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Family Economic Hardship, Corticotropin-Releasing Hormone Receptor Polymorphisms, and Depressive Symptoms in Rural African American Youths

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Abstract

Purpose—To use pooled data from 2 independent studies of rural African American youths to test the moderation effect of the corticotropin-releasing hormone receptor 1 gene (*CRHR1*) on the link between family economic hardship and trajectories of depressive symptoms.

Methods—Two longitudinal studies were conducted involving African Americans, 16 ($N = 474$) and 18 ($N = 419$) years of age, who were randomly recruited in rural Georgia. Family economic hardship and youths' depressive symptoms were assessed 4 times across 2 1/2 years. Genetic data also were collected. Haplotype analysis was performed on single nucleotide polymorphisms of *CRHR1*; 2 haplotypes were aggregated to form a *CRHR1* index. Growth curve models were executed to determine whether *CRHR1* moderated the link between Wave 1 family economic hardship and youths' development of depression.

Results—*CRHR1* $\times$ family economic hardship interactions significantly predicted youths' depressive symptoms. When exposed to family economic hardship 1 standard deviation above the mean at Wave 1, youths who scored 0 on the *CRHR1* index showed high and increasing depressive symptoms across time, whereas those who scored 2 on the index showed a decrease in depressive symptoms.

Conclusions—The *CRHR1* gene reduces the risk for depressive symptoms among youths living in families undergoing high levels of economic hardship.

Conflicts of Interest

The authors have no conflicts of interest to report, financial or otherwise.

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Keywords

African Americans; *CRHRI*; depression; economic hardship; gene $\times$ environment interaction

African American adolescents and young adults have historically lived with high and chronic levels of economic hardship, a situation that continues today. A consistent result is a heightened risk for mental health impairments, particularly elevated depressive symptoms [1, 2]. Contextual pathways from economic hardship to the development of depressive symptoms have been identified among African American youths. A “parental” pathway chronicles the ways in which the stressors associated with coping with chronic economic hardship induces depressive symptoms in African American youths’ caregivers. These symptoms spill over to compromise the quality of parental investment and nurturance the children receive. Depression-associated declines in nurturant-involved caregiving and increases in harsh- inconsistent parenting presage the development of depressive symptoms among African American youths [3–5]. Outside the family, youths living with economic hardship are likely to encounter crime, violence, and drug use, along with a lack of safe recreational areas. Such “neighborhood effects” contribute uniquely to the development of depressive symptoms [6–8]. Although economic hardship heightens the risk for elevated depressive symptoms, not all youths who experience hardship develop symptoms [9]. Recent studies have shown buffering effects of social support [10] and racial identity [1]; however, studies have not examined the possibility that genetic variation may moderate the impact of economic hardship on the development of depressive symptoms among African American youths. In this study, we examined the moderational role of the corticotropin-releasing hormone 1 gene (*CRHRI*) on the longitudinal association between economic hardship and the development of depressive symptoms.

Research on physiological responses to stress using both animal and human models provides a foundation for understanding individual variation in depressive symptoms in response to acute and chronic stress [11–14]. One potential biological process involves overactivation of the hypothalamic-pituitary-adrenal (HPA) axis [15, 16]. Genes associated with regulating HPA activity have been examined for a role in modulating reactivity to stressful environments. An accumulating body of evidence points to the involvement of the receptor for *CRHRI* in this process. In a typical stress response, elevations of cortisol occasioned by CRH on mineralocorticoid and glucocorticoid receptors in the hippocampus, paraventricular nucleus, and pituitary reduce activation of the HPA axis and stabilize glucocorticoid, creating a negative feedback system that modulates the stress response. Repeated activation of the HPA axis in response to chronic or recurring stress can compromise its functioning, as evidenced by a protracted cortisol response to a stressful event or, alternatively, no cortisol response at all [17]. Alterations in HPA axis functioning have been associated with depressive symptoms among a high-risk sample of Caucasian adolescents [18]. Other research has shown that carrying the homozygous *CRHRI* SNP, rs110402, is associated with a higher cortisol response to the Dex/CRH test only when the subjects experienced childhood maltreatment [19] and have high trait anxiety [20].

CRH and CRHR1 are also present in high levels in the amygdala, hippocampus, and frontal cortex [21, 22]. They mediate physiological aspects of the stress response [23–25]. Overactivity of CRH and CRHR1 is found in animal studies with Rhesus monkeys [26] and rodents [27] when exposed to early life stress and trauma. For example, CRHR1 antagonists reduce behavioral fear responses to maternal separation in Rhesus monkeys [26]. Although these antagonists have been examined as possible treatments for depression with mixed results [28], it does underline its role in further understanding individual variation in the effect of life stress on depression [24].

Past studies have demonstrated a role for variation in the *CRHR1* gene in moderating the effects of childhood abuse, reported retrospectively, on depression-related phenotypes in adulthood [29–31]. Each of these studies found several single-nucleotide polymorphisms (SNPs) of *CRHR1* to be protective from elevations in depressive symptoms when individuals experienced high levels of stress. Before definitive conclusions about this effect can be drawn, however, two questions must be answered. The first involves change across time. Existing findings are mainly based on depressive symptoms assessed at a single point of data collection, making it difficult to determine the temporal ordering of a predictor and the depressive symptoms. Longitudinal studies with repeated assessments of depressive symptoms are needed to clarify the direction of the association. The second question concerns the specificity of childhood adversity. Previous research has focused on maltreatment, but other kinds of childhood adversity, such as economic hardship, contribute to depression. The purpose of this study was to examine the moderational role of *CRHR1* in the longitudinal association between economic hardship and the development of depressive symptoms.

To address these questions, we analyzed data from two longitudinal studies of rural African American adolescents in which family economic hardship and depressive symptoms were assessed on four occasions across 2 ½ years. Participants were genotyped for the *CRHR1* SNPs in the aforementioned studies that protected youths from depression. We predicted that African American youths carrying more of these SNPs will evince lower levels of depressive symptoms across 2 ½ years when they live in families with high levels of economic hardship.

Method

Overview

This study is unique in combining data from two longitudinal samples of rural African American adolescents and young adults involving almost 900 participants to test hypotheses about *CRHR1* × family economic hardship interactions. The longitudinal design included parent ratings of economic hardship, youths' reports of depressive symptoms at each wave of data collection, and genotyping of youths for *CRHR1* polymorphisms.

Participants

SAAF-T—We recruited 502 rural African American families (51% with daughters) to participate in the Strong African American Families–Teen (SAAF-T) randomized

prevention trial. Random assignment to the prevention or control condition was controlled in all data analyses. In each family, an adolescent (M age = 16.00 years, SD = .57) and his or her primary caregiver (in most cases, the biological mother) provided pretest data. Data were collected on three additional occasions 5 months, 18 months, and 22 months after the pretest. The retention rate was 95% (478/502) at the fourth data collection. At the third data collection, researchers gathered DNA from 94% (n = 474) of the original sample of youths. These 474 adolescents constituted the SAAF-T segment of the analytic sample for this study. At pretest, families' mean monthly income was \$1482.50, and 63.8% of them lived below federal poverty standards. The primary caregivers worked an average of 41.5 hours per week (SD = 20.36); they can be classified as working poor.

AIM—Youths (M age = 17.02 years, SD = .75; 58.5% female) and primary caregivers from 494 families participated in the Adults in Making (AIM) prevention trial. Again, assignment to the prevention or control condition was controlled in all data analyses. Three visits were made to the original AIM sample 6, 17, and 28 months after the pretest data collection. The retention rate at Wave 4 was 86% (424/494). At the second data collection, researchers gathered DNA from 83.4% (n = 419) of the youths; they constituted the AIM segment of the analytic sample. At pretest, the primary caregivers reported working an average of 38.5 hours per week (SD = 11.1); nevertheless, 41.8% of the families lived below federal poverty standards. Like the SAAF-T families, they can be described as working poor.

In both programs, independent t -tests and chi-square tests were conducted to detect any significant differences in primary caregivers' education, youth gender, or the research variables between families who left the studies and those who continued to participate; none emerged. Attrition analyses were also conducted to detect significant differences in the same variables between families in which youths gave DNA and those in which they did not; again, none emerged.

Procedures

Recruitment and data collection—Recruitment and data collection procedures were similar in SAAF-T and AIM. Public high schools provided lists of eligible students from which families were selected randomly for recruitment. The lists included 10th-grade students for SAAF-T and, for AIM, 11th- and 12th-grade students. Data collection visits, each of which lasted 2 hours, were made to each family's home by two trained African American college students or community members. At each home visit, self-report questionnaires were administered using computer-assisted self-interviewing techniques. Families were compensated for their time and effort. In SAAF-T, caregivers received \$100 and youths received \$50 after each assessment; in AIM, families received \$100. All study protocols were approved by the Institutional Review Board of the university at which the research was conducted.

Measures

Youth depressive symptoms—In both SAAF-T and AIM, youth depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies Depression Scale [32], a self-rated measure of symptoms occurring during the previous week. The response set

ranged from 0 (*rarely or none of the time, less than 1 day*) to 3 (*most or all of the time, 6–7 days*). This scale has been well validated and used extensively with African American populations. The α coefficients for the measure in both studies were above .70, indicating good internal consistency. In each study, responses to the 20 items were summed to derive the depressive symptom score.

Family economic hardship—Two scales and one index to which primary caregivers responded at the first data collection were standardized and summed to create a composite that reflected family economic hardship. The scales, Material Needs and Can't Make Ends Meet, were developed for families in rural areas [5]. These scales have demonstrated reliability and validity with African American populations [5]. For Material Needs, primary caregivers responded to four items. They indicated, on a scale ranging from 4 (*strongly disagree*) to 1 (*strongly agree*), whether they could afford adequate housing, clothing, food, and medical care. For Can't Make Ends Meet, primary caregivers responded to two items. The first, difficulty paying bills during the past 12 months, had a response set ranging from 5 (*a great deal of difficulty*) to 1 (*no difficulty at all*). The second, the amount of money left at the end of the month, was rated on a scale ranging from 5 (*not enough to make ends meet*) to 1 (*more than enough money left over*). Alpha coefficients exceeded .70 in both SAAF-T and AIM.

Seven dichotomous indicators used in prior research [9] were used to create the index of cumulative socioeconomic risk. The seven indicators were family poverty based on federal standards, primary caregiver noncompletion of high school, primary caregiver unemployment, single-parent family structure, maternal age of 17 years or younger at the youth's birth, family receipt of Temporary Assistance for Needy Families, and income that the primary caregiver rated as not adequate to meet all needs. The indicators were summed to form the cumulative risk index, with $M = 2.72$, $SD = 1.37$ for SAAF-T and $M = 2.31$, $SD = 1.55$ for AIM. The index has shown good validity in past studies in predicting African American youths' health outcomes [9].

Genotyping—Youths' DNA was obtained from saliva samples using Oragene DNA kits (DNA Genotek; Kanata, Ontario, Canada). Youths rinsed their mouths with tap water and then deposited 4 ml of saliva in the Oragene sample vial. The sealed vials were shipped via courier to the Psychiatric Genetics Laboratory in Iowa City, Iowa, where samples were prepared according to the manufacturer's instructions. Ten SNPs previously studied in African American populations for their protective capacity were genotyped for *CRHR1* [29]. Frequency distributions for all SNPs conformed to Hardy-Weinberg equilibrium.

Linkage disequilibrium (LD) was calculated among SNPs within genes using Haploview 4.2 [33]. SNPs with high LD were assigned into block groups, resulting in three block groups. We estimated haplotype frequencies in each block group using PHASE 2.11 [34]. The first block group consisted of three SNPs: rs720936, rs4792887, and rs110402. Past studies have shown that this haplotype provides protection against depression in retrospective reports of childhood adversities [29, 30]. We called this the TCA haplotype. Carriers of 1 or 2 copies of TCA were given a 1 and others were given a 0. The second block group, the TG haplotype, consisted of SNPs rs242924 and rs242940. Association analyses demonstrated

that the TG haplotype was related to low levels of depressive symptoms. Carriers of 1 or 2 copies of the TG haplotype were given a 1 and others were assigned 0. The third block group consisted of two SNPs: rs173365 and rs242950. The association analysis showed that carriers of the GC haplotype reported fewer depressive symptoms. Carriers of 1 or 2 copies of the GC haplotype were assigned a 1 and others were assigned a 0. The percentages of participants with 1 or 2 copies of each haplotype are presented in Table 1.

Control variables—Youth gender and intervention status were included in the analyses as control variables. Gender was coded 1 for male and 0 for female; intervention status was coded 1 for those participating in an intervention program and 0 for those assigned to a control group. Research cohort was included as a control variable and a moderating variable; it was coded 0 for SAAF-T and 1 for AIM. Information on ancestry admixture was estimated based on 134 ancestry-informative markers. Maximum likelihood estimation showed a 3-population model best fit the data. Detailed information concerning the ancestry-informative markers can be found elsewhere [35, 36]. Two dummy variables were created to examine and control for population admixture.

Analytic Plan

To test the study hypothesis, we executed a series of growth curve models (GCMs) using a multilevel linear model framework [37]. First, we fitted an unconditional GCM by regressing the scores for depressive symptoms on the age variable, which described change in depressive symptoms across yearly assessments (e.g., across ages 15 to 19). The model was fitted with and without the correlation between the intercept and slope. That correlation was not significant; therefore, the model without the correlation was used in the data analysis. Second, family economic hardship and the control variables, along with the product terms between family economic hardship and age, were included in the model to predict the scores for depressive symptoms. Next, interaction terms between family economic hardship and each of the three haplotype variables were included in the GCM to detect a G×E effect, if present. On the basis of this analysis, a *CRHRI* index was created. An interaction term between family economic hardship and the *CRHRI* index, as well as among family economic hardship, the *CRHRI* index, and age, were included in the GCM. All the models were run in STATA 13.1 (StataCorp, College Station, TX) with bootstrapped standard errors.

Results

Table 1 presents the descriptive statistics for all variables in the study. The GCM on youths' depressive symptoms was executed first. It revealed that the variances of the intercept (value of depressive symptoms at the first assessment) and variances for age were significant at $\alpha = .05$. Significant variation for age indicates that interindividual variation occurred in youths' depressive symptoms over time. The goal of the next analyses was to determine whether the hypothesized G×E interactions clarify this variation. To do this, we first executed analyses to form the *CRHRI* index. Three analyses were executed to detect the effect of each *CRHRI* haplotype (TCA, GC, TG) × family economic hardship × age interaction on growth of depressive symptoms. Significant *CRHRI* haplotype × family

economic hardship $\times$ age interactions were found for the TCA and GC haplotypes ($p < .05$) but not for the TG haplotype (detailed results are available from the authors). On the basis of these findings, the *CRHRI* index was derived by summing the scores for TCA and GC, yielding an index that ranged from 0 (*no copy of either haplotype*) to 2 (*1 or more copies of each haplotype*). More copies of the haplotype were hypothesized to have more of a protective effect from depressive symptoms under higher levels of family economic hardship. This approach has been adopted in past research for enhancing effect size and predictive power [38, 39]. The index distribution can be found in Table 1.

The relation of family economic hardship with the initial level of depressive symptoms and growth in those symptoms over time was significantly moderated by the *CRHRI* index. Models 1 and 2 in Table 2 show the data analyses for these effects, and Figure 1 depicts trajectories of depressive symptoms for low and high levels of family economic hardship and *CRHRI* status. We used 1 SD below and above the mean to define low and high levels of family economic hardship, respectively. For individuals who experienced low levels of family economic hardship, youths who scored 0 on the *CRHRI* index showed, at age 15, the highest initial levels of depressive symptoms that decreased over time (simple slope = $-.88$, $p < .05$). Youths scoring 1 or 2 on the *CRHRI* index showed low and stable levels of depressive symptoms (simple slope = $-.27$, $p > .05$). The data presented in Figure 1 show that youths living with high family economic hardship manifested distinctly different trajectories of depressive symptoms than did youths in the low family hardship subgroup. They evinced high levels of depressive symptoms and showed considerable variation based on *CRHRI* status. High levels of family financial hardship were associated with high and stable levels of depressive symptoms for youths scoring 0 on the *CRHRI* index (simple slope = $.11$, $p > .05$), but were associated with decreases over time in depressive symptoms for youths scoring 2 on the *CRHRI* index (simple slope = $.88$, $p < .05$). Youths scoring 1 on the index had intermediate and stable levels of depressive symptoms. In summary, growing up with high family economic hardship was associated with relatively higher levels of depressive symptoms that decreased for youths with high numbers on the *CRHRI* index.

Discussion

This study was designed to test hypotheses about the link between family economic hardship and rural African American youths' vulnerability to the development of depressive symptoms. The results indicated that the levels and trajectories of depressive symptoms were quite distinct for youths growing up in contexts of low versus high levels of family economic hardship. Over time, youths living in low hardship conditions evinced depressive symptoms that declined across ages 15 to 19. Youths in these conditions who did not carry a *CRHRI* haplotype showed the highest depression levels at age 15. Predicted levels of depressive symptoms were higher over time among youths growing up in high hardship conditions than among those in low hardship circumstances. This was particularly true for youths who scored 0 on the *CRHRI* index. Youths with more scores on the *CRHRI* index evinced a decline in depressive symptoms, whereas youths without this benefit evinced increases in depressive symptoms across time. Thus, for genetic reasons, youths growing up in the midst of economic hardship evinced different trajectories of depressive symptoms.

These results extend the existing literature that is characterized primarily by cross-sectional research designs and adults' retrospective reports of childhood adversity.

The finding that the *CRHRI* index buffered youths from the development of depressive symptoms when experiencing family economic hardship is pertinent to research on youth resilience. Presumably, the presence of a greater number of the *CRHRI* index and their effects contributed to dampening of HPA axis reactivity and diminished levels of glucocorticoids, contributing to stress resistance and resilience. These findings are consistent with prior research that examined the protective effects of *CRHRI* polymorphisms on depressive symptoms among adults with a history of maltreatment [29–31, 40]. The present study provides further support for the role that *CRHRI* contributes to individual variation in depressive symptomatology.

Despite the strengths of the research design, some limitations should be noted. It is not known whether the results generalize to Caucasian or Latino families living in rural or urban communities. A second limitation was use of the study sample to form the *CRHRI* index and removing the TG haplotype in a *post hoc* manner when creating the *CRHRI* index. Although the findings appear relatively robust, findings from this approach require replication in future studies. These limitations notwithstanding, the results document the interplay between economic hardship and variation in *CRHRI* in forecasting the development of depressive symptoms among rural African American youth.

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Abbreviations

AIM	Adults in the Making program
GCM	growth curve model
HPA	hypothalamic-pituitary-adrenal
LD	linkage disequilibrium
SAAF-T	Strong African American Families–Teen program

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Implications and Contribution

The present study extends the literature on the buffering effects of *CRHRI* on the association between family economic hardship and trajectories of depressive symptoms among rural African American youths. Finding a protective role for *CRHRI* in the presence of family economic hardship contributes to genetically informed resilience research.

Highlights

- We examined *CRHRI*'s action on the link between socioeconomic stress and depression.
- Two samples of rural African American youths took part in the study.
- A longitudinal design and polygenetic *CRHRI* score were used in growth curve models.
- *CRHRI* modulated the impact of socioeconomic hardship on change in youth depression.
- *CRHRI* has a moderational role from a person-centered perspective.

Figure 1.
CRHR1 index moderates the impact of family economic hardship on change in youth depressive symptoms.

Table 1

Descriptive Statistics for Demographics and Research Variables at Wave 1

Variables	Mean	SD	Percent
Primary caregiver's education	4.62	1.55	
Per capita income	488.93	513.98	
Number of children in household	2.17	1.34	
Family SES stress	0.00	2.27	
Youth depressive symptoms	13.01	8.61	
Youth gender (male)			42.4
Intervention condition			56.9
TCA haplotype (1 or 2 copies)			50.3
TG haplotype (1 or 2 copies)			46.1
GC haplotype (1 or 2 copies)			62.0
<i>CRHR1</i> index			
0			33.4
1			19.0
2			47.6

SES = socioeconomic status. *SD* = standard deviation.*N* = 893.

Table 2

Growth Curve Models for Youths' Depressive Symptoms Across the Course of the Study

	Model 1		Model 2	
	Coefficient	SE	Coefficient	SE
On Intercept				
Family economic hardship (E)	.29***	.07	-.02	.11
<i>CRHRI</i> index (G)			-.38	.27
G×E			.28***	.07
On Change				
Family economic hardship (E)	.06	.06	.22*	.10
<i>CRHRI</i> index (G)			-.01	.19
G×E			-.14*	.06

Note: Gender, intervention status, birth cohort (SAAF-T or AIM), and population admixture were controlled in each model. E = environment. G = gene. SE = bootstrapped standard error.

*
 $p < .05$.

**
 $p < .01$.

 $p < .001$.