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Longitudinal Associations Between Infections and Atopic Disorders Across Childhood and Dysregulated Adrenocortical Functioning in Early Adolescence

ABSTRACT: The present study sought to determine if exposure to common childhood medical problems (i.e., infections and atopic disorders [e.g., allergies, asthma]) may dysregulate the hypothalamic-pituitary-adrenal (HPA) axis. Longitudinal data from 96 youth were used to examine this possibility. Medical records were drawn from government databases indicating the frequency of visits to healthcare facilities for infections and atopic disorders from infancy to early adolescence. During early adolescence, participants provided salivary cortisol samples from awakening until bedtime over 2 consecutive days. Individuals with a history of increased number visits for infections across childhood displayed elevated levels of cortisol at awakening whereas individuals with childhood histories of visits for atopic disorders displayed blunted diurnal cortisol slopes. These findings build on previous research documenting associations between infections and atopic disorders and cortisol by identifying longitudinal linkages from early health problems to later HPA axis functioning. © 2013 Wiley Periodicals, Inc. *Dev Psychobiol* 9999: 1–11, 2013.

Keywords: cortisol; infections; atopic disorders; longitudinal; hypothalamic-pituitary-adrenal (HPA) axis; childhood; adolescence

LONGITUDINAL ASSOCIATIONS BETWEEN INFECTIONS AND ATOPIC DISORDERS ACROSS CHILDHOOD AND DYSREGULATED ADRENOCORTICAL FUNCTIONING IN EARLY ADOLESCENCE

Research largely focuses on the immunosuppressive or immunostimulatory effects of the hypothalamic-pituitary-adrenal (HPA) axis and its primary adrenal steroid, cortisol, and neglects to consider the inverse: that immune system activation can influence HPA activity.

While basic research and a limited number of preclinical and clinical studies support this association (for reviews see Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Irwin & Cole, 2011; McCusker & Kelley, 2013; for empirical work see Capuron et al., 2003; Pyter, Pineros, Galang, McClintock, & Prendergast, 2009), it has yet to be empirically explored within a community sample. Although common medical problems, such as infections and atopic diseases, have been concurrently linked to dysregulated HPA axis activity in community samples (e.g., Heubeck, Schonberger, & Hornstein, 1988; Lonne-Rahm et al., 2008; Tuner-Cobb, Rixon, & Jessop, 2011; Wilson, Megel, Fredrichs, & McLaughlin, 2003), previous studies lack the long-term, prospective design necessary to examine the effect of common medical problems on HPA axis functioning.

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Two of the most common immune-related health problems in children and adolescents are infections and atopic disorders (e.g., allergies and asthma) (e.g., Braun-Fahrlander et al., 2002; Monto & Ullman, 1974; Ponsonby, Couper, Dwyer, Carmichael, & Kemp, 1999; Ring, Kramer, Schafer, & Behrendt, 2001). Infections are generally more transient, lasting a few days before being remediated by the immune system or via medical intervention (e.g., antibiotics), while atopic disorders are conceptualized as chronic health problems because, even in the absence of an inflammatory attack, immune system activity is persistently elevated due to increased sensitivity to non-harmful environmental antigens, acting as a chronic stressor on the body (e.g., Daruna, 2004; Tsigos, Kyrou, & Chrousos, 2005). Given that an individual's susceptibility to infections and atopic disorders is governed by their immune system, which is highly interconnected with a variety of other physiological systems, repeated or persistent immune system activation may impact other systems, including the HPA axis.

The HPA axis is a primary stress system activated during the stress response. When a situation is perceived to be stressful, a cascade of hormones are released, which ultimately reach the adrenal gland and stimulate the production of the glucocorticoid hormone, cortisol (Sapolsky, 1992). The HPA axis operates via a negative feedback loop, such that elevated levels of stress hormones feedback to the brain in an attempt to return cortisol to basal levels. Basal levels of cortisol are consistently present within the body and follow a diurnal pattern which rise in the morning, peak approximately 20–40 min post-awakening (more commonly known as the cortisol awakening response, CAR), and then proceed to decline over the course of the day, steeper at first and then more gradual until bedtime (Kirschbaum & Hellhammer, 1994; Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001). Persistent, extreme, or repeated stressors, including those physical, social, or psychological in nature, and particularly those occurring early in life, may impair the integrity of the HPA axis resulting in atypically high or low levels of basal cortisol (reviewed in Gunnar & Vazquez, 2006; Trickett, Negri, Ji, & Peckins, 2011). Various mechanisms may be responsible for HPA axis up- and down-regulation including inadequate or excessive release of hormones at various levels of the HPA axis (e.g., CRF/AVP from the hypothalamus, ACTH from the pituitary, or cortisol from the adrenal glands) resulting in subsequent increased or decreased stimulation of the respective target receptors and altered negative feedback (Heim, Ehler, & Hellhammer, 2000; McEwen & Seeman, 1999; Raison & Miller, 2003; Sapolsky, 1999);

however, it is still unclear within the literature as to what level of stress is necessary to prompt up- or down-regulation of the HPA axis. Given that interactions between the immune system and the HPA axis occur at multiple levels, it is possible that the immune system may prompt such changes but research often infers that the association between HPA axis activity and physical health problems are driven by the immunosuppressive effects of HPA axis activity (Silverman, Pearce, Biron, & Miller, 2005), even though the majority is cross-sectional in nature.

Associations Between Infections, Atopic Disorders, and HPA Axis Activity

The association between HPA axis dysregulation and infections is understudied within the general population. The limited research examining this linkage has found increased reactive and recovery cortisol levels in infants with infections (Wilson et al., 2003) and lower evening levels and a steeper diurnal rhythm in young children with elevated rates of respiratory infections (Tuner-Cobb et al., 2011). While little empirical research exists on this topic, strong basic research supports the existence of this association. High levels of immune system activation generally stimulate increased HPA axis activity (Elenkov & Chrousos, 1999), although the interaction between the HPA axis and the immune system is very complex. Overall, theory and research suggests a positive association between children's infections and cortisol may be expected; however, long-term, prospective longitudinal studies that disentangle the directionality of this effect are lacking.

A much larger literature supports the association between HPA axis activity and atopic disorders. Interestingly, two different patterns of results emerge within the cortisol-atopic disease literature. While infants at risk of developing atopic diseases generally demonstrate *elevated* patterns of HPA axis activity (Ball, Anderson, Minto, & Halonen, 2006; Buske-Kirschbaum, Fischbach, Rauh, Hanker, & Hellhammer, 2004; Stenius et al., 2011), children and adolescents with chronic atopic disease often display *lower* levels of HPA axis activity (Bakkeheim, Mowinckel, Carlsen, Burney, & Lodrup Carlsen, 2010; Heubeck et al., 1988; Lonne-Rahm et al., 2008). While these findings are not unequivocal (Rupprecht et al., 1995; Wamboldt, Laudenslager, Wamboldt, Kelsay, & Hewitt, 2003) it appears that blunted or lower levels of cortisol are generally linked to atopic disorders. Moreover, research has also identified blunted patterns of cortisol in individuals with asthma, as demonstrated by lower basal levels (Bakkeheim et al., 2010; Kauffmann, Guiochon-Mantel, & Neukirch, 1999), lower CAR

(Buske-Kirschbaum et al., 2003), and blunted diurnal patterns (Landstra, Postma, Boezen, & van Aalderen, 2002; Tromp, 1968). At least one study has demonstrated higher afternoon, compared to morning levels of cortisol in individuals with severe asthma (Fujitaka et al., 2000); however, these findings may also suggest HPA axis down-regulation, as down-regulation may present as persistently low levels of cortisol across the day or impairment of the integrity of the HPA axis, resulting in lower morning levels (when levels should be higher) and higher afternoon and evening levels (when levels should be lower).

Several limitations exist when examining physical health problems in children and adolescents. Children and adolescents are often poor reporters of their own medical conditions, therefore researchers typically rely on parent-report measures which tend to be retrospective and are often subject to reporter bias and poor memory recall (e.g., Brett, Brief, Burke, George, & Webster, 1990; Edwards, 1953; Parkes, 1990; Weinhardt, Forsyth, Carey, Jaworski, & Durant, 1998). A diagnosis from a healthcare provider is less biased; however, diagnoses generally only provide a snapshot of an individual's health. Medical records of visits to health professionals eliminate the potential biases associated with self- and parent-reports and, when amalgamated across time, may provide a more accurate picture of an individual's overall physical health.

Many factors have been implicated in the association between cortisol and physical health outcomes or independently linked to both variables; necessitating the establishment that associations between cortisol and infections and atopic disorders are not a function of an underlying third variable. Socioeconomic status (SES) has a profound impact on child and adolescent health (for reviews see Aber, Bennett, Conley, & Li, 1997; Jolly, Nolan, Moller, & Vimpani, 1991; Shah, Kahan, & Krauser, 1987), although findings are not nearly as robust compared to findings in adults (see Chen, Matthews, & Boyce, 2002 for a review). Furthermore, a mixed literature links SES to dysregulated levels of cortisol (for a review see Dowd, Simanek, & Aiello, 2009). Research suggests that sex and age may influence the prevalence of atopic disorders (Almqvist, Worm, Leynaert, & the working group of GA²LEN WP 2.5 'Gender', 2008; Kelly & Gangur, 2009) and some evidence suggests that sex and age may influence HPA functioning (Gunnar & Vazquez, 2006; Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Spinrad et al., 2009). Additionally, factors associated with a child's healthcare usage, such as mother's tendency to seek healthcare, must be accounted for as most children and adolescents receive healthcare services because services

are sought by their mother (Broadhurst, 2003; Logan & King, 2001).

The present study explores associations between the prevalence of healthcare visits for infections and atopic disorders across childhood and diurnal cortisol in early adolescence. Using a community sample to explore these associations advances the current literature as most often research examining atopic disorders and infections is conducted in clinical samples and may not be applicable to the general population who may have less severe forms of these problems. Furthermore, longitudinal designs, such as the one employed in the present study, provide temporal sequencing of events from which directionality may be inferred and contain detailed information on numerous control variables. Based on previous evidence, we hypothesize that participants with more visits for infections across childhood would have higher cortisol levels in early adolescence, whereas individuals with more visits for atopic diseases (i.e., asthma and allergies) would display a blunted diurnal cortisol pattern. Additionally, we aimed to explore the role of variables that may potentially mediate or moderate the associations between the aforementioned physical health outcomes and cortisol, including SES, age, sex and mother's healthcare seeking behaviors.

METHOD

Participants

Participants were part of the Concordia Longitudinal Risk Project, a longitudinal intergenerational study that began in 1976, involving a community-based sample of over 4000 French-speaking school children (and their families) in grade 1, 4, or 7. The children were recruited from schools serving economically disadvantaged neighborhoods in Montreal, Quebec, Canada. A subset of these individuals were selected for a more in depth follow-up, including some individuals who displayed high levels of behavioral problems and a control group of typically developing individuals. For a complete description of the original sample population and procedures, see Ledingham (1981) and Schwartzman, Ledingham, and Serbin (1985).

Current Sample. Participants examined in subsequent analyses were the offspring of original participants, primarily Caucasian, and spoke French as their first language. One hundred twenty children were eligible for participation based on the appropriate age range (9–13 years of age) and 109 adolescents agreed to participate in the saliva sampling procedure, of which 96 (56 females; 40 males) participants were able to successfully meet sampling requirements (e.g., sufficient saliva, daily diary, etc.) and were included in the present analyses. Based on original selection criteria (i.e., low

SES neighborhoods and increased sampling for behavior problems), the current sample can be considered an at-risk, community sample.

Health variables were derived from provincial health care records (see below for more information) from infancy until December 31, 2003. Demographic data were collected during prior assessments (maternal education and family income was assessed in 2000) and from the Canadian Census (neighborhood SES was assessed in 2001 based on the first three digits of the participant's home or school postal code). Cortisol was collected between 2003 and 2007, when children ranged in age from 9.3 to 13.5 years ($M = 10.87$; $SD = .90$). Testing sessions were arranged according to age, such that older children were tested first. The majority of participants were able to provide samples over 2 days ($n = 91$) with an average of 8.43 samples/day. Youth and their legal guardians gave informed, written consent before participation and were reimbursed for their time and involvement in the study. The data used in these analyses was collected as part of a larger study that was approved by the Institutional Review Board of Concordia University.

Measures

Cortisol. During early adolescence, participants were instructed to provide saliva samples over 2 consecutive days upon awakening, 20 min post-awakening and then every 2 hr until bedtime. Salivettes were used to collect saliva samples. Participants were instructed to chew on a cotton swab for 30–45 s and then place the swab in a plastic container, trying to refrain from touching it. Participants were also asked to refrain from eating for 30 min before sampling as well as to keep a record of the time of saliva sampling, mood, stress, health, food and medication intake, any exercise performed, as well as time of eating, time of awakening, and bedtime for both days. After collecting the sample, participants were instructed to freeze saliva samples until they were picked up by researchers and samples were kept frozen until brought for assay at the Douglas Hospital Research Laboratories (DHRL). The detection limit of the assay was $.01 \mu\text{g/dl}$ and the mean intra- and inter-assay variability coefficients were 4.0% and 4.6% respectively. Log transformations were performed to normalize the distribution of skewed cortisol data. Nine scores remained as outliers after this process and were Winsorized to within three standard deviations of the mean. Given that various medications may significantly alter HPA axis functioning, medications relevant to the current questions of interest were examined as possible predictors of diurnal cortisol. More specifically, oral and non-oral steroids were coded as “0” or “1” to identify absence or presence of consumption on each day of cortisol collection and a parallel coding scheme was used to examine the effect of medications to treat asthma, allergies, and colds.

Physical Health Measures. Medical records of visits to health professionals were utilized as individuals' histories of physical health problems. Due to the sensitive nature of health-care data, permission was required from the “Commission

d'accès à l'information du Québec” in order to obtain access to participants' healthcare service usage records. Following a careful review of identity and privacy protecting procedures to ensure confidentiality, permission was granted to retrieve service usage information. Provincial medical records regarding service usage from infancy until 2003 were obtained from the Régie de l'Assurance-Maladie du Québec (RAMQ) and the “Ministère de la Santé et des Services Sociaux” (MSSS), which act as a “single-payer” system and cover the costs incurred by medical services for all permanent residents of the province of Québec. These records contained numeric codes pertaining to various medical acts, assessments and diagnostic information. Although a wealth of information was available, three predictor variables were chosen due to increased prevalence rates in childhood: (1) Total number of medical acts performed due to infections, (2) Total number of medical acts due to asthma and (3) Total number of medical acts performed due to allergies. “Total number of medical acts due to asthma” and “Total number of medical acts due to allergies” were averaged together to provide a measure of “Total number of medical acts due to atopic disorders.” The resulting variable was skewed (i.e., a skewness coefficient more than 10 times the standard error of skewness) and required a log transformation to normalize the distribution.

Socioeconomic Status (SES). Various measures of SES have been used when examining the association between SES and health including individual or family income (McDonough, Duncan, William, & Hauser, 1997), education (Ross & Wu, 1995), average income level of the neighborhood (Hou & Myles, 2005), and occupation or ratings of occupational prestige (Marmot, Shipley, & Rose, 1984). Mother's years of education, family income, and level of neighborhood SES have all been shown to predict youth's health outcomes (for a review see Chen et al., 2002), therefore a factor was created with these variables via principal components analysis to provide a more comprehensive measure of the phenomenon. Factor loadings for these variables were in the moderate to high range (.60–.70) and had 44% shared variability.

Mothers Health and Healthcare Seeking Behavior. Healthcare usage reflects both actual health needs (e.g., frequency and severity of illnesses) and patterns of care usage (i.e., likelihood of consulting a physician when ill or for preventive care). Parents' and their children's health are likely to be related, in the sense that aspects of health are inherited genetically and also because parents can impact children's health via shared environment, nutritional patterns, health-related behaviors (such as patterns of hand washing), convenience and availability of care, and many other factors. In addition, parent's patterns of seeking healthcare are likely to carry over to their children, given that youth generally receive medical attention because their primary caregiver brings them (Broadhurst, 2003; Logan & King, 2001). For these reasons we felt it was important to control for mothers' pattern of healthcare usage over time. This was done by averaging the number of times that the mother had seen the doctor in the 3 years before her child was conceived, minus all obstetric

and gynecological visits, and was included as a control in all analyses examining the relation between children's health variables and cortisol patterns. This variable was also skewed therefore a square root transformation was performed to normalize the distribution.

Procedure

Participants were contacted by telephone between 2003 and 2007 to request their participation in the current wave of the study. Those interested in participating affirmed consent at this time and a home visit was scheduled. As part of a larger study, research assistants visited homes during which time participants were given instructions on the saliva collection procedure. Both mother and child were financially compensated with a small honorarium once the questionnaires and vials were returned. Finally, medical information from infancy to early adolescence was collected from the RAMQ database.

Design and Analysis: Hierarchical Linear Modeling.

A three-level hierarchical linear model was created using HLM 6.0 (Bryk & Raudenbush, 1992) to examine sources of variability within diurnal cortisol: within-the-day ($n = 1,578$ samples), day-to-day ($n = 187$ days), and between individual ($N = 96$ participants). The default of HLM provides users with an intercept coefficient which, in the current study, represented the level of cortisol at awakening. In order to model the diurnal decline and associated diurnal curve of cortisol, time since waking (i.e., time of sample controlling for time of awakening; TSW) was entered into the model, along with quadratic (TSW^2) and cubic (TSW^3) functions. Additionally, in order to model the CAR, samples provided approximately 20 min post-awakening were identified as the CAR using a dummy variable (coded 0 = not CAR and 1 = CAR). All time-related variables (i.e., TSW, TSW^2 , TSW^3 , and CAR) were found to be predictors of variability in cortisol ($ps < .10$). Variables measuring mood, stress, health, food intake and exercise were also examined as Level 1 predictors; however, none of these variables had a significant effect on any level of diurnal cortisol ($ps > .10$).

Changes in day-to-day cortisol were captured by Level 2. The model showed substantial variability in cortisol intercept levels, $\chi^2(90) = 302.24$, $p < .001$ and slope, $\chi^2(90) = 235.09$, $p < .001$ between these 2 days. The effect of glucocorticoid-related medication and medication used to treat asthma, allergies, and colds were examined as a Level 2 predictor of cortisol variability. Glucocorticoid-related medication intake, but not medication intake for allergies, asthma, and colds, was significantly related to cortisol slope such that participants who were on medications had a steeper slope and an atypical curve to their diurnal cortisol pattern on the day they took medications (linear slope $B = -.235$, $t = -6.78$, $p < .001$; quadratic slope $B = .037$, $t = 6.58$, $p < .001$; cubic slope $B = -.001$, $t = -5.76$, $p < .001$). Although none of the associations between the between-individual predictors and cortisol changed based on inclusion of glucocorticoid medication, due to its significant effect on cortisol, it was retained in the model for subsequent analyses.

Level 3 captures between-individual changes in cortisol, and examination of this variability revealed that cortisol intercept ($\chi^2(95) = 219.99$, $p < .001$), linear slope ($\chi^2(95) = 149.15$, $p < .001$), and quadratic slope ($\chi^2(95) = 145.11$, $p = .001$) varied across individuals. This suggests that individual differences in morning level of cortisol, degree of decline across the day, and curvature of cortisol slope were able to be identified.

Next, predictors of between-individual cortisol variability were entered at Level 3. Physical health and control variables (i.e., sex, age, SES, and mother's visit to healthcare facilities) were entered into the model, followed by two-way interactions to examine possible moderating effects of the demographic variables on the effect of the physical health variables. Given the large number of predictors, non-significant interaction effects were removed to arrive at parsimonious models, a standard procedure when analyzing data with hierarchical linear modeling (Kreft & De Leeuw, 1998).

RESULTS

Association Between Demographic Variables and Physical Health Variables

Table 1 depicts associations between predictors and visits for infections and atopic diseases. Bivariate associations revealed that individuals who presented more frequently at health care facilities for infections were more likely to be from a high SES background, had a mother who frequented health care facilities often, and also presented more frequently for atopic diseases.

Association Between Infections and Atopic Disorders and Diurnal Cortisol

Infections. Participants who presented more frequently at healthcare facilities for infections had higher CAR samples in early adolescence than individuals who had fewer infections ($B = .0005$, $t = 2.03$, $p < .05$; see Fig. 1).

Atopic Disorders. Participants who presented more frequently at healthcare facilities for atopic disorders had blunted slopes and less curvature to their diurnal rhythms (linear slope $B = .012$, $t = 2.25$, $p < .05$; quadratic slope $B = -.002$, $t = -2.45$, $p < .05$; cubic slope $B = .0001$, $t = 2.28$, $p < .05$), suggesting that individuals with high levels of visits to healthcare facilities for atopic disorders displayed a less steep slope and less of a typical diurnal curve due to elevated afternoon and evening levels of cortisol (see Fig. 2).

CONCLUSION AND DISCUSSION

The present investigation revealed systematic associations between HPA axis activity and common health

Table 1. Correlations Among Predictor and Outcome Variables

Variable	1	2	3	4	5	6
1. Sex	—	-.09	.08	.04	-.28**	-.10
2. Age		—	.03	-.05	.03	-.06
3. Mother health care visits			—	-.06	.32**	.10
4. SES				—	.19	.11
5. Infection visits					—	.33**
6. Atopic disorders visits						—

** $p < .01$.

problems in youth. More specifically, individuals who had a higher number of doctor visits for infections displayed higher CARs in early adolescence whereas those who visited the doctor for allergies and/or asthma displayed blunted levels of cortisol characterized by a flattened diurnal rhythm. These findings were present even when controlling for variables such as mother's health seeking behaviors, SES, age, sex, and medication intake.

Bivariate associations revealed that mothers who sought out more health care for their own problems were more likely to bring their child to the doctor for infections. This supports research suggesting that parent and offspring health-seeking behaviors are related, via

genetic, behavioral, and environmental factors (Broadhurst, 2003; Logan & King, 2001). Children from high SES backgrounds were more likely to be brought to a healthcare facility for infections. While individuals from low SES backgrounds often demonstrate increased service usage for a variety of healthcare related problems (e.g., lifestyle illnesses, injuries, etc.), this association was not previously found for infections (Martin-Storey et al., 2012). Individuals from high SES backgrounds may have increased access to healthcare facilities for a variety of reasons, including more job flexibility and resources, which enable parents to bring their children to the doctor for more minor infections. Supporting some previous literature examining the

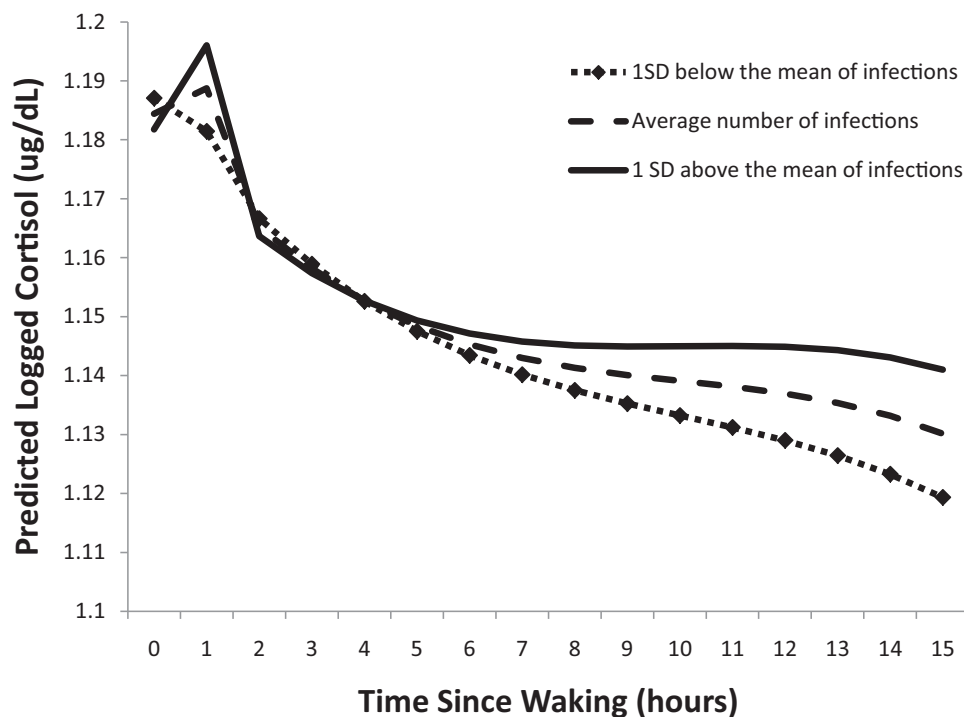


FIGURE 1 Association between number of healthcare visits from infancy to early adolescence for infections and diurnal cortisol in early adolescence.

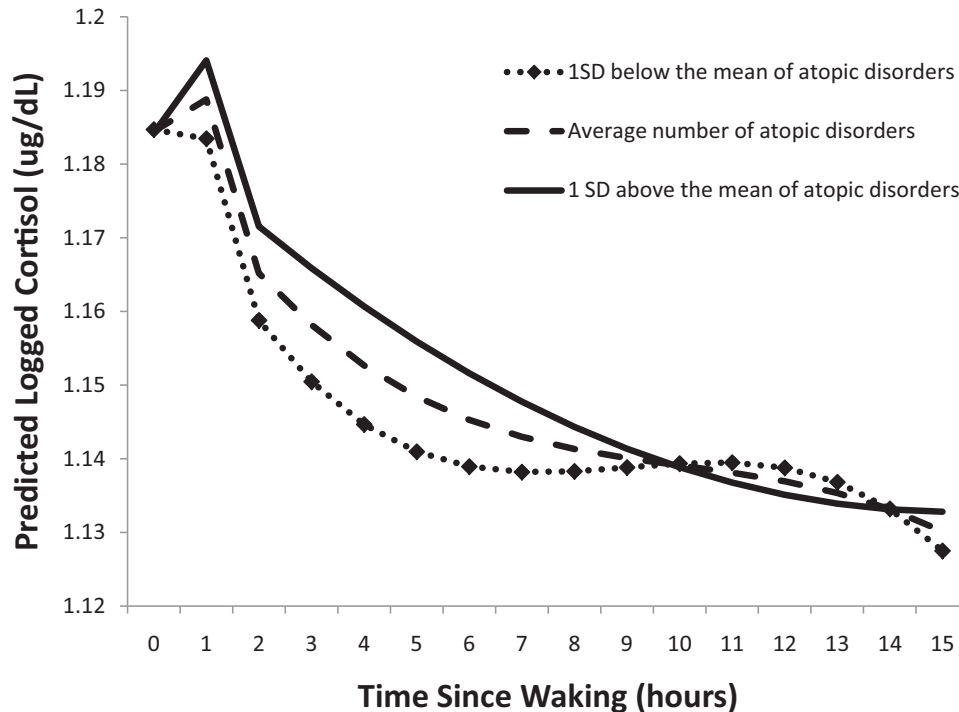


FIGURE 2 Association between the number of healthcare visits from infancy to early adolescence for atopic disorders and diurnal cortisol in early adolescence.

association between infections and atopic disorders, particularly asthma (Proud, 2011), a positive association was found between infections and atopic disorders. Increased number of respiratory infections may result in high levels of damage at the cellular level, resulting in increased susceptibility to asthma (Proud, 2011); however, mechanisms supporting the opposite association have been posited (see Lewis, 1998), suggesting the need for more research in this area.

Increased visits to healthcare facilities for infections were specifically associated with high CARs. The CAR is a peak in cortisol shortly after awakening and it seems to be particularly susceptible to certain outside influences, in particular, stress (Wright & Steptoe, 2005). Individuals reporting high levels of stress typically demonstrate increased CARs compared to individuals who are less stressed (Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Schulz, Kirschbaum, Pruessner, & Hellhammer, 1998; Wust et al., 2000). Therefore, elevated levels of cortisol at the CAR may be indicative of the up-regulation of the HPA axis following acute stressors such as increased rates of infections in childhood. Conversely, youth with increased visits for atopic health problems across childhood displayed compromised diurnal patterns of cortisol in early adolescence as evidenced by loss of the diurnal decline and rhythm. This is in line with

previous research that suggests individuals with atopic disorders display a blunting of HPA axis activity (Bakkeheim et al., 2010; Heubeck et al., 1988; Landstra et al., 2002; Lonne-Rahm et al., 2008; Tromp, 1968; Wilson et al., 2003). Loss of curvature to the diurnal rhythm may reflect compromised integrity of the HPA axis and may be indicative of HPA axis down-regulation.

Although the present study did not specifically test for such an effect, it is possible the present findings fit with the notion of HPA axis up- versus down-regulation (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Miller, Chen, & Zhou, 2007). These findings suggest that initial or intermittent exposure to a stressor may be associated with HPA axis up-regulation and elevated levels of cortisol, whereas prolonged exposure to a stressor may down-regulate the HPA axis, compromising the integrity of the HPA axis and its ability to follow a typical diurnal pattern. There are two mechanisms through which HPA axis up-/down-regulation may occur. First, the physical health problem may be perceived as stressful. Short-term exposure to intermittent problems (e.g., infections) may elicit increased HPA axis activity; however, if the problem is chronic (e.g., atopic disorders), persistent HPA axis activation may lead to down-regulation of the HPA axis. Previous studies have identified similar patterns of up- versus

down-regulation of the HPA axis when examining exposure to stress (Gustafsson, Anckarsater, Lichtenstein, Nelson, & Gustafsson, 2010) and mental health problems (Ruttle et al., 2011). An alternate, but not mutually exclusive, explanation is that the HPA axis may up-regulate as a function of intermittent immune activation, such as that often observed with infections, but down-regulate as a function of the chronic irritation and inflammation, such as that often associated with atopic disorders. Given that infants *at risk* of developing asthma display increased levels of cortisol (Ball et al., 2006; Buske-Kirschbaum et al., 2004; Stenius et al., 2011) and individuals with chronic infections, such as the human immunodeficiency virus (HIV), often display blunted levels of cortisol (Abbott, Khoo, Hammer, & Wilkins, 1995), regulation of the HPA axis as a function of chronicity of the health problem remains a definite possibility. Unfortunately, we are unable to definitively state that the present findings are indeed modeling HPA axis up- and down-regulation as a function of the chronicity of the health problem as it is unclear whether the children with atopic disorders initially had elevated levels of cortisol and whether the individuals with chronic infections eventually developed blunted levels of cortisol. Future research should consider examining both HPA axis functioning and physical health problems longitudinally, beginning in infancy, to determine if HPA activity is initially elevated but then becomes blunted as a function of persistent health problems.

This study provides an important starting point for future research examining the effect of physical health problems on HPA axis functioning in a community sample, but it is not without limitations. A major limitation is the non-specificity of the health variables used in the current study. Only the total number of visits for infections and the combined amount of visits for asthma and allergies was able to be explored, rather than more specific health information (e.g., diagnosis of asthma by a respirologist rather than visits for asthma-like problems). Furthermore, low prevalence rates necessitated amalgamating all atopic diseases and infections rather than examining associations with distinct subtypes of atopic diseases or infections, potentially reducing the ability to detect associations. Replication examining subtypes of atopic diseases and different types of infections as well as confirming the presence of atopic diseases via doctor diagnosis will add support to these findings. Moreover, the health variables retrieved from the RAMQ records did not provide information concerning severity of the disease and response to treatment. Given that these variables are likely to influence various aspects of physiological functioning, such variables should be examined in

future studies. Additionally, while we were able to examine the effect of medication intake on the days of cortisol collection, data on medication intake over the course of childhood was not assessed. Given that individuals with a history of atopic disorders may have received long-term treatments with glucocorticoid-related medications, which may impact HPA functioning, future studies should ensure the inclusion of such variables.

By focusing on both acute and chronic health problems, these findings make a compelling argument that the infections and atopic diseases may result in prolonged HPA axis dysregulation within a community sample. The complex intricacies of the links between the HPA axis and the immune system, however, should not be overlooked. These two systems are inextricably connected and, while a unidirectional association has been presented, this depiction is short-sighted. A bidirectional association exists between the HPA axis and the immune system (Elenkov & Chrousos, 1999) and many devastating disorders (e.g., autoimmune disorders) have been linked to chronic activation in one, or both, of these systems. As such, it is of the utmost importance to conduct prospective, longitudinal studies that are able to determine how these systems interact over time to precipitate dysfunction and negatively impact health, ultimately leading to a better understanding of the impact of chronic and acute of childhood illness on later health and functioning.

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