence of 17% of major depressive episodes (National Institute of Mental Health [NIMH], 2020). Recent research reveals that the elevated rate of depression has persisted into 2021, climbing up to 32.8 percent (Ettman et al., 2022). MDD is also highly recurrent, with a 60% lifetime risk of recurrence after the first episode (Monroe, 2011).

Despite its high prevalence, the causes of depression remain unknown. While it is well established that genetic factors and adverse experiences, such as exposure to stress and disruptions in social relationships increase the risk for depression, the neurobiological substrates underlying depression have not been established. But research findings have suggested several different neurobiological pathways. For example, neurotransmitter systems, especially dopamine and serotonin (Kambeitz and Howes, 2015), inflammatory processes (Nikkheslat et al., 2020; Nettis et al., 2021), neurotrophic factors (Lee and Kim, 2010), oxidative stress (Park et al., 2019; Lindqvist et al.,2017) and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Cattaneo et al., 2020; Nikkheslat et al., 2020), have been implicated in MDD. The HPA axis is the neural system that governs the secretion of the stress hormone, cortisol and has been hypothesized to mediate the relation between stress exposure and risk for MDD. As described below, the proposed study is concerned with the relation of cortisol with depression in youth.

Stress, the HPA Axis, and Depression

It has been estimated that exposure to chronic stress accounts for 80% of the onset of major depressive episodes (Slavich and Irwin, 2014). This estimation is based on the 80% of

community cases of depression are preceded by stressors (Mazure, 2006). The HPA axis plays a key role in maintaining body homeostasis and the body's responses to stress. Stress results in the hypothalamus's release of a corticotropin-releasing hormone (CRH), activating the pituitary gland to secrete adrenocorticotropic hormone (ACTH). This information was then transferred to the adrenal cortex where cortisol is released into the blood (Jacobson, 2005; Mikulska et al., 2021). Increased cortisol level then leads to the inhibition of CRH and ACTH secretion by a negative feedback loop through glucocorticoid receptors in the hippocampus (Liberzon et al., 2001).

Cortisol and Stress

Cortisol is secreted in response to stressful situations in order to enhance return to homeostasis (Stetler et al., 2011). It reduces the inflammatory response and is responsible for protecting the body from an excessive immune response (Morey et al., 2015; Vitlic et al., 2014). The impact of the severity of early life stress is also found to be associated with diurnal cortisol (Hunter et al., 2011), and this effect is moderated by puberty (King et al., 2017). Changes in the activity of the HPA axis also occur diurnally. This is related to the regulation of circadian rhythms, which explains why cortisol levels are observed the highest in the morning (i.e. cortisol awakening response, or CAR) (Pruessner et al., 1997; Wust et al., 2020). Following the CAR, the total diurnal cortisol release is sometimes estimated as the area under the curve with respect to ground (AUCg) (Golden et al., 2013).

Cortisol and Depression

Cross-sectional studies showed elevated cortisol levels in those with MDD compared to healthy controls (Islam et al., 2018; Khan et al., 2019; Bertollo et al., 2020). Previous studies also show that increased depressive symptoms are associated with elevated hair cortisol (Freeney

& Kenny, 2022), elevated CAR response (Baliyan et al., 2022), and elevated AUCg (LeMoult et al., 2015; Nikkheslat et al., 2020). This association is found to be especially robust in depression with psychotic and melancholic features (Owens et al., 2014; Schatzberg et al., 2013; Lamers et al., 2013; Keller et al., 2016), but not always in mild or atypical forms of MDD (Nandam et al., 2020; Herane-Vives et al., 2018; Keller et al., 2016). However, contradictory findings were also reported suggesting that long-term hair cortisol and short-term saliva cortisol showed inconsistent association with MDD (Herane-Vives et al., 2020; Steudte-Schmiedgen et al., 2017; Ford et al., 2019; Zajkowska et al., 2022). Atypical depression was also found to have lower cortisol levels (Herane-Vives et al., 2018; Juruena et al., 2018; Yehuda et al., 2011).

Clinical High-Risk for Psychosis

In early detection and prevention of schizophrenia and other psychotic disorders, researchers suggest the pre-onset or "prodromal period" that stems from the evidence of brain structural changes and decline in function around the time of psychosis onset (Addington et al., 2012). Identifying predictors and mechanisms of conversion to psychosis among such individuals ascertained to be in a clinical high-risk (CHR) or prodromal clinical state are critical steps in the search for preventive interventions (Cannon et al., 2008). Achieving these aims requires large sample sizes and long-term follow-ups, and most of the time requires collaborated consortiums.

Cortisol and Psychosis

Cortisol hypersecretion is also linked with psychosis, and it has been suggested that it may result from increased dopaminergic activity (Schatzberg et al., 1985). In one of the largest longitudinal studies of individuals at Clinical High Risk (CHR) for psychosis, the North American Prodrome Longitudinal Study (NAPLS 2), elevated cortisol levels predicted

prodromal progression (Cullen et al., 2020; Walker et al., 2013; Worthington et al., 2021). Studies using other cohorts also found similar outcomes, where daily stressors and elevations in diurnal cortisol in late childhood/early adolescence were associated with an increased risk for developing attenuated psychotic symptoms (Cullen, et al., 2021). However, meta-analyses showed a mixed relationship between cortisol and psychosis progression (Chaumette et al., 2016). The effects of psychotropic medications, including antipsychotics and antidepressants, may account for the variable findings (Subramaniam et al., 2019).

Depression and Schizophrenia

It has been shown that depression and schizophrenia are highly comorbid (Dai et al., 2018). A meta-analysis found that the pooled prevalence of comorbid depression and schizophrenia was 28.6% (Li et al., 2020). Depression is also the most common comorbid diagnosis in CHR individuals NAPLS-3, with 49% of enhanced and 44% of non-enhanced participants meeting the criteria for depression (Addington et al., 2022). Depression was found to be one of the leading causes of suicide in schizophrenia (Hettige et al., 2018; Shargh et al., 2016; Yan et al ., 2012; Sher & Kahn, 2019).

The Current Study

The current study examined the relationship between trauma and depression symptoms in the NAPLS-3 cohort and found that CHR participants who experience trauma have statistically significantly higher baseline depression compared to those who did not experience trauma (Farris, 2022). However, the association between life event stress and depressive symptom severity in NAPLS-3 has not been examined. And the interaction between life events stress and baseline cortisol levels in depressive symptoms is still unknown.

The present study will utilize data from the North American Prodrome Longitudinal Study 3 [NAPLS 3, (Addington et al., 2022). The purpose of this study is to investigate whether exposure and sensitivity to stress and basal cortisol differed between CHR subgroups with and without depression and whether depression ratings are correlated with cortisol levels at baseline. Based on the literature, it is hypothesized that a) CHR youth with depression will have greater exposure and distress in relation to stressors, and elevated basal cortisol compared to CHR youth without depression; b) individuals with more severe depression ratings will manifest higher stress exposure and cortisol levels.

Methods:

Participants:

The study sample included participants between the ages of 12 and 30 years from the multisite NAPLS-3 (Addington et al., 2022). To increase the likelihood of predicting transition to psychosis, they enriched the sample of CHR participants who met CHR criteria to predict a 40% likelihood of transition. This "enhanced criteria" was based on the Risk Calculator designed from NAPLS-2 (Cannon et al., 2016). Enhanced criteria were that participants had to (i) rate 4 (moderately severe) or higher on either P1-unusual thought content or P2-suspiciousness, or (ii) rate 3 (moderate) on both P1 and P2 or (iii) demonstrate impaired performance on either the Hopkins Verbal Learning Test-Revised (HVLT-R) or the Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding. Impaired performance was a score on the HVLT-R or BACS symbol coding that was at or below the 10th percentile base on norms for youth or for adults (Addington et al., 2022).

NAPLS-3 consists of 560 CHR participants who met enhanced criteria, and 96 healthy controls. All participants were recruited between February 2015 and November 2018 through extensive referral networks at each participating site (eg, healthcare providers, educators, mailings, and postings). NAPLS-3 is a five-year study with recruitment for three years and follow-up assessments for two years. Clinical and biomarker assessments were conducted every two months for the first 8-months with clinical follow-up assessments occurring at 12, 18, and 24 months. If an individual made the transition to psychosis, they received a full clinical and biomarker assessment at that time. This assessment would then be followed up one year later for a clinical assessment. This study presented here will only include baseline measures to avoid the caveat of attrition.

Measures:

Structured Clinical Interview for the DSM-5 (SCID-5)

Structured Clinical Interview for DSM-V was conducted used assess current and lifetime depression as well as other Axis 1 disorders (First et al., 2015).

Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS (Addington et al., 2007) was used to measure current depressive symptom severity over the past two weeks and has been validated in CHR individuals and demonstrated good psychometric properties (Addington et al., 2014).

Life Events Scale (LES)

The Peri Life Events Scale (LES) was administered for life events and sensitivity to stress (Dohrenwend et al., 1978). The LES was modified to exclude items that would be of unlikely relevance to the adolescent/young adult age range included in this study (e.g., getting a divorce, encountering serious financial loss). The modified version of the LES included 59-items pertaining to significant events or life changes that could conceivably be experienced at any of the ages included in the study sample. Events on the LES have been designated as “independent” of or “dependent” on an individual's characteristics. Items are also classified as positive or negative (Dohrenwend et al., 1978). Participants indicated whether the LE occurred at any point in their life. Interviewers queried participants about their level of subjective stress for each LE endorsed on a 7-point Likert scale ranging from “occurred but was not very stressful” to “caused me to panic.”

Cortisol

To assess cortisol, a minimum of three saliva samples were obtained at each of the five assessments over eight months (Addington et al., 2022). In order to maintain uniformity, samples

were collected at hourly intervals during the baseline and follow-up assessments. The samples were obtained in specimen tubes prelabeled with an ID, sample numbers, and collection time, and samples were stored at −20 °C until assayed. Participants were given instructions about food, beverage, substance consumption, and exercise; these data were also recorded for the previous evening and morning. All sites sent samples via commercial carrier on dry ice to Emory University where they were inventoried and stored in freezers upon arrival. For the salivary cortisol assay, the Salimetrics (Salimetrics, LLC, College Park, Pa) High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit was used. This assay captures the full range of salivary cortisol levels (0.003 to 3.0 μg/dL) requiring only 25 uL of saliva per test. Samples were assayed in duplicate.

Daily Stress Inventory (DSI)

Daily Stress Inventory (DSI) is a 58-item measure to examine the impact of minor stressful events over the last 24 hours (Brantley et al., 1987; Addington et al., 2022). Examples of such items include “interrupted while talking”, “had a minor accident (broke something, tore clothing)”, “had your sleep disturbed.” Participants indicated if the event occurred and rated each event on a 7-point Likert scale (Brantley et al., 1987).

Results:

In this study, data analysis was conducted using the R programming language. Demographic characteristics for each diagnostic group are presented in Table 1. Independent sample t-tests were conducted for continuous measures and gender. Cohen's D was calculated for effect sizes of the significance. Consistent with previous reports, CHR-P individuals have significantly higher LES, stress sensitivity, DSI, and CDSS scores compared to controls ($p<.01$). However, contrary to previous research that look at CHR and control groups (Carol and Mittal, 2015; Carol et al., 2017), basal cortisol levels are not significantly higher in CHR group compared to controls ($p >0.1$, see Table 1). This result, however, is consistent with a recent study that also found an insignificant difference in resting cortisol between the two groups (Ristanovic et al., 2023). Consistent with previous research, females have higher stress sensitivity ($F=21.71$, $p<.001$) and higher CDSS scores than males ($F=10.07$, $p<.01$) (Nayak et al., 2018). LES, DSI, and cortisol did not yield significant sex differences. Additionally, bivariate correlations among continuous variables of interest are presented in Table 2. CDSS is positively correlated with LES sum of stress ($r=0.36$, $p<.001$), DSI total ($r=0.38$, $p<.001$), and stress sensitivity ($r=0.45$, $p<.001$). Cortisol is positively correlated with age ($r=0.21$, $p<.001$) alone. However, after correcting for sampling time, none of the measures were correlated with basal cortisol.

A stepwise linear regression with age and sex as covariates were then performed to find the best-fitting model (See Figure 1). Adding cortisol into the regression model does not significantly improve the model's fitness. Life Event Stress total score ($b=0.28$, $SE=0.04$, $p<0.001$), CHR ($b=-0.47$, $SE=0.30$, $p<.001$), and stress sensitivity ($b=0.13$, $SE=0.01$, $p<0.001$) together were positively associated with CDSS ($R2=0.41$, $p<0.001$), with age and sex as

covariates (See Table 3). To avoid multicollinearity, total DSI is not included, because stress sensitivity is a measure derived from DSI total score and the two are therefore highly correlated.

A multivariate linear regression by CHR and control subgroups was performed (See Table 4). LES, DSI, and stress sensitivity were significantly associated with CDSS in all CHR-P groups ($p<.001$). Specifically, stress sensitivity accounts for the largest amount of variance in CDSS ($R^2=0.21$, $b=0.15$, $SE=0.01$, $p<.001$). None of the predictors are associated with CDSS in the control group, perhaps because the control group's variance in the predictors and CDSS is lower in magnitude (range = 0-7, mean =0.59, SE = 0.13).

Moderation Effect

Given that significant main effects was found for all those variables, the interaction term for CHR: LES or CHR: stress sensitivity was added to the main regression model using the same stepwise procedure. The interaction effect between LES and CHR is not statistically significant ($p = 0.08$), although there may be a potential effect (See Figure 2). No interaction effect was found between stress sensitivity and CHR or cortisol and LES. The addition of the interaction term did increase the model's R-squared value slightly from 0.4102 to 0.4127. However, further analysis or larger sample size (for example, looking at the long-term follow-ups) may be needed to determine the significance of this potential effect.

It does not appear that there is a significant moderation effect of either LES: CHR or stress sensitivity: CHR on the relationship between LES or stress sensitivity, respectively, and CDSS scores. While some of the models showed potential effects, none of them reached statistical significance. Therefore, it may be concluded that the relationship between LES and stress sensitivity with CDSS is not significantly moderated by the CHR diagnostic group.

No moderation effect of cortisol in any models (LES, CHR, stress sensitivity) was found to be significant ($p > 0.1$), suggesting that cortisol might not be a contributing factor in a higher CDSS score.

Mediation Effect

To further examine the relationship between LES, CHR status, and stress sensitivity, mediation analyses were conducted in R using the mediation package (Tingley et al., 2014). The results indicate that stress sensitivity partially mediates the relationship between LES and CDSS, with a significant average causal mediation effect (ACME) of 0.1046 ($p < 0.001$) and an average direct effect (ADE) of 0.2894 ($p < 0.001$). The total effect of LES on CDSS (i.e., the sum of the direct and indirect effects) is 0.3940 ($p < 0.001$). The proportion of the total effect mediated by stress sensitivity is 0.2643, indicating that approximately 26% of the total effect of LES on CDSS is mediated by stress sensitivity. Overall, the analysis suggests that stress sensitivity plays a partial mediating role in the relationship between LES and CDSS.

The mediation effect was also tested for cortisol. As described above, cortisol is not a significant contributor to the main model. When cortisol was added as the mediator in the model, the ADE and Total Effect are both significant ($p < 0.001$), meaning that there is a direct effect of LES on CDSS, regardless of the level of cortisol. However, the ACME and Proportional Mediation are not significant ($p = 0.92$), indicating that there is no evidence of a mediated effect of LES on CDSS through cortisol.

Discussion:

The current study aims to examine the HPA axis dysfunction and how cortisol might act as a biomarker that influences stress and depression symptom severity in a large sample of CHR youth and controls. As the first study that looks at stress and cortisol levels in NAPLS-3, we investigate the associations of LES, DSI, stress sensitivity, and basal cortisol with depressive symptoms in CHR-P youth. In line with the hypotheses, CHR-P individuals report more daily stressors and stressful life events. They also scored higher on CDSS. However, after adjusting for potential confounders (age and sex) and correcting for sampling time, cortisol does not differ significantly between the two diagnostic groups (CHR-P versus Healthy Controls). This contrasts previous studies that found CHR has elevated baseline cortisol compared to controls using the NAPLS-1 dataset (Walker et al., 2013). However, a recent study using the NAPLS-2 cohort also found that only CHR converters were characterized by elevated basal cortisol relative to healthy controls (Cullen et al., 2020). This might explain the non-significant distinction between CHR and Controls in baseline cortisol levels. Thus, employing longitudinal follow-ups might therefore reveal different patterns across CHR individuals and controls.

The regression analysis showed that age, sex, LES, stress sensitivity, and CHR status were all significant predictors of CDSS scores, explaining 41% of the variance in CDSS scores. Specifically, stress sensitivity was found to be the strongest predictor of CDSS scores, with a partial mediating effect on the relationship between LES and CDSS scores. Multivariate regression based on the group also found that this association is only statistically significant in the CHR group but not in the control group. This suggests that individuals who have experienced more stress in their lives may be more susceptible to depression, and stress sensitivity may be a

key factor in the higher depression symptom severity in CHR individuals, but this association might not be prominent in healthy controls.

We did not find a significant moderation effect of cortisol on any of our models, suggesting that basal cortisol levels may not play a significant role in more severe depression symptoms in CHR individuals. However, it is important to note that the mediation analysis did not completely rule out the possibility of cortisol playing a mediating role in the relationship between LES and CDSS scores. Longitudinal follow-ups should be included for further analyses.

Overall, our findings highlight the importance of considering life stressors and stress sensitivity in the development of depression in CHR individuals. Future research may benefit from investigating other potential mediators, such as cognitive or emotional factors, that may help explain the relationship between life stressors and depression in this population.

Limitations:

While this study provides important insights into the relationship between life stressors, cortisol levels, and depressive symptoms in CHR-P youth, there are several limitations that must be acknowledged. Firstly, this is the first study that primarily looks at depression symptom severity instead of psychosis symptom severity in CHR-P cohorts. Although we did not find a significant association between cortisol levels and depression symptom severity, there might still be some relatedness of cortisol with other diagnostic measures such as the Structured Interview for Psychosis-Risk Syndromes (SIPS) and others. Future studies could explore the relationship between cortisol levels and other diagnostic measures in CHR-P youth to gain a more comprehensive understanding of the role of cortisol in the development of psychosis.

Secondly, this study did not assess other potential confounders that could impact the relationship between stress, cortisol, and depressive symptoms. These include psychiatric

medications, socioeconomic status, childhood trauma, and genetic vulnerability. Previous research has demonstrated that these factors can significantly impact HPA axis function and stress response in individuals with psychosis (Labad et al., 2015; Lederbogen et al., 2011; Mondelli and Ciufolini, 2017). Therefore, the lack of assessment of these factors in our study is a limitation that should be addressed in future research.

In conclusion, while this study provides important insights into the relationship between life stressors, cortisol levels, and depressive symptoms in CHR-P youth, the limitations of this study should be considered when interpreting the results. Future research should aim to address these limitations and further explore the complex relationship between stress, cortisol, and psychosis risk.

Directions for Future Research:

These results highlight the complex nature of the relationship between stress, cortisol levels, and depressive symptoms in the context of CHR-P. It is possible that other factors, such as genetic susceptibility or neurobiological changes, may play a more prominent role in the development of depressive symptoms in this population. This inconsistency in the association between stress and cortisol levels in at-risk youth has been noted in previous studies that employed different measures (Cullen et al., 2014b; Labad et al., 2015; Thompson et al., 2007). Additionally, studies in healthy subjects have not shown correlations between self-reported stress and cortisol (Cummins and Gevirtz, 1993; Vedhara et al., 2003). It has been suggested that individual differences in HPA responsivity to stress, which are influenced by genetic variants such as FKBP5, CRHR1, NR3C1, NR3C2, and other vulnerability factors, may be responsible for the inconsistent patterns of association between stressors and cortisol levels that have been observed (Hartling et al., 2019; Mondelli and Ciufolini, 2017; Starr et al., 2019; Utge et al.,

2018). Therefore, further research is needed to fully understand the complex mechanisms underlying HPA responsivity to stress and its relationship with depressive symptoms in CHR-P individuals. Additionally, future studies could benefit from using more extensive cortisol sampling protocols and taking into account the impact of psychiatric medications and other confounding factors.

Recent research has also suggested that the relationship between cortisol levels and psychiatric symptoms in CHR-P individuals may be influenced by other factors, such as hippocampal volume (Bohlken et al., 2020; Rosell et al., 2021). Research has suggested that chronic stress exposure and elevated cortisol levels may lead to hippocampal volume reduction in individuals with psychosis (Ristanovic et al., 2023; Lataster et al., 2011; Mondelli et al., 2011). Additionally, in CHR-P individuals, a smaller hippocampal volume has been associated with a higher risk of converting to psychosis (Carrión et al., 2011). Future studies could investigate the potential mediating effect of cortisol levels on hippocampal volume in CHR converters and explore the implications of these findings for the development of interventions targeting the HPA axis in this population. Furthermore, it is important for future studies to consider the impact of psychiatric medications and other confounding factors on cortisol levels in CHR-P individuals. This would provide insight into the potential biological mechanisms underlying the association between stress, cortisol, and psychosis development in at-risk youth.

Conclusion:

The present study investigated the association between depression in individuals at CHR-P and life stressors and basal cortisol levels. Our results suggest that stress sensitivity may be a key factor in the development of depression in CHR individuals, with stress sensitivity partially mediating the relationship between life stressors and depression. However, we did not

find significant evidence of a mediating role of basal cortisol levels in this relationship. These findings emphasize the importance of considering the impact of life stressors and stress sensitivity when developing interventions for depression in CHR individuals.

Overall, our study contributes to the growing body of literature on the relationship between stress, cortisol levels, and depression in the context of CHR-P. The findings suggest that stress sensitivity and stress exposure may be important factors to consider in the assessment and treatment of depressive symptoms in this population, while cortisol levels may not be as informative.

Tables and Figures

Table 1. Demographics based on Diagnostic Groups

		All	Subject Types	
			Control	CHR-P
N (%)		806	96 (11.9%)	710 (88.1%)
Sex	Male (%)	433 (53.7%)	48 (50%)	385 (54.3%)
	Female (%)	373 (46.3%)	48 (50%)	325 (45.7%)
Age (SE)		18.24 (0.14)	18.60 (0.43)	18.27 (0.16)
Major Depressive Disorder (296.20-311) (%)		348 (43.2%)	2 (2%)	346 (48.7%)

Table 2. Descriptive Statistics for Predictor Variables in NAPLS 3

		Subject Types		t-test	
	All (n=747)	**Control (96)**	**CHR (651)**	Sig.	Cohen's d
LES sum	95.73(4.91)	53.48(5.26)	101.65(5.51)	0.001*	0.355
Stress Sensitivity	3.01(0.04)	2.04(0.08)	3.14(0.04)	<0.001*	1.015
DSI	65.41(1.89)	34.86(4.00)	69.63(2.03)	<0.001*	0.679
CDSS	5.65(.16)	0.59(.13)	6.35(.17)	<0.001*	1.364
Baseline Cortisol	.139 (4.6E-3)	.137 (9.3E-3)	.140 (5.1E-3)	0.25	0.042

Standard errors of the means (SE) were shown in parenthesis.

Table 3. Bivariate Correlations among Variables

	Age	CDSS	Cortisol	Sensitivity	LES sum
1. CDSS	0.08*				
2. Baseline Cortisol	0.10**	0.05			
3. DSI stress sensitivity	0.00	0.45**	0.00		
4. LES sum of stress	0.42**	0.36**	0.03	0.25**	
5. DSI total	0.04	0.38**	-0.01	0.74**	0.34**

* P<0.05

** P<0.001

Table 4. Final Multivariate Linear Regression for CDSS

	CDSS		
Predictor	R^2	b(SE)	p
	0.41		<.001
Intercept		0.024(.07)	0.74
LES sum of stress		0.21(.04)	<.001
CHR | Control		-0.47(04)	<.001
Stress Sensitivity		0.09(.01)	<.001
Age		.0021(.00)	0.504
Sex		0.03(.03)	0.211

Table 5. Multivariate Linear Regression by Group

	All			CHR			Control		
Predictor	R^2	b(SE)	p	R^2	b(SE)	p	R^2	b(SE)	p
LES	.13	0.42(.04)	<.001	.35	0.29(.04)	<.001	.03	0.09(.07)	0.36
Cortisol	.02	0.24(.20)	0.22	.03	0.05(.19))	0.8	.04	0.46(.32)	0.25
Stress Sensitivity	.21	0.15(.01)	<.001	.15	0.11(.01)	<.001	.07	0.06(.03)	0.1
DSI	.15	0.37(.03)	<.001	.11	0.27(.03)	<.001	.04	0.09(.06)	0.1

All predictors were adjusted for age and sex as covariates.

Figure 1. Stepwise Linear Regression

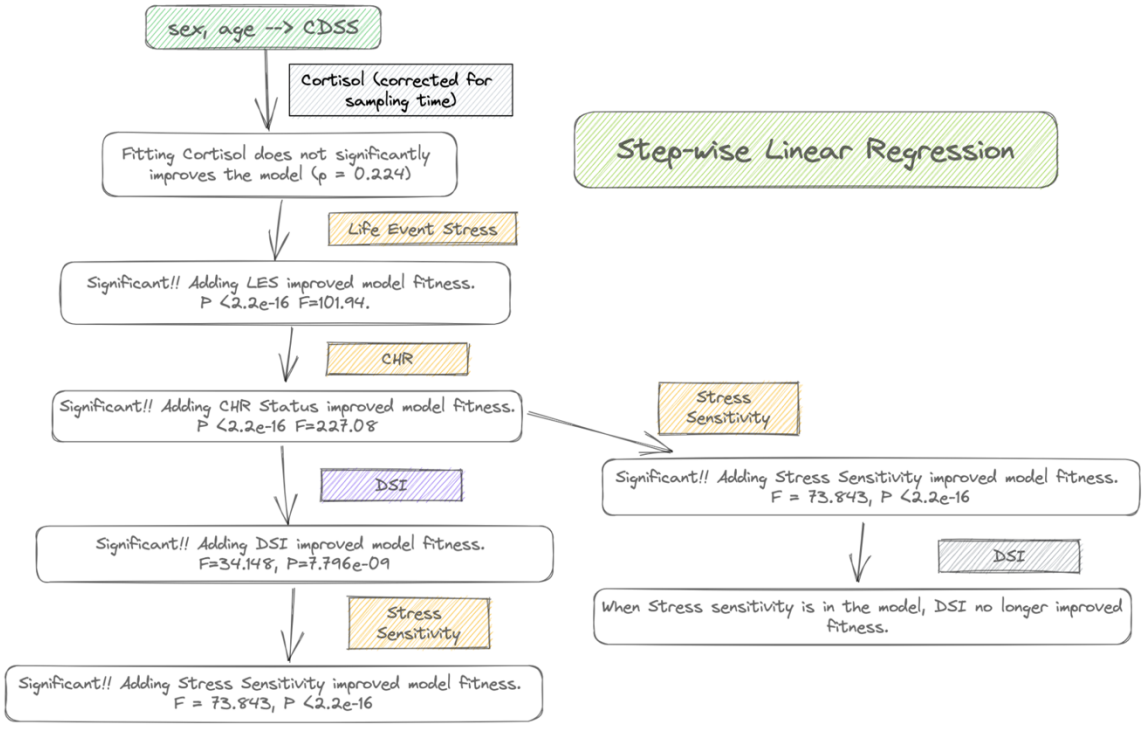

Figure 1. A stepwise linear regression with age and sex as covariates were performed to find the best-fitting model. Adding cortisol into the regression model does not significantly improve it, but others (LES, CHR status, Stress Sensitivity) all contribute significantly ($p<.01$) to the model, and the final model results in an R square of 0.41 (See Table 3). To avoid multicollinearity, total DSI is not included, because stress sensitivity is a measure derived from DSI total score and the two are therefore highly correlated.

Figure 2. LES and CDSS colored with Stress Sensitivity

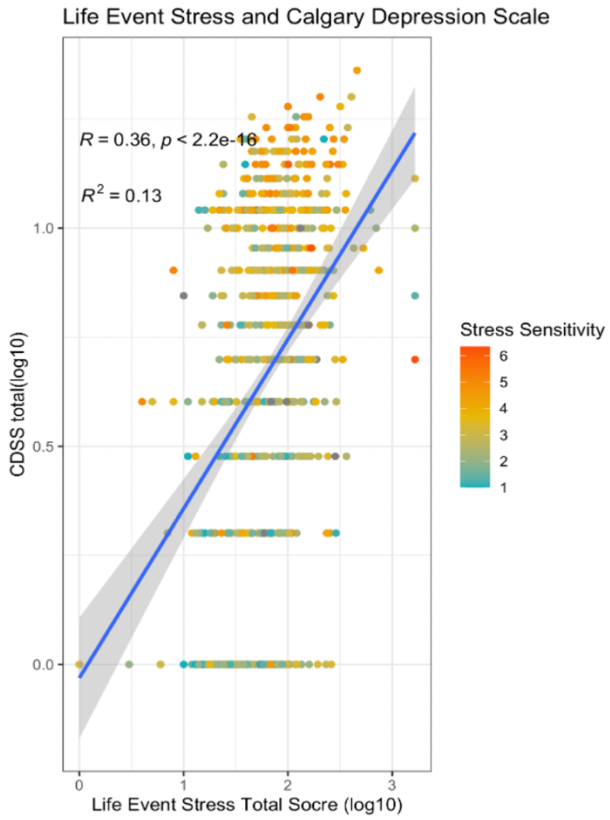

Figure 2. LES total score showed a positive correlation with CDSS scores. Each color-coded dots represent one individual subject. As we can see from the graph, individual dots with stronger colors tend to cluster with higher CDSS and higher LES scores.

Figure 3. Moderation Effect of CHR on LES and Stress Sensitivity respectively

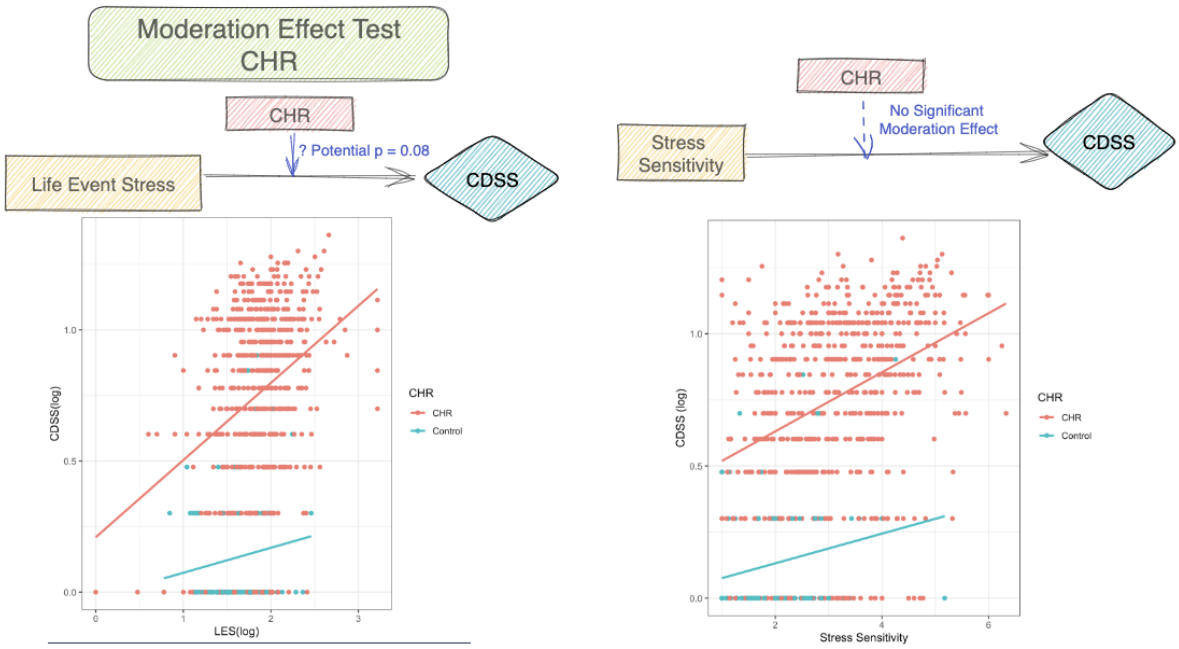

Figure 3. The interaction effect between LES and CHR is not statistically significant (p = 0.08), although there may be a potential effect. No interaction effect was found between stress sensitivity and CHR or cortisol and LES. It does not appear that there is a significant moderation effect of either LES: CHR or stress sensitivity: CHR on the relationship between LES or stress sensitivity, respectively, and CDSS scores. While some of the models showed potential effects, none of them reached statistical significance.

Figure 4. Mediation Effect of Stress Sensitivity on LES to CDSS.

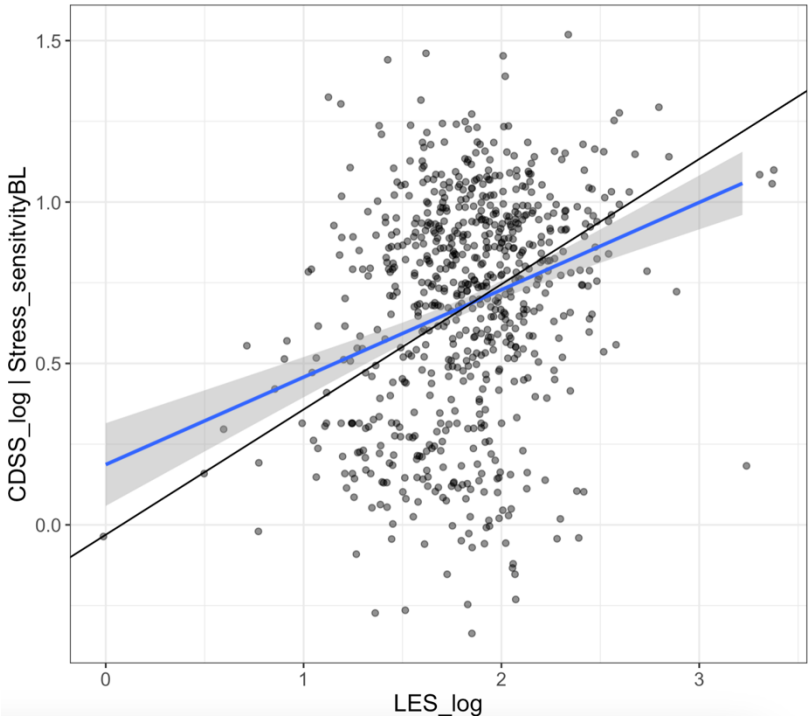

Figure 4. Based on the results and the provided mediation plot, it appears that stress sensitivity partially mediates the relationship between LES and CDSS. This is shown by the significant average causal mediation effect (ACME) of 0.1046 ($p < 0.001$) and an average direct effect (ADE) of 0.2894 ($p < 0.001$). The total effect of LES on CDSS is 0.3940 ($p < 0.001$), with approximately 26% of the total effect mediated by stress sensitivity.

The black line represents the model before mediation, and the blue line represents the model after mediation. The black line has a steeper slope, while the blue line is flatter, indicating the mediating effect of stress sensitivity. It is important to note that other potential mediators and moderators may also influence this relationship and should be considered in future research.

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