The impact of the severity of early life stress on diurnal cortisol: The role of puberty

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\textbf{A B S T R A C T}

Researchers have documented dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in children and adolescents who experienced early life stress (ELS). The precise nature of this dysregulation, however, has been difficult to discern. In fact, both elevated and blunted patterns of diurnal cortisol regulation have been reported in children and adolescents exposed to greater ELS, including both reduced and heightened cortisol levels and change in cortisol across the day. These divergent findings may be due to developmental changes in the relation between ELS and HPA-axis functioning. The present study was designed to examine the role of puberty in the impact of the severity of ELS on the regulation of diurnal cortisol. Boys and girls (N = 145) ages 9–13 years recruited from lower-risk communities completed an interview about their ELS experiences and at-home collection of diurnal cortisol. ELS experiences were objectively coded for severity, and children’s level of pubertal development was measured using Tanner Staging. Multi-level piecewise mixed-effects models tested the effects of ELS severity and pubertal stage on cortisol levels at waking, the cortisol awakening response (CAR), and the daytime cortisol slope. While we found no significant interactive effects of pubertal stage and ELS severity on cortisol levels at waking or the daytime cortisol slope, findings indicated that pubertal stage interacted with ELS severity to predict the cortisol awakening response (CAR). Specifically, in earlier puberty, higher ELS was associated with a blunted CAR compared to lower ELS; in contrast, in later puberty, higher ELS was associated with a heightened CAR compared to lower ELS. Differences in the relation between ELS severity and the CAR were uniquely determined by puberty, and not by age. By considering and examining the role of puberty, the current study provides a developmental explanation for previous divergent findings of both blunted and heightened patterns of diurnal cortisol following ELS. These results indicate that careful attention should be given to children’s pubertal status before drawing conclusions concerning the nature of diurnal cortisol dysregulation.

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1. \textbf{Introduction}

A growing body of research has documented adverse consequences of stressful experiences in early life for mental and physical health across the lifespan (e.g., Felitti et al., 1998; Green et al., 2010; McLaughlin et al., 2016). Although early life stress (ELS) has been associated with a wide range of negative outcomes, the mechanisms by which ELS confers risk have not been fully elucidated. Changes in the hypothalamic-pituitary-adrenal (HPA) axis, a central stress response system, may mediate the association between ELS and negative health outcomes (McCory et al., 2010). Stress in early life may have powerful effects on the HPA axis because this system has not yet reached maturity (Gunnar and Quevedo, 2007). There is a dearth of research, however, exploring the role of potentially relevant developmental processes, such as puberty, in understanding the effects of ELS on the HPA axis.

The HPA axis governs the release of cortisol, which follows a characteristic diurnal rhythm. Specifically, on average, individuals exhibit increases in cortisol in the morning (the cortisol awakening response; CAR) followed by gradual decreases across the rest of the day (the daytime slope). Atypical activation of the HPA axis in response to persistent or overwhelming environmental stress is posited to disturb the diurnal rhythm, leading to a profile of diurnal cortisol dysregulation (McEwen and Wingfield, 2003). The precise

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nature of this dysregulation, however, has been difficult to discern. In fact, both elevated and blunted patterns of diurnal cortisol have been reported in youth who have been exposed to various types of ELS (Hunter et al., 2011). While some researchers have identified higher morning, afternoon, and bedtime cortisol levels in children and adolescents who have been exposed to ELS in the form of trauma (Carrión et al. 2002; Weems and Carrión, 2009), other investigators have identified attenuation of the CAR in adolescents exposed to suboptimal caregiving (Roisman et al., 2009) and lower cortisol levels 30-min post-waking in young children exposed to maltreatment (Bernard et al., 2010).

Although both atypically heightened and reduced production of diurnal cortisol have been posited to be problematic for neurodevelopment and risk for disease (Gunnar and Quevedo, 2007), we do not have a clear understanding of why different patterns of diurnal cortisol production are manifested following ELS. In this context, it is important to identify the factors that underlie diverse effects across the full diurnal pattern, including differences in cortisol levels at waking, the CAR, and the daytime slope. It is noteworthy that the specific pattern of diurnal cortisol regulation exhibited by children exposed to ELS may not be permanent. Rather, the impact of ELS on diurnal cortisol may change over the course of development. In particular, the developmental process of puberty, which is defined by endocrine and physical changes, has been posited to influence HPA-axis functioning (Marceau et al., 2015). Specifically, endocrine changes that occur with adrenarche and gonadarche, including a rise in androgens and gonadotropins and concomitant growth in pubic hair, breast tissue, and external genitalia (Dorn and Biro, 2011), are initiated and regulated by the same neural and endocrine systems that are responsible for the release of cortisol (Dismukes et al., 2015).

Human and animal research suggests that there are both age- and puberty-related changes in HPA-axis functioning, including increases in cortisol reactivity to stress (Romeo, 2010; van den Bos et al., 2014) and normative attenuations in diurnal cortisol slopes (modeled as change in cortisol from morning to evening) at later developmental stages (Shirtcliff et al., 2013). Few investigators, however, have explicitly examined how puberty may affect the relation between ELS and diurnal cortisol. Research with children who were institutionalized in early life, however, indicates that the relation between early caregiving deprivation and diurnal functioning of the HPA axis changes over puberty. Specifically, Quevedo et al. (2012) found that whereas prior institutionalization was associated with a blunted CAR in pre/early puberty, by mid/late puberty institutionalization was associated with a higher CAR that was more similar to a family-reared control group. These findings support the formulation that the form of dysregulation of diurnal cortisol, specifically the manifestation of the CAR, depends on the stage of pubertal development.

By considering the role of puberty in the association between ELS and diurnal cortisol regulation, we might increase our understanding of how to define dysregulation and, consequently, of how to prevent and intervene to enhance regulation. In particular, it is important to investigate these associations in a sample of children recruited from the community. Although studies of institutionalized children have been vital for understanding the impact of early caregiving deprivation, this extreme and circumscribed form of ELS is not typical. Children developing in more normative contexts may be exposed to a broad range of ELS experiences across childhood that vary in severity. For these children, dysregulation of diurnal cortisol may persist through adolescence, but its manifestation may change.

Based on the literature reviewed above, the current study examined, for the first time, the role of pubertal stage in affecting the relation between the severity of ELS and diurnal cortisol, including the cortisol level at waking, the CAR, and the daytime slope, in a sample of community children. First, we tested the hypothesis that in a sample of community children, the impact of the severity of ELS on diurnal cortisol regulation depends on the stage of pubertal development. Second, given that some studies have reported age-related changes in diurnal cortisol regulation, we examined the unique influences of stage of pubertal development and age on the relation between the severity of ELS and diurnal cortisol regulation.

2. Methods

2.1. Participants

Participants were 145 children (57% female) ages 9–13 years (M = 11.40, SD = 1.07) who completed collection of diurnal cortisol as part of a longitudinal study of the psychobiological effects of ELS across the transition through puberty (descriptive statistics by child sex are presented in Table 1). Participants were recruited using a combination of media and online advertisements posted in local communities around Stanford University. Because the larger study involved a magnetic resonance imaging (MRI) session, criteria for exclusion from the study included factors that would preclude an MRI scan (e.g., metal implants, braces), as well as a history of major neurological or medical illness, severe learning disabilities that would make it difficult to comprehend the study procedures, and, for females, the onset of menses. Inclusion criteria were that children were ages 9–13 years and were proficient in spoken English. In addition, participants were recruited in order to match males and females based on pubertal stage as measured by the Tanner Staging questionnaire (described in Section 2.3.2).

2.2. Procedure

The protocol for this study was approved by the Stanford University Institutional Review Board. In an initial telephone call, research staff provided information about the research protocol to families and screened participants for inclusion/exclusion criteria. Eligible families were then invited to attend a laboratory session during which research staff obtained consent from parents and assent from children. In this session, children reported their Tanner stages, and both parents and children completed interview and questionnaire measures about the child and family. At the end of the session, staff provided families with kits and instructions to collect saliva samples at home for the assessment of diurnal cortisol. Families returned the samples to the laboratory at a subsequent visit.

2.3. Measures

2.3.1. Severity of early life stress

Children were interviewed about their lifetime exposure to 30 types of stressful experiences using a modified version of the Traumatic Events Screening Inventory for Children (TESI-C; Ribbe, 1996). A panel of three coders, blind to the children’s reactions and behaviors during the interview, then rated the objective severity of each type of stressor endorsed using a modified version of the UCLA Life Stress Interview coding system (Rudolph and Hammen, 1999; Rudolph et al., 2000). Specifically, a trained research assistant transcribed and delivered to the panel a description of each stressor, removing details that would reveal the child’s subjective perception of severity. Coders then made severity ratings on a scale of 0–4, increasing in half-point increments (0 = non-event or no impact; 4 = extremely severe impact; ICC = 0.99). Following coding, we created an index of the level of ELS severity by summing the severity ratings for each type of stressor the child endorsed. This method overcomes problems with operationalizing ELS as the number of stressors that children report (Jenness and McLaughlin, 2015). Such methods inaccurately equate children who report the same number...
Table 1
Descriptive Statistics for Males and Females.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>t or χ²</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.83 (0.964)</td>
<td>11.08 (1.03)</td>
<td>-4.45</td>
<td>143</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pubertal Stage</td>
<td>1.50 (0.666)</td>
<td>2.13 (0.796)</td>
<td>1.85</td>
<td>143</td>
<td>0.066</td>
</tr>
<tr>
<td>ELS Severity</td>
<td>5.25 (4.32)</td>
<td>5.24 (4.35)</td>
<td>-0.012</td>
<td>143</td>
<td>0.990</td>
</tr>
<tr>
<td>BMI</td>
<td>19.51 (3.53)</td>
<td>18.31 (3.78)</td>
<td>-1.87</td>
<td>131</td>
<td>0.064</td>
</tr>
<tr>
<td>Medication Use</td>
<td>11%</td>
<td>12%</td>
<td>0.020</td>
<td>1</td>
<td>0.888</td>
</tr>
</tbody>
</table>

\( \text{Note: } M(\text{SD}) \text{ or } \% ; \text{ sex coded female } = 0, \text{ male } = 1; \text{ ELS } = \text{ Early Life Stress.} \)

- Chi-square with non-concorticosteroid medication use (taking medication or medication-free).
- Chi-square with minority status (White/Caucasian or minority).
- Chi-square with median split at $100,001–150,000.
- Chi-square with number of people living in home of child’s primary parent \((<4 \text{ or } >4 \text{ people})\).
- Chi-square with primary parent completed education level \(<\text{college degree} \text{ or } \geq \text{college degree})\).

of stressful experiences but who differ substantially in their experiences of severity. Final ELS severity scores ranged from 0 to 19 \((M = 5.24, SD = 4.32)\). See supplement for further details.

2.3.2. Stage of pubertal development

Pubertal stage was assessed using the self-report Tanner Staging questionnaire (Marshall and Tanner, 1968). Tanner staging scores in the current sample ranged from 1 to 4 \((M = 2.03, SD = 0.749)\). Thirty-six percent of children had an average Tanner stage above 2—the median for the current sample.

2.3.3. Diurnal cortisol

Within two weeks of completing the ELS interview, children completed at-home saliva collection to assess diurnal cortisol on two consecutive weekdays using SalivaBio Children's Swabs (Salimetrics, LLC). Participants were provided with face-to-face and take-home written instructions for saliva collection. They were instructed not to eat or drink before collection of each sample at four time points: awakening (while still lying in bed); 30 min post-waking; mid-afternoon (as close to 3:00pm as possible); and in the late evening \((2 \text{ hr after dinner})\). Participants recorded collection times in a diary and placed samples in their home freezers. In previous research using this protocol in adolescents, we found that self-reported times did not significantly differ from times tracked with smart caps (LeMoult et al., 2015). See supplement for further details.

Participants returned the samples to the laboratory at a subsequent visit. Samples were stored in a \(-20^\circ \text{C} \text{ freezer} \text{ at Stanford University until they were assayed using a high-sensitivity (0.004 µg/dL) immunoassay kit from Immuno-Biological Laboratories Inc. (Hamburg, Germany; both intra- and inter-assay coefficients of variation (CV) for the kit ranged from 3 to 5%). To control for inter-assay error, samples were assayed together in large batches; all samples from the same child were assayed in duplicate. To reduce positive skew in resulting salivary cortisol data, we winsorized values greater than 2 SD above the mean to the 2-SD value following current guidelines (Stalder et al., 2016).}

2.4. Data analysis

Visual inspection indicated that cortisol levels increased from waking to 30-min post-waking and then gradually decreased throughout the day. Given this nonlinear pattern, we implemented
3. Results

3.1. Descriptive statistics

Descriptive statistics by child sex are presented in Table 1. Males and females did not differ significantly from each other in pubertal stage, severity of ELS, minority status, or income (ps > 0.050). There was, however, a non-significant trend such that girls were more advanced in puberty than boys (p = 0.066). As expected because pubertal stage was matched across sexes, males were significantly older than females (p < 0.001). Pearson’s bivariate correlations indicated that pubertal stage was positively associated with child age (r = 0.309, p = 0.001) and ELS severity (r = 0.179, p = 0.031); child age was not significantly related to ELS (r = -0.007, p = 0.933).

3.2. Average diurnal cortisol pattern and covariates

The baseline (level 1) model examining the pattern of diurnal cortisol across all participants indicated that children’s cortisol at waking (the model intercept) was significantly greater than zero (β = 0.516, SE = 0.016, t(145.83) = 31.74, p < 0.001), increased significantly from waking to 30-min post-waking (β = 0.129, SE = 0.036, t(131.54) = 3.55, p < 0.001), and decreased significantly across the rest of the day (β = -0.040, SE = 0.002, t(154.82) = -23.77, p < 0.001). The random effect for the CAR (variance = 0.073, SD = 0.270) was larger than the random effects for cortisol level at waking (variance = 0.021, SD = 0.147) and the daytime slope (variance = 0.0002, SD = 0.015), indicating that individual variability in the CAR was greatest. We then tested whether age, sex, body mass index (BMI), non-corticosteroid medication use, income, minority status, or wake time (hours from midnight) accounted for individual differences in patterns of diurnal cortisol by adding each separately as a predictor of the baseline model coefficients. Age, sex, BMI, medication use, income, and minority status did not have significant effects on cortisol levels at waking, the CAR, or the daytime slope (ps > 0.050). Therefore, in order to preserve model parsimony, we did not include these variables as covariates in the final level 2 analyses (Adam, 2006; Human et al., 2015). There was, however, a significant effect of wake time on cortisol levels at waking (β = -0.037, SE = 0.013, t(143.02) = -2.81, p = 0.006), such that later wake times were associated with lower levels of cortisol at waking; wake time had no effect on the CAR or the daytime slope. Therefore, we included wake time as a covariate in the level 2 analyses.

3.3. Effects of pubertal stage and ELS severity on diurnal cortisol pattern

We then tested the hypothesis that the impact of the severity of ELS on diurnal cortisol regulation depends on stage of pubertal development by adding these variables to a level 2 model predicting the baseline model coefficients. This analysis (presented in Table 2) yielded a significant interactive effect of pubertal stage and ELS on the CAR when controlling for wake time, indicating that the CAR depended on both level of pubertal stage and ELS. There were no significant main or interactive effects of ELS or pubertal stage on level of cortisol at waking or on the daytime slope. Given the nonsignificant trend for girls to be more advanced in puberty than boys, we conducted additional analyses to examine whether these findings were affected or explained by sex. All findings held when controlling for sex; furthermore, sex did not significantly interact with puberty or ELS to predict level of cortisol at waking, the CAR, or the daytime slope.

We used simple slopes analyses to examine further the significant interactive effect of ELS severity and pubertal stage on the CAR. Specifically, we estimated the CAR at the +/− 1-SD values above/below the mean of ELS and pubertal stage (Aiken and West, 1991). As depicted in Fig. 1, we found that in earlier puberty (approximately Tanner stage 1), higher ELS severity was associated with a blunted CAR compared to lower ELS severity. Specifically, the CAR was significantly positive when ELS was lower (β = 0.199, SE = 0.069, t(133.2) = 2.84, p = 0.005), but the CAR was nonsignificant when ELS was higher (β = 0.045, SE = 0.080, t(140.3) = 0.562, p = 0.575). This pattern was reversed in later puberty (approximately Tanner stage 3), such that higher ELS severity was associated with heightened CAR compared to lower ELS severity. Specifically, the CAR was nonsignificant when ELS was lower (β = 0.027, SE = 0.075, t(118.2) = 0.354, p = 0.724), but was significantly positive when ELS was higher (β = 0.204, SE = 0.063, t(141.7) = 3.24, p = 0.001).

3.4. Age and ELS severity

In order to clarify the unique influence of pubertal development on the relation between ELS severity and diurnal cortisol, a final level 2 model tested whether age interacted with ELS to predict diurnal cortisol when controlling for wake time. There were no significant interactive effects of age and ELS on cortisol levels at waking (β = -0.004, SE = 0.003, t(142.4) = -1.30, p = 0.195), on the CAR (β = 0.002, SE = 0.008, t(147.5) = 0.261, p = 0.795), or on the daytime slope (β = 0.0002, SE = 0.0003, t(155.5) = 0.583, p = 0.561).
4. Discussion

Previous research has documented that compared to their lesser- or non-exposed peers, children exposed to higher levels or extreme forms of ELS demonstrate aberrant patterns of diurnal cortisol regulation, as evidenced by differences in cortisol levels at particular times of day (e.g., morning or bedtime) and/or in change in cortisol across the day (e.g., the CAR); (Gunnar and Quevedo, 2007). The literature has been equivocal, however, in identifying the nature of diurnal cortisol regulation following ELS, with researchers reporting both blunted and heightened levels and slopes of cortisol (Hunter et al., 2011). Furthermore, there is limited research examining factors that underlie these divergent profiles of diurnal cortisol, especially in samples of children recruited from the community who have been exposed to ELS of varying severity. To address this issue, the present study extended previous work by elucidating the unique role of puberty in understanding the association between the severity of ELS and diurnal cortisol regulation.

While we found no significant interactive effects of pubertal stage and ELS severity on cortisol levels at waking or the daytime cortisol slope, our findings indicate that the manifestation of the CAR following ELS depends on current pubertal stage. Studying a sample of community children ages 9–13 years who were exposed to a range of ELS experiences, we found that pubertal stage interacted with the severity of ELS to predict the CAR. Specifically, in earlier puberty, higher ELS severity was associated with a blunted CAR compared to lower levels of ELS severity; in contrast, in later puberty, higher ELS severity was associated with a heightened CAR compared to lower levels of ELS severity. Importantly, differences in the manifestation of the CAR in the context of higher severity of ELS were uniquely determined by puberty; age had no influence on the relation between ELS severity and any of the indices of diurnal cortisol. While we should be cautious in making comparisons given considerable differences between samples, these results reflect findings of prior research in institutionalized children exposed to caregiving deprivation (Quevedo et al., 2012) in which institutionalization was associated with a blunted CAR only in early puberty.

Although we do not yet fully understand the mechanisms by which puberty influences the HPA axis, the biological and social changes associated with puberty may underlie a pubertal shift in the effects of ELS on the HPA axis. Indeed, research indicates that
the pubertal androgen, dehydroepiandrosterone (DHEA), modulates the effects of cortisol (Pinto et al., 2015), that higher ratios of cortisol to DHEA in adults are associated with exposure to ELS (Van Voorhees et al., 2014), and that the coupling of DHEA and cortisol becomes stronger from ages 11–15 years (Ruttle et al., 2013). Thus, exposure to ELS may have a pervasive impact on endocrinology, including changes in pubertal hormones that influence the production of cortisol. Furthermore, puberty is associated with significant changes in social dynamics that may affect stress response systems (Nelson et al., 2005). In particular, animal and human studies have documented changes in social buffering during adolescence, such that caregiver support ceases to serve a supplementary role in child regulation (Hostinar et al., 2014). For example, Doom et al. (2015) found that when caregiver support was provided during a psychosocial stressor, compared with when support was absent, children in pre/early puberty showed significantly reduced cortisol reactivity; for children in mid/later puberty, however, caregiver support did not have a significant effect on cortisol reactivity. Thus, changes in the influence of caregiver support on the HPA axis may also explain the different patterns of diurnal cortisol regulation associated with ELS severity in earlier and later puberty.

It is noteworthy that we found no significant effects of pubertal development or ELS severity on the cortisol level at waking or the daytime slope. The CAR is a particularly relevant index in the context of ELS research because it “combines features of a reactivity index (response to awakening) with aspects tied to circadian regulation” (Stalder et al., 2016). Previous findings indicate that although the CAR has a trait-like component, it also represents a response to the anticipated challenges of the day (Powell and Schlott, 2012) and, in addition, is relatively distinct from cortisol levels across the rest of the day (Stalder et al., 2016). Children exposed to ELS may show an aberrant response to awakening because they anticipate engaging in an atypical environment defined by threat. The HPA axis is responsible for helping to maintain allostatics (McEwen and Wingfield, 2003); therefore, differential cortisol responses to awakening at different stages of puberty may be related to other important changes. In terms of mental health, it is well documented that specific disorders are likely to emerge and intensify during adolescence (CDC, 2016). Although hyporesponsivity of the HPA axis prior to puberty may be temporarily protective (Gunnar and Quevedo, 2007), Colich et al. (2015) found that both blunted cortisol responses to stress in early puberty and heightened cortisol responses to stress in later puberty foreshadow the development of depression. Adam et al. (2014) found that an elevated CAR in late adolescence prospectively predicted first onset of anxiety disorders. Thus, a shift toward a heightened CAR over the course of pubertal development may be implicated in the increasing rates of disorder during adolescence.

4.1. Limitations

There are limitations of this study that highlight opportunities for future research. For example, this study was cross-sectional, which precluded examining the role of intra-individual changes in puberty on changes in the relation between ELS and diurnal cortisol. In addition, we used self-report Tanner staging to assess pubertal development to reduce participant burden. Although prior work indicates this method is reliable with the “gold standard” of physician assessment (Brooks-Gunn et al., 1987; Chan et al., 2008; Desmangles et al., 2006) and that self-report measures of puberty reflect levels of pubertal hormones (Shirtcliff et al., 2009), future research might track changes in hormones from earlier to later puberty in order to assess their influence on diurnal cortisol. We should also note that the range of puberty was limited in this sample to Tanner stages 1–4. Thus, we were unable to examine potential further differences in the relation between the severity of ELS and diurnal cortisol at full pubertal maturation (Tanner stage 5).

Income and parental education levels in the current study sample were representative of the relatively low-risk communities from which we recruited children, and thus higher than national averages. ELS experiences were also heterogeneous in nature, with children exposed to various types and levels of severity. Consequently, these findings may not generalize to children who develop in higher-risk environments and/or who are more homogeneously exposed to severe stressors (e.g., children in the child welfare system). Indeed, the non-significant effects of puberty and ELS severity on cortisol levels at waking and the daytime slope might be attributed to the fact that this was a lower-risk community sample of children. Finally, exposure to ELS was assessed in this study through retrospective self-report. Although we overcame many of the limitations of self-report by objectively coding the severity of ELS, some children may have under-reported their experiences due to discomfort in discussing distressing events or amnesia for events occurring during young childhood. Although there are numerous challenges to the assessment of ELS, future research should continue to improve methods of measuring ELS.

4.2. Conclusions

This is the first study to examine the role of pubertal stage in affecting the relation between the severity of ELS and diurnal cortisol in a community sample of children. By examining the role of puberty, the current study provides a developmental explanation for previous divergent findings of both blunted and heightened patterns of diurnal cortisol following ELS. In particular, our findings suggest that researchers should consider the pubertal status of children in drawing conclusions about the nature of deviations in the CAR. Adding to a growing body of research indicating that the HPA axis is highly plastic during the pubertal period, the results of this study have important implications for the timing of interventions to improve cortisol regulation. Specifically, interventions occurring prior to a pubertal shift in HPA-axis regulation may mitigate the long-term negative health outcomes associated with ELS.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.11.024.

References


