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## Early Adversity, Elevated Stress Physiology, Accelerated Sexual Maturation and Poor Health in Females

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### Abstract

Evolutionary-minded developmentalists studying predictive-adaptive-response processes linking childhood adversity with accelerated female reproductive development and health scientists investigating the developmental origins of health and disease (DOoHaD) may be tapping the same process, whereby *longer-term health costs are traded off for increased probability of reproducing before dying via a process of accelerated reproductive maturation*. Using data from 73 females, we test the following propositions using path analysis: (a) greater exposure to prenatal stress predicts greater maternal depression and negative parenting in infancy, (b) which predicts elevated basal cortisol at 4.5 years, (c) which predicts accelerated adrenarcheal development, (d) which predicts more physical and mental health problems at age 18. Results prove generally consistent with these propositions, including a direct link from cortisol to mental health problems. DOoHaD investigators should consider including early sexual maturation as a core component linking early adversity and stress physiology with poor health later in life in females.

### Keywords

predictive adaptive response; developmental origins of health and disease; adrenarche; prenatal stress; stress physiology; health

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Research on the developmental origins of health and disease indicates that adverse developmental experiences and environmental exposures early in life undermine later physical health and well-being (Evans, 2003; Hertzman & Power, 2004) and mental health (e.g., Anda et al., 2006; Poulton et al., 2002; Schilling, Aseltine, & Gore, 2007). Thus,

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investigators have chronicled links between low childhood socioeconomic status and increased morbidity in mid-life (Melchior, Moffitt, Milne, Poulton, & Caspi, 2007; Poulton et al., 2002), between childhood maltreatment and compromised adolescent health (Flaherty et al., 2013), and between cumulative contextual risk and allostatic load in adulthood (Brody et al., 2013). Health-minded scholars have even begun to illuminate plausible mediating biological mechanisms—or at least biomarkers of the presumed health-deterioration process (Carroll et al., 2013)—including inflammation (Chen, Miller, Kobor, & Cole, 2011; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Miller, Chen, & Parker, 2011), immune competence (e.g., O'Connor et al., 2013; Shirtcliff, Coe, & Pollak, 2009), metabolic functioning (Lehman, Taylor, Kiefe, & Seeman, 2005) and chromosomal integrity as indexed by telomere length (e.g., Entringer, Buss, & Wadhwa, 2012; Epel et al., 2004; Kiecolt-Glaser, Jaremka, Derry, & Glaser, 2013; Shalev, 2012). Here we seek to extend such work when linking prenatal stress with physical and mental health at age 18—by considering the role of stress physiology and sexual maturation.

Given our view that two different models of accelerated aging may reflect a single evolved process of accelerated development (Belsky & Shalev, in press)—the developmental-origins-of-health-and-disease framework linking early adversity with increased morbidity and early mortality later in life (Epel, Blackburn, Lin, Dhabhar, Adler, Morrow & Cawthon, 2004; Shalev, 2012; Shalev, Caspi, Ambler, D.Belsky, D. W., Chapple, S., Cohen et al., 2014) and a reproductive-strategy one linking similar early experiences with earlier sexual maturation in females (Belsky, 2012; Belsky, Steinberg & Draper, 1991)—we seek to test the following Propositions (a) that greater prenatal stress exposure will predict greater maternal depression and negative parenting in infancy—both known to forecast more problematic child functioning (NICHD Early Child Care Research Network, 1999) and to be interrelated (Lovejoy, Graczyk, O'Hare, & Neuman, 2000); and (b) that such early experiences will themselves predict elevated basal cortisol at age 4.5 years, (c) which itself will predict accelerated adrenarcheal development in first grade, (d) which itself will predict poorer physical and mental health at age 18. We also evaluate whether pubertal status at age 11 mediates the association between adrenarche and later health.

## The Role of Stress Physiology

Stress physiology is presumed to play an important role in the development process just outlined. Indeed, there is extensive evidence that early exposures to environmental stressors, both within the family and larger social and physical contexts, predict systematic differences in stress physiology later in childhood, most notably, the hypothalamic-pituitary-adrenal (HPA) axis (Ellis, Essex, & Boyce, 2005; Essex, Klein, Cho, & Kalin, 2002; Mackrell et al., 2014). Just as important is evidence showing that elevated levels of basal cortisol—the stress-physiology index used in this inquiry—are associated with increased risk for maladaptive development and perturbations of both mental and physical health (e.g., Doom & Gunnar, 2013; Essex, Klein, et al., 2002). And this is true even though some theory and empirical findings suggest that stress-physiology linkages may be non-linear and/or bidirectional in character (Boyce & Ellis, 2005; Ellis et al., 2005; Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006) research.

## The Role of Sexual Maturation

Where we break new ground in investigating the developmental origins of health and disease is by considering the role of sexual maturation, a process regulated in part by the HPA axis (Ellis, 2004) and thus linked to cortisol-related indices of stress physiology (Saxbe, Negriff, Susman, & Trickett, in press). In fact, we focus on adrenarche, considered the first stage of pubertal development occurring around 6-8 years of age (Campbell, 2006; McClintock & Herdt, 1996), for two reasons. The first is that cortisol and dehydroepiandrosterone (DHEA), a hormonal index of adrenarcheal development, share the same hormone that triggers their synthesis and release, ACTH. The second is that DHEA plays a role in the stress system (Saczawa, Graber, Brooks-Gunn & Warren, 2013).

To our knowledge, no prior work, including that of the larger project from which the data for this report derive, has sought to link, in a single inquiry, exposure to adversity, stress physiology, sexual maturation and physical and mental health. What has been examined in prior reports using the current sample are (a) links between early family stress exposure and later mental—but not physical—health problems, with childhood cortisol sometimes treated as a mediating mechanism (e.g., Essex et al, 2002), and, separately, (b) those between early adversity and sexual maturation, including adrenarche (Ellis et al., 2007, 2012). Thus, what we endeavor to do herein is novel: Evaluate, using data from an 18-year longitudinal study, whether there is a shared pathway whereby early family stress, measured for the first time during pregnancy, forecasts mental and physical health problems at age 18 via childhood cortisol and adrenarche.

It is noteworthy, given this developmental model, that higher levels of DHEA are positively related to mental health problems (Dmitrieva, Oades, Hauffa & Eggers, 2001; van Goozen et al., 2000), with Dorn and colleagues (1999, 2008) reporting that children with premature adrenarche manifest increased levels of depression, anxiety and behavioral problems relative to their normatively developing peers. And this may be because higher levels of DHEA are associated with neurological processes reflective of emotion dysregulation; in fact, fMRI measurements to this effect mediated the link between higher DHEA levels and externalizing problems in Whittle and associates (in press) work with nine-year olds, a result which remained even with Tanner Stage controlled. Seemingly in line with such results are Klauser and colleagues' (2015) data indicating that higher levels of DHEA in nine-year olds are associated with delayed development of frontal white matter in the left corona radiata, as anomalies in this brain region have been linked to irritability symptoms in adolescent depression (Henderson et al., 2013).

## An Evolutionary Trade-Off Model

Whereas most theory and research on the developmental origins of health and disease is based on the view that exposure to adversity early in life generates “wear and tear” on developing systems, thereby undermining health in the long-term (Evans, 2003; Hertzman & Power, 2004), evolutionary theorizing calls attention to a process of “predictive adaptive response” which serves to “program” the developing organism to fit the context that is likely to be encountered later in life (Bateson et al., 2004; Belsky et al., 1991; Ellis & Del Giudice,

2014; Gluckman, Hanson, & Spencer, 2005). This framework stipulates that natural selection shaped child development to be sensitive to environmental cues pertaining to risk and opportunity, treating these as a “weather forecast” (Bateson, 2008) to regulate development. And because the central goal of all living things is to pass genes on to future generations, developmental experiences that reflect increased risk of dying before reproducing—as poverty, maltreatment, neglect, and harsh parenting are presumed to do—should accelerate reproductive maturation (Belsky et al., 1991; Chisholm, 1993). Extensive evidence proves consistent with this view—in the case of females—as they evince earlier sexual maturation than age-mates when exposed to sexual abuse, harsh parenting, father absence, conflicted marriages and related adverse family experiences (Belsky, 2012; Ellis, 2004). Indeed, prior research on the children studied for this report links unsupportive family relationships with earlier adrenarche (Ellis & Essex, 2007).

To summarize, two separate lines of research independently link early adversity with stress physiology, accelerated reproductive development (in females) and/or poor health later in life, considered to reflect accelerated aging. This raises the prospect that evolutionary-minded scholars who study the predictive-adaptive-response process and focus on reproductive maturity and health scientists who investigate the developmental origins of health and disease and focus on poor health in midlife may well be tapping into the same evolutionary developmental process, one in which *longer-term health costs are traded off for increased probability of reproducing before dying via a process of accelerated reproductive maturation* (Belsky, 2014; Belsky & Shalev, in press; Ellis, Del Giudice, & Shirtcliff, 2013; Rickard, Frankenhuis, & Nettle, 2014). Not inconsistent with such a view is extensive evidence that early sexual maturation in females is associated with increased morbidity in later life (Ellis, 2004).

## Method

### Participants

When children originally recruited at birth to participate in the Wisconsin Study of Families and Work were in grade 1, a subsample of 120 participants (73 female) was re-recruited for additional study, consisting of individuals scoring either high or low on mental health problems. For details on the overall sample, recruitment procedures, and eligibility criteria, see Hyde, Klein, Essex, and Clark (1995); for subsample details, see Ellis and Essex, (2007). None (0%) of the female participants were missing prenatal maternal stress, infancy maternal depression, negative parenting, or child adrenarche data; 13 (17.8%) were missing childhood cortisol data; and 7 (9.6%) were missing mental and physical health data.

At recruitment, the 73 mothers ranged in age from 22-41 years (Mdn = 30) and the majority were Caucasian (86%), well-educated (e.g., 80% had some level of post-secondary education) and married (94%). Family incomes ranged from less than \$10,000 to \$120,000 (Mdn = \$50,000). Importantly, there were no significant differences on these demographic characteristics or the specific variables of interest in the present study between the 73 participating families and the remainder of the 570 original families.

## Measures

**Prenatal Maternal Stress**—Prenatal maternal stress scores were composites of maternal reports of 1) maternal depression symptoms, 2) marital conflict, and 3) financial stress, created on the basis of Principal Components Analysis. Maternal depression was assessed by the 20-item Center for Epidemiologic Studies—Depression scale (CES-D, Radloff, 1977). Marital conflict was assessed with the average of three items from the Partner Role Quality scale (Barnett & Marshall, 1989) tapping overt marital conflict (e.g., concerned about “arguing or fighting”). Financial stress was the average of four items (e.g., “how much difficulty making monthly payments”).

**Infancy Maternal Depression**—Maternal report of depression symptoms was assessed repeatedly in infancy with the CES-D in infancy. Scores obtained at 1-, 4- and 12-month measurement occasions were averaged to create a composite measure.

**Infancy Negative Parenting**—Maternal report of negative parenting was assessed with the Sense of Competence and Child Reinforces Parent scales of the Parental Stress Index (PSI) (Abidin, 1986) and a Negative Affect scale from the Block Childrearing Practices Report (CRPR) (Block, 1965); see Ellis and Essex (2007) for details. Measures were obtained in infancy (child ages 1, 4, and 12 months for the PSI, 12 months for the CRPR). PSI scores were averaged over time and then combined with CRPR Negative Affect based on Principal Components Analysis.

**Basal Cortisol**—Child salivary cortisol (mean age = 4.64 years, SD = 0.05 years) was sampled at home over 3 days, at a target time between 3:00 p.m. and 7:00 p.m., prior to dinner, to capture cortisol levels reflecting more environmental than genetic influences (Schreiber et al., 2006). Additional details have been reported previously (Essex, Klein, et al., 2002; Smider et al., 2002).

**Adrenarche**—Saliva was sampled four times over a home visit following grade 1, and dehydroepiandrosterone (DHEA) was assayed in duplicate. Participants were coded as preadrenarcheal (41%) if six or more of their eight DHEA assays were below the detection threshold (10.0 pg/ml) and all DHEA scores were <16 pg/ml. All other participants were coded as adrenarcheal (59%). Assay (Salimetrics, State College, PA) specifications and additional details are reported elsewhere (Ellis & Essex, 2007).

**Pubertal Status**—In the summer following 5th grade (mean age = 11.25 years, SD = 0.30 years) pubertal status was assessed via child report of Tanner stages using standard line drawings (Morris & Udry, 1980) and mother report of both Tanner stages and a questionnaire version (Carskadon & Acebo, 1993) of the Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). A single score combined ratings across measures and respondents as detailed elsewhere (Ellis & Essex, 2007; Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011).

**Adolescent Mental and Physical Health Problems**—Adolescents (mean age = 17.84 years, SD = 0.30 years) completed an age-appropriate version (Burk et al., 2011) of the

MacArthur Health and Behavior Questionnaire (Boyce et al., 2002; Essex, Boyce, et al., 2002) to assess 1) overall mental health symptoms (i.e., the average of scores for internalizing (depression, anxiety) and externalizing (conduct problems, oppositional-defiance, aggression)), and 2) global physical health problems (e.g., “I am/am not healthy enough to do the things I want to do”). For both variables, higher scores reflect more health problems.

## Results

Descriptive statistics are presented in Table 1. Bivariate Pearson-*r* (two-tailed) correlations indicate that all anticipated associations were significant (*ps* < .05) and in the expected direction, except for those involving negative parenting in infancy. A path analysis was constructed using Mplus version 5.2 (Muthén & Muthén, 1998-2012) to examine the hypothesized temporal ordering of the variables via an indirect pathway from prenatal stress to the health outcomes via maternal depression and negative parenting in infancy, childhood cortisol and adrenarche. In addition to modeling temporal associations, Mplus affords the opportunity to impute missing data using full information maximum likelihood estimation. Little's Missing Completely At Random test revealed that the data were missing at random; thus we imputed at the data analysis stage, permitting the inclusion of all 73 female participants in the path analyses. The resulting model demonstrated acceptable fit:  $\chi^2(11) = 12.63, p = .32$ ; root-mean-square error of approximation (RMSEA) = .04 (90% CI = [.00, .14]); standardized root mean residual (SRMR) = .09; comparative fit index (CFI) = 0.98).

Inspection of Figure 1 reveals that results proved generally consistent with our hypothesized multi-stage developmental model after adding a direct path linking basal cortisol with mental-health problems, with the exception of the role of negative parenting in infancy, and accounted for 15.9% of the variance in mental health symptoms and 6.4% of the variance in physical health problems. In a secondary analysis, the addition of pubertal status at age 11 as a mediator between adrenarche and age-18 health outcomes failed to improve model fit ( $\chi^2(4) = 1.77, p = 0.78$ ). Moreover, age 11 pubertal status did not significantly mediate the association between adrenarche and either age-18 mental health (Est. = .05, *p* = .18) or physical health problems (Est. = .04, *p* = .45); therefore, only the original, more parsimonious model (excluding puberty) is displayed.

## Discussion

Many scholars have long regarded experiences in the family early in life as formative in shaping psychological and behavioral development. More recently, health scientists have documented the influence of such developmental experiences on adult morbidity and mortality. The fact that many of the same environmental exposures found to link early-life adversity with compromised mental and physical health in adulthood also predict accelerated sexual maturation in females, as theorized some time ago (Belsky et al., 1991), raised the prospect that those studying the developmental origins of health and disease and those investigating contextually regulated reproductive maturation were tapping into the very same evolutionary-developmental process—whereby compromised health in later life



is traded off against increased probability of reproducing before dying, which is instantiated via accelerated reproductive maturation (Belsky & Shalev, in press).

Results presented in this longitudinal and observational study proved tolerably consistent with this trade-off view while highlighting a plausible mediating stress-physiology process involving elevated basal cortisol in early childhood—and thus one involving the HPA axis which has previously been implicated in linking early adversity with both accelerated reproductive development and compromised health (Ellis & Del Giudice, 2014). Thus, the longitudinal modeling revealed that greater prenatal stress exposure predicted greater maternal depression—but not negative parenting—in infancy, which itself predicted elevated basal cortisol levels at age 4.5 years, which itself predicted earlier age of adrenarche, which itself predicted poorer physical and mental health at age 18. As Figure 1 indicates, it was also the case that greater basal cortisol itself directly predicted poorer mental health. This likely reflects the fact that additional mechanisms not included in this inquiry merit future study.

The fact that the effect of adrenarche on mental and physical health was not mediated by pubertal development may appear surprising, but the fact remains that the relation between these two phases of pubertal development “has been debated controversially for decades” (Remer, Shi, Buyken, Maser-Gluth, Hartmann & Wudy, 2010, p. 3002). Conceivably, the reason we did not detect any association between the two phases of pubertal development was because of the differential precision and parameterization of the two measures used in this inquiry. Recall that adrenarche was assessed by means of a laboratory assay of salivary DHEA, whereas Tanner Stage was based on consensus estimates of secondary sex characteristics by children and their mothers. In any event, one should not lose sight of the fact that pubertal development is characterized by a series of hormonal events leading to the attainment of adult reproductive capacity. What this means, then, is that it should not be presumed that one index of this complex process is a better reflection of it than another, especially with regard to the issues addressed herein.

Due to the observational and correlational nature of these longitudinal results, as well as the modest sample size, the findings do not necessarily document causal effects. Moreover, it would be a mistake to infer that either exposure to prenatal stress or maternal depression in infancy are the only, or even most important, adverse early experiences regulating reproductive development and, thereby, physical and mental health. And the same goes for stress physiology as operationalized by means of basal cortisol when considering mediating biological mechanisms. It would also be misguided to conclude that parenting plays no role whatsoever in the developmental process under consideration. The null findings involving negative parenting in infancy could be a result of the particular measures of parenting included in our model and/or their timing of assessment. Investigators should thus expand targets of inquiry when testing the hypothesized evolutionary trade off central to this study. Despite these limits, the reported findings document, at the very least, proof of principle—namely, that the acceleration of reproductive development may be an important, but as yet, unaddressed component in the developmental origins of health and disease among females. Additionally, to our knowledge this is the first study to chronicle links between cortisol and adrenarche.

Whether or not one embraces the trade-off view that gave birth to the research reported herein, implying that scholars studying the developmental origins of health and disease would benefit from viewing the subject from an evolutionary and not just medical, wear-and-tear perspective, the implications of the results are in line with those which typically derive from the traditional view. That is, later-life health is, at least in part, forged much earlier in life than once thought. In consequence, mid-life health costs would likely be reduced by intervening early in life, long before health problems emerge. But to the extent that the process linking early adversity with poor health in adulthood is part and parcel of an evolutionary trade-off process crafted by natural selection, then it may be the case that health-related interventions implemented after the onset of reproductive maturation could be especially unlikely to succeed.

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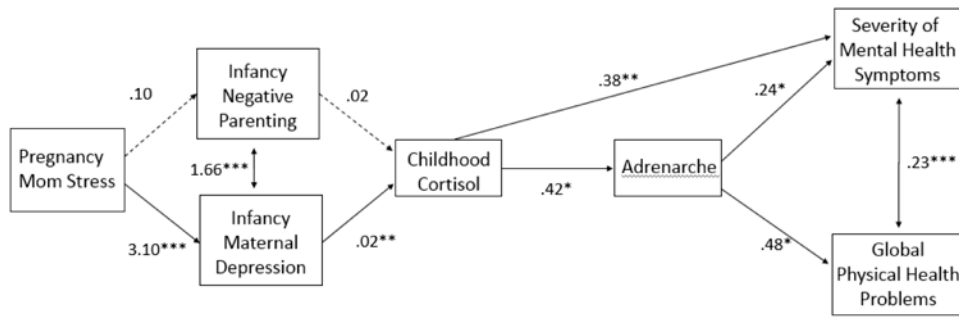
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**Fig. 1.** Path analysis demonstrating longitudinal associations between negative early environments, altered cortisol, early adrenarche, and health outcomes in girls. Asterisks indicate statistically significant paths (\*  $p < .05$ , \*\*  $p < .01$ , \*\*\*  $p < .001$ ).

**Table 1**  
**Descriptive Statistics and Correlations among Predictor and Outcome Variables in Girls**

Variables	Descriptive Statistics			Correlations						
	Mean	SD		Prenatal stress	Infancy maternal depression	Infancy negative parenting	Cortisol	Adrenarche	Mental health symptoms	Physical health problems
1. Prenatal stress	0.09	1.10	--	--	.64***	.12	.22 <sup>f</sup>	.06	.23 <sup>f</sup>	.22 <sup>f</sup>
2. Infancy maternal depression	6.76	5.36	--	--	--	.42***	.35***	.20 <sup>f</sup>	.38***	.33***
3. Infancy negative parenting	-0.18	0.92	--	--	--	--	.21	.26*	.17	.14
4. Cortisol	0.04	0.31	--	--	--	--	--	.25*	.29*	.02
5. Adrenarche	0.59	0.50	--	--	--	--	--	--	.32***	.25*
6. Mental health symptoms	1.86	0.47	--	--	--	--	--	--	--	.60***
7. Physical health problems	4.87	0.95	--	--	--	--	--	--	--	--

<sup>f</sup> *p* .10;  
 \* *p* .05;  
 \*\* *p* .01;  
 \*\*\* *p* .001

Note: Adrenarche was coded as 0 for preadrenarcheal and +1 for adrenarcheal.