



# HPA-axis reactivity interacts with stage of pubertal development to predict the onset of depression

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**Summary** Both elevated and blunted levels of cortisol secretion during childhood and adolescence have been linked to the subsequent onset of major depressive disorder (MDD). These mixed findings may be due to developmental changes in HPA-axis functioning, which have not been previously assessed in the context of risk. In the present study, therefore, we examined whether pubertal development moderated the influence of cortisol secretion on the subsequent development of MDD. Eighty-nine never-disordered girls ages 9–15 years, many of whom were at high risk for depression by virtue of having a maternal history of the disorder, completed a laboratory stress task. To index cortisol reactivity, salivary cortisol samples were collected at baseline and 15 min following the onset of the stressor. Girls' levels of pubertal development were measured using Tanner staging. All participants were followed through age 18 in order to assess the subsequent development of MDD. Pubertal stage moderated the effects of cortisol stress reactivity on the development of MDD. Specifically, the onset of MDD was predicted by cortisol *hyporeactivity* in girls who were earlier in pubertal development (Tanner stage  $\leq 2$ ), but by cortisol *hyperreactivity* in girls who were later in pubertal development (Tanner stage  $\geq 3.5$ ). **Conclusions:** These findings demonstrate that girls' cortisol stress reactivity predicts the subsequent onset of MDD, and further, that the nature of this effect depends on the girls' level of pubertal development. Results are discussed in the context of clarifying previous findings, and directions for future research are offered.

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## 1. Introduction

Major depressive disorder (MDD) affects nearly 20% of all Americans and is the most common of all psychiatric disorders (Kessler et al., 2014). One of the most striking features

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of MDD is the gender difference in incidence that emerges in early adolescence, when females begin to be twice as likely as males to develop the disorder (Stroud et al., 2004; Hilt and Nolen-Hoeksema, 2014). Importantly, the age at which this gender divergence arises corresponds to the complex transition through puberty. Pubertal development involves a host of biological, psychological, and social changes that researchers posit contribute to the increase in rates of MDD in adolescent girls; in fact, investigators have found pubertal stage to be a stronger predictor of the onset of depression than is chronological age (Angold et al., 1998). Thus, puberty is a critical period during which to examine factors that increase the risk of young adolescents, particularly females, for developing MDD.

In this context, investigators have implicated stress and stress responsivity in females' pubertal development as a potential mechanism that underlies the gender difference in rates of MDD. For example, starting in early adolescence, girls report experiencing higher overall levels of stress than do boys (Brooks-Gunn, 1991; Ge et al., 2001). Moreover, sex-specific changes in the responsivity of the hypothalamic–pituitary–adrenal (HPA) axis, as assessed by levels of the stress hormone cortisol, have also been noted during puberty (Young and Altemus, 2004; Romeo, 2010; Young and Korszun, 2010). For example, in a cross-sectional study of stress reactivity across pubertal development, Gunnar et al. (2009) found not only that baseline cortisol levels and cortisol response to a laboratory stress-induction task (Trier Social Stress Task) increased as a function of level of pubertal development, but that around age 13, this increase in response to a stressor was more pronounced in girls than boys. Similarly, Stroud et al. (2009) found that with greater pubertal maturation, girls, but not boys, exhibited an increase in cortisol secretion following a corticotropin releasing hormone challenge. More recently, Blumenthal et al. (2014) found a positive association between cortisol response to a novel social setting and pubertal stage in adolescent girls, controlling for chronological age. Taken together, therefore, these findings document increases in cortisol responsivity in girls through puberty, which may underlie the elevated risk for depression in females that begins at this developmental period.

Consistent with this formulation, higher levels of cortisol over the transition through puberty have been found to be related to a greater vulnerability to depression in adolescence (Dahl and Gunnar, 2009; Stroud et al., 2009). For example, several investigators have found that higher levels of morning cortisol predict the subsequent onset of depression in adolescence (Adam et al., 2010; Vrshek-Schallhorn et al., 2013; Owens et al., 2014). Importantly, however, findings regarding cortisol stress responsivity as a predictor of subsequent changes in depressive symptoms are less consistent. For example, Susman et al. (1997) found that 9- to 15-year-old adolescents who had a greater cortisol response to a novel and challenging situation reported higher levels of depressive symptoms one year later. In contrast, however, Keenan et al. (2013) found that younger, 10- to 12-year-old, girls who exhibited a *blunted* cortisol response to a laboratory stressor and who had low absolute levels of cortisol secretion at age 12 experienced a subsequent increase in depressive symptoms. Given the changes in cortisol functioning that accompany pubertal development, it is possible

that inconsistencies in previous findings are due, in part, to the different developmental stages at which participants were assessed across studies; that is, it appears that increases in depressive symptoms are predicted by blunted cortisol reactivity in younger girls, but by elevated cortisol reactivity in older girls.

The present study was designed to examine this formulation by assessing whether cortisol stress reactivity measured across puberty predicts the subsequent onset of MDD. We recruited 9- to 15-year-old never-disordered girls who spanned the full range of pubertal development, examined their patterns of cortisol stress reactivity, and followed them regularly through age 18 to assess the subsequent onset of depression. Specifically, we tested whether pubertal status at the time of cortisol assessment moderated the relation between cortisol reactivity and the subsequent development of MDD. To maximize the likelihood that a significant proportion of the girls would develop an episode of depression, we included in our sample girls at familial risk for the disorder by virtue of having a mother with a history of depressive episodes. Given the documented increase in cortisol secretion in girls across the transition through puberty (Gunnar et al., 2009; Blumenthal et al., 2014), combined with the increase in females' rates of depression during and after this period, we hypothesized that girls at later stages of pubertal development who exhibit greater cortisol reactivity to a laboratory stressor would be more likely to experience a subsequent depressive episode than would comparable girls at earlier stages of pubertal development. Thus, we tested the prediction that cortisol reactivity would be a more sensitive marker of risk for the onset of MDD at later than at earlier stages of puberty.

## 2. Method

### 2.1. Participants

Participants were 89 girls who, at entry into the study at Time 1 (T1), were between 9 and 15 years of age and had no past or current Axis I disorder. Forty-seven girls had mothers who also had no past or current Axis I disorder (low risk for depression; CTL), and 42 girls were at high risk for developing depression (RSK) by virtue of having mothers who had recurrent episodes of MDD during their daughters' lifetime. As we noted above, given that maternal history of depression is a strong predictor of depression in adolescence (Gotlib and Colich, 2014), we included daughters of depressed mothers in our sample to ensure that a meaningful proportion of our study participants would experience a depressive episode at follow-up. As part of a larger study examining the intergenerational transmission of depression, participants were recruited through local community outreach. A telephone screening interview established that both the participants and their mothers were fluent in English. Girls were excluded from participating in the study if they had experienced severe head trauma or learning disabilities. Neither the participants nor their mothers had current or past substance abuse and, consistent with the absence of diagnosed depression in the daughters, no girls in the study were taking

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