

# Differentiating the Impact of Episodic and Chronic Stressors on Hypothalamic–Pituitary–Adrenocortical Axis Regulation in Young Women

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**Objective:** The goal of this study was to examine the impact of episodic stress and chronic interpersonal stress on indices of HPA regulation. To explore the potential downstream consequences of altered HPA dynamics, the authors also assessed indicators of metabolic control and systemic inflammation. **Design:** One hundred four medically healthy women between the ages of 15 and 19 participated. Following an in-depth interview of life stress, a sample of blood was drawn through antecubital venipuncture. Over the course of the next 2 days, participants gathered salivary cortisol samples. **Main Outcome Measures:** Cortisol morning response, cortisol daily output, glucocorticoid receptor (GR) mRNA, C-reactive protein (CRP), insulin, and glucose. **Results:** The simple presence of episodic stress or chronic interpersonal stress was not reliably associated with cortisol output, GR mRNA, insulin, or glucose. When women were exposed to an episodic stressor in the midst of chronic stress they showed increased cortisol output and reduced expression of GR mRNA. By contrast, when women had low levels of chronic stress, episodic events were associated with decreased cortisol output and increased GR mRNA. Episodic and chronic stress also interacted to predict CRP, but not insulin or glucose. **Conclusions:** The impact of episodic stress is accentuated in the midst of chronic interpersonal stress and diminished in its absence. Simultaneous exposure to episodic and chronic stress may create wear and tear on the body, whereas exposure to episodic stress in the context of a supportive environment may toughen the body, protecting it against subsequent stressors.

**Keywords:** episodic stress, chronic stress, cortisol, glucocorticoid receptor, young women

Psychological stress is associated with morbidity and mortality across a variety of medical conditions. Prolonged exposure to stress can increase susceptibility to upper respiratory illness, accelerate progression of cardiovascular and infectious diseases, and foster exacerbations of autoimmune conditions such as multiple sclerosis and rheumatoid arthritis (Miller & Cohen, 2005; Mohr, Hart, Julian, Cox, & Pelletier, 2004; Pereira & Penedo, 2005; Rozanski, Blumenthal, & Kaplan, 1999). Given the widespread evidence that stressful experiences are related to adverse health outcomes, current research aims to understand the biological mechanisms through which stressors exert their influence. One candidate mechanism that has received a great deal of attention is the hypothalamic–pituitary–adrenocortical (HPA) axis. Activation of this system initiates a hormonal cascade that results in the secretion of cortisol, a glucocorticoid that has wide-ranging effects

on the metabolic, immune, and nervous systems. For this reason, cortisol is often viewed as a primary mechanism through which stressors “get inside the body” to bring about disease (Dickerson & Kemeny, 2004; Heim, Ehlert, & Hellhammer, 2000; Miller, Chen, & Zhou, 2007).

Although the impact of stressful experience on HPA regulation is of considerable theoretical interest, our knowledge of this phenomenon is limited in several important respects. One of the most salient problems is that little is known about how real-world stressors modify functions of the HPA axis. The vast majority of studies in this area have been conducted with animals or have examined people’s hormonal responses to acute stressors in the laboratory (Dickerson & Kemeny, 2004). There have been studies of longer term stressors in the real world, but they have yielded conflicting and ambiguous findings, perhaps because they overlooked distinctions between stressors, such as the duration or frequency of exposure (Miller et al., 2007). In this regard, it is important to differentiate between episodic stressors, such as an isolated social conflict or a move to a new city, and more enduring difficulties, such as being part of a marriage that lacks trust, intimacy, and mutual respect. There are compelling reasons to believe that these situations will elicit different biological responses (see Baum, Cohen, & Hall, 1993; Kop, 1999; Mohr & Pelletier, 2006). Although we have a limited understanding of why HPA responses differ under conditions of acute versus chronic stress, there appears to be a reregulation of the system that occurs with increased duration of the stressor. This reregulation involves a transition from excess to diminished cortisol production (Miller et al., 2007).

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Apart from differentiating between stressors that are episodic and chronic, research has indicated that there is value in considering their co-occurrence. When people facing chronic difficulties are exposed to an episodic stressor, that event's biological consequences can be markedly accentuated (Matthews, Gump, Block, & Allen, 1997; Miller & Chen, 2006). By contrast, the impact of episodic stressors on biological systems is attenuated (and sometimes eliminated altogether) among people who are not facing chronic difficulties (Matthews et al., 1997; Miller & Chen, 2006). Finally, some research has indicated that in the absence of chronic stress, episodic stressors may even confer physiological benefits such as a reduced risk for infectious disease (Boyce et al., 1995).

Knowledge regarding stressful experience and HPA regulation is also limited by the fact that many studies have focused solely on hormone dynamics. For cortisol to act on target tissues in the body, it must bind to a glucocorticoid receptor (GR) inside cells. This receptor-hormone complex can then initiate a molecular cascade, which eventually results in the cell's program of genetic expression being modified. The extent of GR expression can therefore provide an indication of how sensitive a biological system will be to cortisol's influence (Rohleder, Wolf, & Kirschbaum, 2003). It can also provide an index of recent exposure to cortisol, as cells often downregulate GR when exposed to increased hormone concentrations. In fact, a number of theories have suggested that by triggering persistent cortisol secretion, stressful experiences downregulate the expression of GR in various bodily tissues. This downregulation is thought to facilitate a low-grade inflammatory response in the body and give rise to metabolic dysfunctions like impaired glucose control (Bjorntrop & Rosmond, 1999; Miller, Cohen, & Ritchey, 2002).

A final limit of existing research in this area is that it has focused mainly on middle-aged and older adults. Although much can be learned from people at this phase of life, adolescence and early adulthood may represent other important stages at which to consider stressful experience and HPA regulation. These are times of life that can be particularly stressful, with young people struggling to develop a sense of personal identity, maintain close relationships with friends and peers, and attain an increasing amount of independence from their parents (Laursen & Collins, 1994). Indeed, young people with family and personal difficulties exhibit a number of health risks, including higher ambulatory blood pressure, enhanced autonomic reactivity to stress, poorer glycemic control, and abnormal cortisol responses to laboratory stress (Jacobson et al., 1994; Repetti, Taylor, & Seeman, 2002; Salomon, Matthews, & Allen, 2000; Taylor, Lerner, Sage, Lehman, & Seeman, 2004; Troxel & Matthews, 2004). There is also mounting evidence that disease processes, especially those related to diabetes mellitus and cardiac disease, begin to develop in the early decades of life (Berenson & Srivivasan, 2005; Berenson et al., 1998; Berenson et al., 1992). Researchers have thus called for increasing attention to stressful experience, and its biological consequences, in populations of children, adolescents, and young adults (Matthews, 2005).

In the current article, we examine episodic and chronic stressors in a cohort of young women ages 15–19 and how they relate to cortisol output and GR expression. To explore the potential downstream consequences of altered HPA dynamics, we also assessed indicators of metabolic control (glucose, insulin) and systemic inflammation (C-reactive protein [CRP]), which are more prox-

imally related to the development and progression of disease ("Third Report of the Expert Panel," 2002; Willerson & Ridker, 2004). We hypothesized that episodic stressors would be unrelated to biological outcomes because of their time-limited nature. However, to the extent that adolescents had chronic interpersonal stressors in their lives, we expected that they would exhibit increased basal cortisol output, reduced expression of GR, and higher levels of CRP, glucose, and insulin. Finally, we expected that the most pronounced alterations in biological outcomes would occur in those participants exposed simultaneously to episodic and chronic stressors (Gump & Matthews, 1999; Miller & Chen, 2006). Conversely, the biological consequences of episodic stressors were expected to be attenuated among those without chronic difficulties.

## Method

### *Participants*

Data for the present study were collected as part of a larger research project involving young women at high risk for depression. Female adolescents were recruited from the Vancouver, British Columbia, community through advertisements in newspapers and magazines. Young women were eligible for the study if they were (a) between the ages of 15 and 19, (b) fluent in the English language, (c) free of acute and chronic medical conditions, (d) without a lifetime history of major psychiatric disorders, and (e) at high risk for developing an initial episode of major depression. High risk was defined as having a first-degree relative with a history of depression or as scoring in the top quartile of the sample distribution on one of two indices of cognitive vulnerability, the Dysfunctional Attitudes Scale (Weissman & Beck, 1978) or the Adolescent Cognitive Style Questionnaire (Hankin & Abramson, 2002). The study was approved by the institutional review board at the University of British Columbia, and participants were paid Can\$70 (U.S. \$61.60) for completion of this portion of the research. The final sample consisted of 104 young women whose characteristics are described in Table 1.

### *Procedures*

All participants attended an initial laboratory session. On arriving at our laboratory, a research assistant described the study procedures in detail. Written consent was obtained from the participant, or if she was younger than 18 years, written assent was obtained from her and formal consent was obtained from her parent. The Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002) was then administered to determine eligibility in terms of lifetime history of psychiatric disorders. Next, research assistants administered an in-depth interview regarding life stress (see below). Following the interview, the participant was seated in a comfortable chair, and 30 ml of blood was collected through antecubital venipuncture.

Over the course of the next 2 days, participants gathered salivary cortisol samples as they went about their normal daily activities. To facilitate the collection process, we lent participants a handheld computer (Palm Zire 21) that signaled them to collect saliva at waking and at 0.5, 1.0, 4.0, 9.0, and 14.0 hours after waking. Specifically, when participants woke up, they took their first saliva

Table 1  
Demographic and Health-Related Characteristics of Participants

Characteristic	Statistic
Age ( $M \pm SD$ )	17.2 $\pm$ 1.34
Ethnicity (%)	
Caucasian	42
East Asian	48
Other	10
Parents' education (%)	
High school or less	25.1
Some college	15.9
College graduate	59.2
Parents married (%)	82
Risk for depression <sup>a</sup> (%)	
Family history	11
Cognitive vulnerability	64
Both	21
Cortisol 2-day means (nmol/L; $M \pm SD$ )	
Waking	9.10 $\pm$ 8.34
0.5 hr after waking	12.57 $\pm$ 8.50
1 hr after waking	11.96 $\pm$ 11.75
4 hr after waking	4.40 $\pm$ 4.89
9 hr after waking	2.76 $\pm$ 4.18
14 hr after waking	1.76 $\pm$ 2.62
Cortisol morning response	0.89 $\pm$ 0.29
Cortisol daily output	6.66 $\pm$ 2.76
CRP (mg/L)	0.61 $\pm$ 0.74
Glucose (mmol/L)	4.48 $\pm$ 0.36
Insulin (pmol/L)	53.63 $\pm$ 23.83
GR mRNA (RQ)	4.15 $\pm$ 1.93

Note. CRP = C-reactive protein; GR = glucocorticoid receptor; RQ = relative quality.

<sup>a</sup> Four percent of young women in our sample were not considered to be at high risk for depression. Excluding these women from our analyses did not affect our findings.

sample and activated a customized software application on the Palm. This application "programmed" the computer so that it would sound alarms at the appropriate times for the rest of the day's samples. To collect the saliva samples, participants chewed lightly on a cotton dental roll for 1 min so that it became saturated in saliva (Salivette; Sartstedt Corp., Numbrecht, Germany). Participants were instructed to avoid taking saliva samples immediately following tooth brushing and food intake. The dental roll was then placed in a plastic container and stored in the refrigerator until the end of the ambulatory monitoring period. To ensure compliance with the saliva sample protocol, the computer flashed a three-digit code each time the alarm sounded. Participants recorded the code on the plastic container. When the Salivettes were returned to the lab, a research assistant matched the computer codes with those recorded by the participant, and samples without proper codes were excluded from analyses.

### Life Stress Interview

To assess participants' exposure to stressful experiences, we administered the UCLA Life Stress Interview—Adolescent Version, which was developed from earlier versions for adults and children (e.g., Hammen, 1991). This semistructured interview covers episodic and chronic forms of stress over the past 6 months. It focuses on stress in multiple domains, including romantic relationships, friendships, and family relationships. In each domain, a

trained interviewer asks a series of open-ended questions and uses the information gathered to rate the level of chronic, ongoing stress. Ratings range from 1 to 5, with a rating of 1 reflecting superior functioning and higher numbers reflecting more severe and persistent difficulties. Separate ratings are made in each domain. This interview also yields information regarding the occurrence of episodic stressors, which in this context were defined as specific events with a discrete onset and offset. To judge the objective impact of an episodic event, our research team made a consensus impact rating after being briefed on event details by the primary interviewer. Impact ratings can range from 1 (*no long-term impact*) to 5 (*severe long-term impact*), and they explicitly consider the context in which an event has occurred. Thus, higher ratings represent greater contextual threat. For example, if a participant was expelled from school, we would make a rating based on a number of factors, such as reactions from parents and friends and the extent to which the expulsion interfered with academic progress. The goal would be to capture how the average person in similar biographical circumstances would respond. The rating process is also meant to eliminate the influence of reporting biases; thus, a participant's subjective experience is not discussed by the team or factored into its rating. This interview has been used successfully in adolescent populations (e.g., Hammen, Brennan, & Shih, 2004), and there is evidence to support its reliability and validity. In the current project, our raters agreed with each other on chronic stress ratings 91% of the time. Agreement in this case was defined as being within a half point of each other. In terms of validity, high stress ratings predict the onset of a depressive episode among children and adolescents (Adrian & Hammen, 1993; Hammen, Adrian, & Hiroto, 1988; Rudolph & Hammen, 1999), as well as biological outcomes among children with asthma (Miller & Chen, 2006).

Chronic stress ratings were averaged across four domains (i.e., family life, social life, romantic, and closest friend) to create an interpersonal chronic stress score for each participant. We focused on interpersonal chronic stress because peer and family relationships are an important focus in adolescence and adulthood, and past research has shown that interpersonal stress is a strong predictor of disease outcomes (Smith & Ruiz, 2002). Examples of chronic interpersonal stressors in this sample include having a sibling with a mental illness, living in a conflictual family environment, feeling rejected by a peer group, and the absence of a confidant. The mean interpersonal chronic stress score was 2.40 ( $SD = 0.49$ ). Each participant's maximum episodic event rating in the past 6 months was used to create an episodic stress score. Participants with no episodic event were given a score of 1 (*no long-term impact*). The average episodic rating across the sample was 1.92 ( $SD = 0.86$ ), which corresponds to an event with mild impact.

### Cortisol Secretion

Cortisol was measured by means of a commercially available chemiluminescent technique (IBL—Hamburg; Hamburg, Germany) at the Technical University of Dresden. This assay has a sensitivity of 0.16 ng/ml and intra- and interassay coefficients of variation less than 12%. After cortisol values had been log-transformed, each day's data were used to create two area-under-the-curve (AUC) indices of secretion for later analysis. The first index was

the morning response measure, reflecting the volume of cortisol secretion over the first hour after waking.<sup>1</sup> Cortisol values at waking, 0.5 hr after waking, and 1.0 hr after waking were used for these calculations. The second index was the total volume of cortisol secretion over the day. For these calculations, we used all cortisol values across the day, excluding the 0.5-hr sample, which is an indicator of morning response and has a disproportionate influence on daily output calculations. Both of these measures were computed by using a trapezoidal method, such that higher values reflect greater cortisol release. To obtain more reliable indices of cortisol secretion, we averaged the AUC values calculated for each day of ambulatory data collection. The correlation between morning response values from the 2 days was  $r = .45$  ( $p < .001$ ), and the correlation between daily output values was  $r = .58$  ( $p < .001$ ). AUC values are in arbitrary units that reflect nmol/L over time.

Because the sampling schedule we used was specially designed to capture diurnal fluctuations in cortisol secretion, we felt that it was important to monitor participants' compliance with ambulatory monitoring carefully and to exclude any samples that did not conform to the protocol's requirements. The handheld computers' capacity to time-state and date-stamp each diary entry facilitated this process greatly. On an a priori basis, we chose to define compliance as taking a sample within 20 min of target in either direction for the waking, 0.5-hr, and 1-hr samples and within 60 min of target for the remainder of the samples. When this definition was applied, a total of 1,037 of the 1,248 samples (83%) met our criteria for compliance. Only these values were used to compute morning cortisol response and daily cortisol output AUC scores. In the case of a missing sample at waking, 0.5 hr after waking, or 1 hr after waking, we did not compute a morning cortisol response score for that day. We computed daily output scores when we had at least four samples across the day.

### *CRP, Glucose, and Insulin*

Blood draw was collected in the morning following a 12-hr fast. Ten milliliters was drawn into a serum separator tube and then centrifuged at  $1,000 \times g$  for 25 min. The serum was then aspirated, divided into 1-ml aliquots, and frozen at  $-20^\circ\text{C}$  until analysis. CRP was analyzed using a high-sensitivity, chemiluminescent technique on an IMMULITE 2000 (Diagnostic Products Corporation, Los Angeles, California). This assay has an interassay coefficient of variation of 2.2% and a detection threshold of 0.20 mg/L. Glucose analyses were carried out on an ADVIA 1650 Chemistry System (Bayer Diagnostics, Tarrytown, New York). This analysis is an enzymatic technique that uses hexokinase and glucose-6-phosphate dehydrogenase enzymes. The assay has an interassay coefficient of variation of 1.2%. Insulin analyses were carried out on the IMMULITE 2000 using a solid-phase, two-site chemiluminescent immunometric assay with an interassay coefficient of 3.1%.

### *GRs*

The expression of GR was quantified by measuring mRNA in leukocytes through real-time reverse-transcriptase polymerase-chain reaction with a commercially available one-step assay purchased from Applied Biosystems (see Miller & Chen, 2006).

Results are expressed as relative quantities of GR mRNA, such that higher relative quantities indicate greater expression of the GR.

### *Potential Confounders*

We measured a number of processes that could provide alternative explanations for relations between stressors and biological outcomes. We collected demographic information, including participant age and ethnicity. Because the majority of the sample (90%) was of Caucasian or Asian descent, we created a dichotomous ethnicity variable coded as 1 for Caucasian and 0 for other. Participants reported on tobacco use and alcohol consumption. There were no cigarette smokers in the sample, defined as smoking daily. The mean number of alcoholic beverages consumed per week was 1.28 ( $SD = 4.93$ ). Body mass index (BMI) was calculated on the basis of height and weight measures obtained in the lab using a medical-grade scale balance-beam score. The average BMI was 21.63 ( $SD = 2.72$ ).

### *Statistical Analyses*

In the first wave of analyses, we examined the distribution of study variables. The distribution of CRP scores was substantially positively skewed, so this variable was analyzed following a log-10 transformation. We also screened for outliers and found a score in the daily cortisol distribution greater than 3 standard deviations from the sample mean. We performed a log-10 transformation that brought the outlier within 3 standard deviations of the mean, and the data were analyzed using these transformed scores. In the second wave, we conducted bivariate analyses to assess the relationship between study variables and potential confounds. In the third wave of analyses, we tested our major hypotheses. We analyzed the main effects of episodic and chronic stressors using first-order and partial correlations. Finally, we tested the interaction between episodic and chronic stressors using multiple regression. The interaction term was created by taking the cross-product of centered episodic stress and chronic stress scores. When testing the interaction, main effects and the interaction term were entered together into the same regression equation. When a statistically significant interaction emerged, it was interpreted according to Aiken and West's (1991) guidelines. We plotted predicted scores at low, medium, and high levels of chronic and episodic stress, which corresponded to  $-1$  standard deviation, the mean, and 1 standard deviation.

## Results

### *Preliminary Analyses*

To identify potential confounders, correlations were computed between young women's demographic and behavioral character-

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<sup>1</sup> We also calculated the morning response to reflect the cortisol rise in response to awakening (AUC of cortisol across first hour after waking with subtraction of the AUC at waking; see Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). With the new method of calculating the morning AUC, there was no effect of stressors. This suggests that our findings reflect differences in overall morning cortisol secretion rather than the postwaking rise per se.

istics and study variables. Episodic and chronic interpersonal stress, cortisol indices, and GRs were not significantly associated with age, ethnicity, alcohol consumption, or BMI ( $ps > .05$ ). Glucose was significantly associated with age, such that older participants had lower glucose levels ( $r = -.20, p < .05$ ). Both higher CRP and insulin were significantly associated with higher BMI ( $r = .311, p < .001$ , and  $r = .26, p < .05$ , respectively). On the basis of the results of these analyses, we included age as a covariate in analyses of glucose, and we included BMI as a covariate in analyses of CRP and insulin.

### Exposure to Chronic and Episodic Stressors

Pearson correlations indicated that the extent of chronic interpersonal stress was unrelated to biological outcomes. This was true for daily cortisol output, morning cortisol response, GR mRNA, CRP, glucose, and insulin ( $ps > .10$ ).

Pearson correlations indicated that episodic stressors were inversely related to CRP. To the extent that they had experienced a more contextually threatening event in the past 6 months, participants exhibited lower circulating concentrations of the inflammatory molecule ( $r = -.23, p < .05$ ). The extent of contextual threat in the past 6 months was unrelated to daily cortisol output, morning cortisol response, GR mRNA, glucose, and insulin ( $ps > .10$ ). Owing to the fact that our interview captured episodic stressors as far back as 6 months, we also examined whether recent events were more strongly related to outcomes. However, analyses indicated that episodic stressors in the 1- and 3-month periods before enrollment were unrelated to outcomes ( $p > .05$ ).

### Interaction of Chronic and Episodic Stressors

We used multiple regression to test the interaction between chronic and episodic stress in the prediction of cortisol secretion. These analyses indicated that episodic stress and chronic interpersonal stress interacted in the prediction of daily cortisol output,

$\beta = 0.21, t(87) = 1.99, p < .05$ . As Figure 1 illustrates, the impact of episodic stressors depended on the amount of chronic interpersonal stress a participant was experiencing. Among young women facing higher levels of chronic interpersonal stress, daily cortisol output increased with the severity of episodic stressors. The opposite pattern emerged among young women with the lowest levels of chronic interpersonal stress; daily output was reduced to the extent that they experienced more contextually threatening episodic events. Among young women rated as having relatively moderate levels of chronic interpersonal stress, cortisol output did not vary as a function of episodic stressors.

Analyses indicated an interaction between chronic interpersonal stress and episodic stress in the prediction of the morning cortisol response,  $\beta = 0.37, t(87) = 3.29, p < .01$ . As shown in Figure 2, the interaction of episodic and chronic stress predicted the morning cortisol response in a pattern similar to that of daily cortisol output. Specifically, among young women who faced higher levels of chronic interpersonal stress, the morning cortisol response increased as they experienced more contextually threatening events, whereas among young women who experienced lower levels of interpersonal stress, the morning cortisol response decreased with the extent of contextual threat. Again, episodic stress had minimal impact on cortisol secretion among young women who experienced relatively moderate levels of ongoing interpersonal stress.

A similar pattern emerged in the prediction of GR mRNA,  $\beta = -0.26, t(93) = -2.58, p < .05$ . Figure 3 shows that among young women facing higher levels of chronic interpersonal stress, GR mRNA declined to the extent that they experienced more contextually threatening events. Again, the opposite pattern was evident among young women with lower levels of chronic interpersonal stress, and GR mRNA was not affected by episodic stressors in young women with relatively moderate levels of chronic interpersonal stress.

Episodic and chronic stress also interacted significantly to predict CRP,  $\beta = -0.20, t(93) = -2.03, p < .05$ . However, the

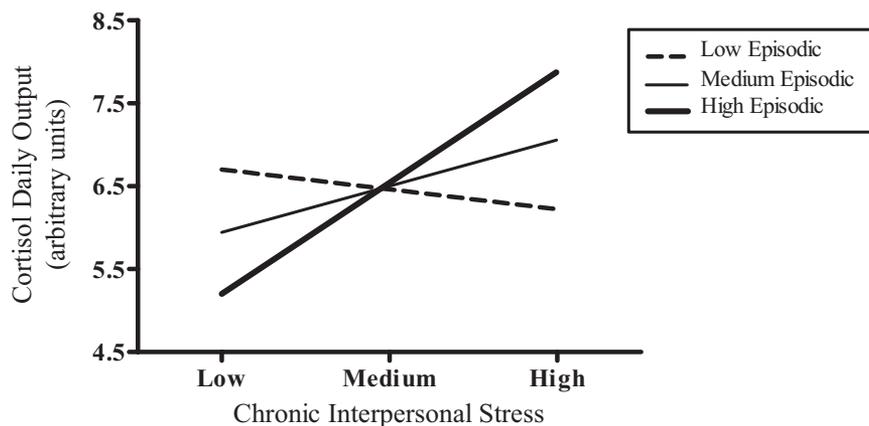


Figure 1. Daily cortisol output as a function of episodic stressor exposure and chronic interpersonal stress. Episodic stressors are specific events with a discrete onset and offset, and higher scores indicate events with greater impact. Chronic interpersonal stress represents ongoing family, social, and/or romantic difficulties, with higher scores indicating more severe and persistent difficulties. Predicted scores are plotted at low, medium, and high levels of chronic and episodic stress, which corresponds to  $-1$  standard deviation, the mean, and  $1$  standard deviation.

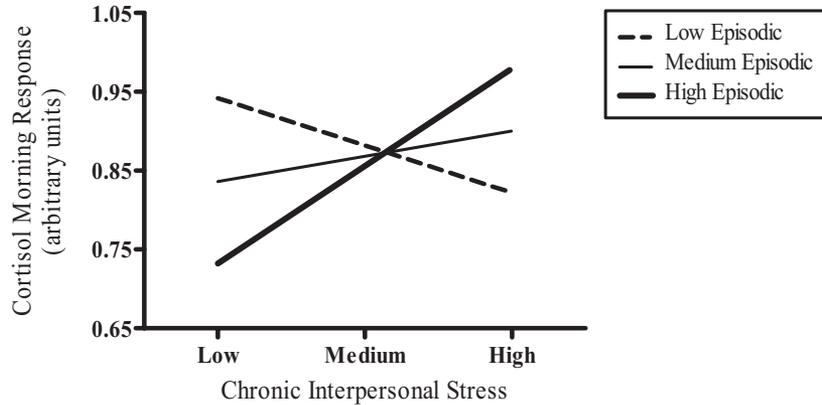


Figure 2. Morning cortisol response as a function of episodic stressor exposure and chronic interpersonal stress. Episodic stressors are specific events with a discrete onset and offset, and higher scores indicate events with greater impact. Chronic interpersonal stress represents ongoing family, social, and/or romantic difficulties, with higher scores indicating more severe and persistent difficulties. Predicted scores are plotted at low, medium, and high levels of chronic and episodic stress, which corresponds to -1 standard deviation, the mean, and 1 standard deviation.

pattern was somewhat different, as shown in Figure 4. As chronic interpersonal stress increased, so too did the impact of episodic events. Specifically, under conditions of low chronic interpersonal stress, ratings of contextual threat had no effect on CRP. However, as young women faced increased chronic interpersonal stress the impact of episodic events increased in magnitude, such that young women who experienced more contextually threatening events had lower levels of circulating CRP.

Episodic and chronic interpersonal stress scores did not interact in the prediction of glucose and insulin ( $p > .10$ ).

Discussion

This study had three major hypotheses: (a) that by virtue of their time-limited nature, episodic stressors would be unrelated to bio-

logical outcomes; (b) to the extent that they had chronic interpersonal stress, young women would show evidence of hormonal, inflammatory, and metabolic dysregulation; and (c) that episodic and chronic stressors would interact to predict these outcomes, such that the impact of acute events would be accentuated by chronic interpersonal stress. Our first two hypotheses proved to be incorrect. There was no consistent pattern of associations between episodic or chronic interpersonal stressors and any of the biological outcomes we measured. However, there was strikingly consistent evidence in support of our last hypothesis, as chronic and episodic stressors interacted to predict four separate outcomes: daily cortisol output, morning cortisol response, GR mRNA, and CRP. By exploring the pattern of these interactions, it became evident why neither episodic nor chronic interpersonal stress res-

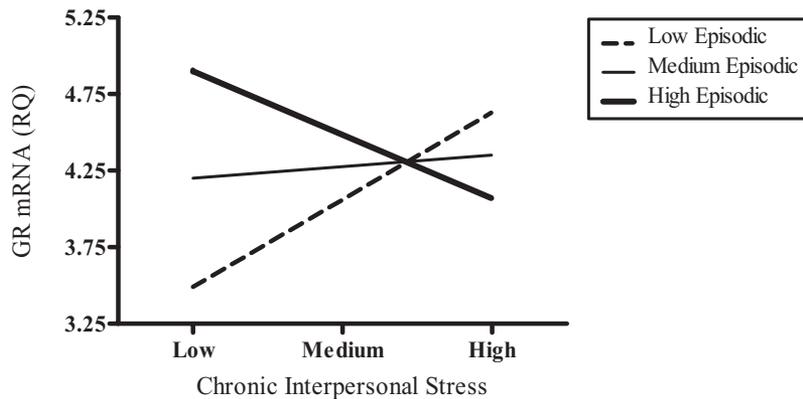
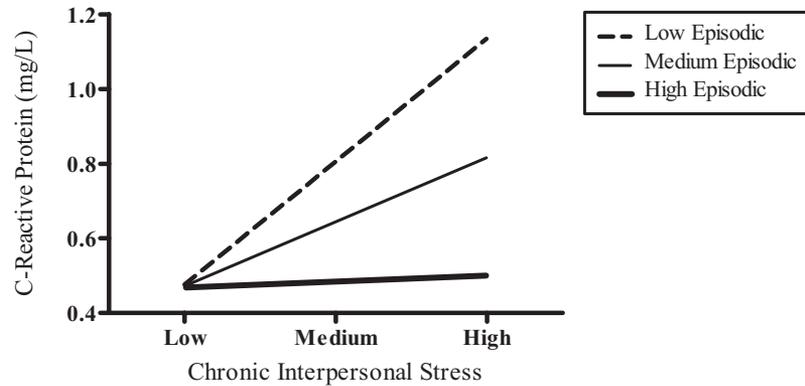


Figure 3. Glucocorticoid receptor (GR) mRNA as a function of episodic stressor exposure and chronic interpersonal stress. Episodic stressors are specific events with a discrete onset and offset, and higher scores indicate events with greater impact. Chronic interpersonal stress represents ongoing family, social, and/or romantic difficulties, with higher scores indicating more severe and persistent difficulties. Predicted scores are plotted at low, medium, and high levels of chronic and episodic stress, which corresponds to -1 standard deviation, the mean, and 1 standard deviation. RQ = relative quality.



*Figure 4.* C-reactive protein as a function of episodic stressor exposure and chronic interpersonal stress. Episodic stressors are specific events with a discrete onset and offset, and higher scores indicate events with greater impact. Chronic interpersonal stress represents ongoing family, social, and/or romantic difficulties, with higher scores indicating more severe and persistent difficulties. Predicted scores are plotted at low, medium, and high levels of chronic and episodic stress, which corresponds to  $-1$  standard deviation, the mean, and  $1$  standard deviation.

lated directly to outcomes; the influence of episodic events depended entirely on the extent of chronic interpersonal stress, and vice versa.

Among young women facing higher levels of chronic interpersonal stress, more severe episodic stressors (during the previous 6 months) were associated with amplified cortisol output, both in the morning and across the day, reduced expression of GR mRNA, and lower concentrations of CRP. These findings are in line with research showing that the impact of acute events is accentuated in people who are in the midst of chronic stressors (Gump & Matthews, 1999; Miller & Chen, 2006). This may be the case because people generally do not have the coping resources, emotional energy, or social support to manage acute and chronic demands simultaneously. Our findings suggest that when people face these situations, the magnitude of their cortisol output is increased, both in the morning hours and through the daytime and evening. Persistently increased output of this nature might then foster a compensatory downregulation of GR mRNA in leukocytes.

Among young women with relatively moderate levels of chronic interpersonal stress, episodic events were unrelated to morning cortisol response, daily cortisol output, or GR mRNA. Why might the impact of episodic stressors be attenuated in these young women? We know that the transition to adulthood is a time filled with interpersonal successes and failures, as teenagers try to negotiate close relationships with friends and peers and become more independent from their parents (Laursen & Collins, 1994). Some degree of tension seems to be inherent in women's lives at this stage; those with moderate difficulties are likely to be having developmentally normative experiences. Furthermore, young women who fall into this group have a chronic interpersonal stress score of around 2.4, suggesting that they have basically stable and positive relationships, with some occasional but not serious problems in them. When a stressor arises, these young women are likely to have at least adequate social resources to call on. These resources may be what help them to minimize the biological consequences of exposure to an episodic stressor.

Among young women with the lowest levels of chronic interpersonal stress, episodic stressors were related to reductions in the

morning cortisol response and daily cortisol output, as well as increased expression of GR mRNA by leukocytes. How do we explain these effects? It is clear that these young women have strong relations with friends and family, marked by high levels of trust and intimacy. So when they are exposed to episodic stressors, these teenagers have many resources to call on, and they may emerge from these experiences looking healthier than if they had not been exposed. These findings add to a growing literature suggesting that children in supportive environments can develop physiological resilience in response to stressful experiences (Boyce et al., 1995; Bugental, 2005). In other words, the combination of supportive parenting history and confrontations with stressors and challenges may provide inoculation against subsequent stressors (physiological toughening; Dienstbier, 1989). To test this hypothesis more completely, relations between the social environment, stressful events, and health trajectories would need to be examined prospectively over the course of development.

To examine any downstream consequences of hormonal alterations, we assessed indicators of metabolic functioning and systemic inflammation. Episodic and chronic stressors were unrelated to levels of glucose and insulin. We had expected that stressful life experiences would be associated with altered metabolism, as indicated by higher levels of glucose and insulin. It is possible that the impact of stress on metabolic functioning accumulates slowly over time, requiring prolonged elevations in the amount of cortisol before it emerges. Our focus on relatively recent stressors (those that had occurred within the past 6 months) rather than ongoing stressors over the course of childhood and adolescence may account for these null findings.

Episodic stress and chronic interpersonal stress did, however, interact to predict CRP concentrations, but in a fashion that was partially inconsistent with our initial hypothesis. For young women with the lowest amount of chronic interpersonal stress, episodic stressors were unrelated to the expression of CRP. This pattern of findings makes sense conceptually, given the high quality of social relations in this subgroup of young women. However, as chronic interpersonal stress increased in magnitude, so did the impact of episodic stressors on CRP. The direction of this association was

negative—with more severe episodic stressors, participants exhibited smaller amounts of CRP. This was unexpected. We predicted that in this cohort of double-exposed young women, systemic inflammation would be the most pronounced. It is not clear what accounts for these findings. Output of cortisol in these young women was significantly elevated, and according to our model, this should result in greater systemic inflammation, secondary to the downregulation of GR numbers or function (Miller et al., 2002). We are not sure why this pattern failed to emerge, but it may be due to the study's cross-sectional design. Our findings suggest that, at high levels of chronic interpersonal stress, cortisol concentrations and GR numbers are adjusted depending on the presence or absence of episodic stressors. Thus, HPA responses to these types of stressors may not persist long enough to affect systemic inflammation. A multiwave study that tracks changes in these parameters over time is needed to clarify these points.

To the extent that this scenario is accurate, it has interesting theoretical and practical implications for research. Double-exposed young women showed a variety of biological alterations, and they were not uniformly negative or positive. Although increased morning cortisol and reduced expression of GR in leukocytes could heighten risk for later metabolic and cardiac disease, reduced concentrations of inflammatory molecules like CRP would offset this to a large extent. This pattern of findings suggests that simple theories linking stressful experience, increased cortisol output, and metabolic or inflammatory dysregulation are likely to be incorrect (Miller, Chen, & Zhou, 2007). Collectively, these findings highlight the need for more complex accounts of the pathways linking stressors and disease. Such accounts will need to acknowledge that stressful experiences can activate multiple interacting biological systems, which have differing and sometimes opposing consequences for later disease (McEwen, 1998; Weiner, 1992).

There are a number of limitations to this study that should be noted. First, young women in this sample were at high risk of developing an initial episode of depression. It is likely that these women are generally more susceptible to the effects of stress. So our findings may exaggerate the relationship between stress and hormonal and inflammatory responses in the general population of female adolescents. It is therefore necessary to replicate these findings among more diverse samples. Second, our inability to detect main effects of episodic events may reflect the fact that HPA indices were not always assessed shortly after the stressor occurred, when they would be most likely to emerge. Future research that examines HPA activity within weeks of the stressful event may be more likely to detect such findings. Third, this study used a cross-sectional design. To clarify the temporal relations between stressful experiences and biological processes, we will need to test these associations longitudinally. Fourth, our GR findings were in leukocytes, and it will be important for future research to determine whether they extend to other tissues. Finally, our findings may be better explained by an underlying personality characteristic. For instance, if hostile or neurotic young women are prone to experiencing (or simply reporting) episodic stressors and chronic interpersonal stressors, their biological outcomes might be better explained by personality features than by life events. However, we used objective contextual interviews that minimize the influence of self-report biases and as a result are unlikely to reflect the influence of personality.

Despite these limitations, our findings provide several interesting contributions to the literature. First, they suggest that stressor impact is a complex phenomenon and depends on both episodic and chronic exposure. The simple presence of an episodic or chronic stressor did not reliably affect biological outcomes. Thus, future research must assess both types of stress to clarify the biological consequences of either. Only then will we be able to identify people who may be susceptible to HPA dysregulation and its subsequent impact on other systems. Second, among young women in this study, episodic events and chronic interpersonal stressors were most strongly related to hormonal and inflammatory outcomes, suggesting that these biological processes are particularly sensitive to social stressors in adolescent life. Metabolic indicators may be less sensitive to these types of stressors, or they may be better examined in longitudinal designs that capture the impact of cumulative stress over time. Finally, we found that adolescents with low to moderate chronic interpersonal stress showed relatively adaptive biological responses to episodic stressors. These results contribute to existing literature that challenges the assumption that stress is uniformly bad for one's health. In the context of a supportive environment, stressful experiences may toughen the body, rendering it more resilient to subsequent stressors. With future studies in this area, we will be able to clarify the conditions under which hormonal and inflammatory responses to stressful experiences are risk factors for versus protective factors against future health problems.

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