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Cortisol in the morning and dimensions of anxiety, depression, and aggression in children from a general population and clinic-referred cohort: An integrated analysis. The TRAILS study

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Summary Anxiety and depressive problems have often been related to higher hypothalamic–pituitary–adrenal (HPA)-axis activity (basal morning cortisol levels and cortisol awakening response [CAR]) and externalizing problems to lower HPA-axis activity. However, associations appear weaker and more inconsistent than initially assumed. Previous studies from the Tracking Adolescents Individual Lives Study (TRAILS) suggested sex-differences in these relationships and differential associations with specific dimensions of depressive problems in a general population sample of children (10–12 years). Using the TRAILS population sample ($n = 1604$), we tested hypotheses on the association between single day cortisol (basal morning levels and CAR) and specifically constructed dimensions of anxiety (cognitive versus somatic), depressive (cognitive-affective versus somatic), and externalizing problems (reactive versus proactive aggression), and explored the modifying role of sex. Moreover, we repeated analyses in an independent same-aged clinic-referred sample ($n = 357$). Structural Equation Modeling was used to investigate the association between cortisol and higher- and lower-order (thus, broad and specific) problem dimensions based on self-reports in an integrated model. Overall, findings were consistent across the population and clinic-referred samples, as well as with the existing literature. Most support

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was found for higher cortisol (mainly CAR) in relation to depressive problems. However, in general, associations were weak in both samples. Therefore, the present results shed doubt on the relevance of single day cortisol measurements for problem behaviors in the milder range. Associations may be stronger in more severe or persistent psychopathology.

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1. Introduction

Psychosocial stress is an important factor in the development and course of mental disorders. However, there is substantial intra-individual variability with regard to the impact of psychosocial stress on mental health. This may be related to differences in hypothalamic–pituitary–adrenal (HPA)-axis activity, being one of the major physiological stress-related bodily systems. The overall goal of the present study was to shed more light on the relationship between cortisol (the major stress-related hormone) and different dimensions of psychopathology in children. We studied the role of both basal morning cortisol levels and the cortisol awakening response (CAR). The CAR plays an important role in preparing the body for action and in dealing with the challenges of the upcoming day (see e.g., Klimes-Dougan et al., 2001; Fries et al., 2009). Theoretical assumptions point to the upregulation of the HPA-axis due to the experience of stress and the notion of hypersensitivity to stress in relation to internalizing problems on the one hand (Klimes-Dougan et al., 2001; Fries et al., 2009; Lopez-Duran et al., 2009a; Slavich et al., 2010) and to the notion of hyposensitivity to stress, hypoarousal, or fearlessness in relation to externalizing problems on the other hand (Van Goozen et al., 2007; Alink et al., 2008; Shirtcliff et al., 2009). Indeed, higher activity of the HPA-axis, as reflected in higher basal morning cortisol levels or a higher CAR, has been related to anxiety and depressive (internalizing) symptoms not only in adults (Vreeburg et al., 2009, 2010; Knorr et al., 2010; Stetler and Miller, 2011) but also in children and adolescents (Lopez-Duran et al., 2009a; Ruttle et al., 2011; Stetler and Miller, 2011; Garcia de Miguel et al., 2012), albeit relationships in children are less well-established and investigated than in adults. In contrast, lower HPA-axis activity has been found to be associated with externalizing problems in youth (for reviews see Van Goozen et al., 2007; Alink et al., 2008; Shirtcliff et al., 2009).

In the past years, however, it has been increasingly recognized that associations between cortisol and internalizing and externalizing problems are weaker and more inconsistent than previously assumed (Birmaher and Heydl, 2001; Klimes-Dougan et al., 2001; Feder et al., 2004; Hawes et al., 2009; Garcia de Miguel et al., 2012). Two interesting suggestions to better understand inconsistent findings have been offered in recent studies from a population sample of 10-to-12-year-old children, as part of our cohort study Tracking Adolescents' Individual Lives Survey (TRAILS; Huisman et al., 2008). First, sex differences have been suggested to modify the relation between HPA-axis activity and internalizing and externalizing problems (Sondejker et al., 2007; Marsman et al., 2008; Bosch et al., 2009) and second, a differential relationship has been proposed between HPA-axis activity and specific depressive subdimensions (such as a distinction between cognitive-affective and somatic depressive symptoms; Bosch

et al., 2009). Thus, associations in mixed-sex samples or with respect to overall depression problems might go undetected.

We aimed to investigate these aspects further in an independent cohort as part of TRAILS. Replication of findings could substantiate the possible importance of sex differences and of differential associations between cortisol and specific subdimensions of externalizing and internalizing problems. So far, each of the published TRAILS papers in the baseline population cohort had focused on specific domains of psychopathology in their relation with cortisol assessed in the morning (Greaves-Lord et al., 2007; Sondejker et al., 2007; Marsman et al., 2008; Bosch et al., 2009), using various analytical approaches and cortisol indices. Therefore, we believed it would be timely to provide an integrated analysis of the TRAILS behavioral data (including all three problem dimensions of anxiety, depression, and aggression) in one overarching analytical model investigating all available cortisol indices assessed in the morning (basal morning cortisol levels and CAR), and to try to replicate findings in an independent sample. We used Structural Equation Modeling (SEM) to distinguish between higher-order (broad) versus lower-order (specific) problem dimensions of anxiety (cognitive versus somatic anxiety), depression (cognitive-affective versus somatic depression), and aggression (reactive versus proactive aggression) and focused on the sex-specificity of relationships by investigating boys and girls separately. Our independent sample, the TRAILS clinic-referred cohort consisted of children of the same age who had at least once been referred to our mental health outpatient clinic. A priori we assumed a higher level of psychopathology in the clinic-referred cohort and therefore expected to find stronger associations in the clinic-referred than in the population cohort.

We formulated the following hypotheses regarding the relationships between cortisol (basal morning cortisol levels and CAR) and the different specific problem dimensions. First, we hypothesized a differential association of cortisol with the cognitive (reflecting worry, rumination, or anticipatory anxiety) versus the somatic (reflecting bodily, panic-related symptoms) anxiety dimension. This might explain the lack of a relationship between morning cortisol and current-only anxiety problems in the previous TRAILS study of Greaves-Lord et al. (2007). Specifically, we expected higher cortisol to be associated most strongly with somatic anxiety, based on the notion that stress-related physiological activation would be intimately connected with bodily arousal symptoms of anxiety (e.g., Craske et al., 2009). Second, we expected that somatic depressive problems would be related to higher cortisol (higher CAR), and cognitive-affective depressive problems to lower cortisol (lower CAR), as suggested by Kuehner et al. (2007), and, particularly in boys, by Bosch et al. (2009). The former study found a lower CAR to be associated with self-focused rumination, a cognitive vulnerability marker of depression. Authors suggested possible

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