# Lifetime Adversity Leads to Blunted Stress Axis Reactivity: Studies from the Oklahoma Family Health Patterns Project

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**Background:** Can stressful events in early life alter the response characteristics of the human stress axis? Individual differences in stress reactivity are considered potentially important in long-term health and disease; however, little is known about the sources of these individual differences. We present evidence that adverse experience in childhood and adolescence can alter core components of the stress axis, including cortisol and heart rate reactivity.

**Methods:** We exposed 354 healthy young adults (196 women) to public speaking and mental arithmetic stressors in the laboratory. Stress responses were indexed by self-report, heart rate, and cortisol levels relative to measures on a nonstress control day. Subjects were grouped into those who had experienced 0, 1, or 2 or more significant adverse life events, including Physical or Sexual Adversity (mugged, threatened with a weapon, experienced a break-in or robbery or raped or sexually assaulted by a relative or nonrelative) or Emotional Adversity (separation from biological mother or father for at least 6 months before age 15).

**Results:** Experience of adversity predicted smaller heart rate and cortisol responses to the stressors in a dose-dependent fashion ($0 > 1 >$ 2 or more events) ($F$ values $= 5.79$ and $8.11$, $p$ values $< .004$) for both men and women. This was not explained by differences in socioeconomic status, the underlying cortisol diurnal cycle, or subjective experience during the stress procedure.

**Conclusions:** The results indicate a long-term impact of stressful life experience on the reactivity of the human stress axis.

**Key Words:** Cortisol, gender, heart rate, lifetime adversity, mental stress, stress reactivity

Cortisol release during acute stress represents both a mobilization of resources and a homeostatic moderator of the stress response (1). Accordingly, a normal cortisol response is taken as a sign of good systems integrity, and by extension stress responses much larger or smaller than normal might indicate systemic dysregulation with potential health implications (2–5). Although there are large individual differences in responses to psychological stress, the primary contributors to this individual difference factor remain poorly understood (6). Recent studies have suggested that the experience of adverse life events in childhood and adolescence might alter regulation of the hypothalamic-pituitary-adrenocortical axis (HPA) and contribute to increased rates of psychiatric disorders (7–10). However, most studies of early life adversity and altered HPA function have been done on persons with comorbid severe trauma and depression or posttraumatic stress disorder, making it difficult to estimate the effect of adversity independent of potential psychiatric vulnerabilities. Carpenter *et al.* (11,12) have recently shown that blunted stress cortisol responses might occur in otherwise healthy young adults exposed to childhood trauma and maltreatment. In agreement with these findings of diminished response to psychological stress are studies showing diminished reactions to direct endocrine challenges in healthy persons with a history of adversity (13,14). This literature has focused on adversity and the HPA, leaving unanswered the question of the impact of adversity on other components of the stress axis, in particular the cardiovascular system.

The present study examines cortisol and heart rate responses to a standardized psychological stress protocol incorporating simulated public speaking and mental arithmetic challenges (15). The study population included healthy young adults free of psychiatric comorbidities but who had experienced a range of physical and psychological adverse events in childhood and early adolescence.

## Methods and Materials

### Overview

The Oklahoma Family Health Patterns Project is a study of healthy young adults with and without a family history of alcoholism ($n = 156$ and $n = 198$, respectively). Because of the sample size and consistent protocol, the dataset provides a useful resource for assessing the individual differences in stress reactivity in healthy young adults. In preliminary analyses, family history of alcoholism was not a significant predictor of heart rate or cortisol reactivity when adversity was accounted for ($F$ values $< 1.0$). We therefore considered the present dataset suitable for examining adversity independent of family history.

### Subjects

The sample includes 354 persons (158 men, 196 women) recruited through community advertisement. Each subject signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center in Oklahoma City, Oklahoma, and received financial compensation for participating.

### Inclusion and Exclusion Criteria

Prospective volunteers were excluded if they: had a history of alcohol or drug dependence; met criteria for substance abuse

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within the past 2 months; failed a urine drug screen or a breath-alcohol test on days of testing; or had a history of any Axis I disorder other than past depression, as defined by the *Diagnostic and Statistical Manual of Mental disorders, 4th ed.* (16). Women were required to have a negative urine pregnancy test on each day of testing. All participants were in good physical health, had a body mass index $<30$, were not taking prescription medications, and had no reported history of serious medical disorder. Smoking and smokeless tobacco use were not exclusionary. Preliminary analyses showed no difference in cortisol reactivity between tobacco users and nonusers.

Because cortisol secretion is dependent on the sleep-wake cycle (17), volunteers were required to have a normal work or school schedule and to have a nighttime sleep pattern. Also, because acute cortisol secretion is affected by prevailing blood glucose levels (18), all volunteers ate a standard meal before beginning the protocol.

### Subject Background and Psychological Assessments

A preliminary telephone screening was followed by a lab visit for a psychiatric history assessed with the computerized version of the Diagnostic Interview Schedule-IV (C-DIS-IV) (19), conducted by a trained assistant under the supervision of a licensed clinical psychologist and assessment of family history of alcoholism.

Lifetime adversity was based on C-DIS-IV items that were closely similar to the life events assessed retrospectively in the studies by Caspi (20,21) as follows: Physical or Sexual Adversity (Have you ever been mugged or threatened with a weapon? Have you ever experienced a break-in or robbery? Have you ever been raped or sexually assaulted by a relative? Have you ever been raped or sexually assaulted by someone not related to you?) and Emotional Adversity (Before you were 15, was there a time when you did not live with your biological mother for at least 6 months? Before you were 15, was there a time when you did not live with your biological father for at least 6 months?). Each person was assigned an adversity score ranging from 0 (no adverse events) to a maximum of 5. Social status was estimated with Hollingshead's measure of socioeconomic status (SES), defined as the highest occupational level of the head of household in which the subject grew up (22).

### Study Design and Procedure

Subjects visited the lab twice for behavioral and psychophysiological testing, and were tested at the same time on both days, either in the morning at 9:00 AM ($n = 169$) or in the afternoon at 1:00 PM ($n = 185$). To maximize stress responses, the first day in the lab involved the stress procedure, and the second day was designated the resting control day. Subjects were briefed in advance of this test order and were told to expect to deliver short speeches and a mental arithmetic task. Placing stress exposure on day 1 is comparable to the use of a single study day as done in most stress research, as discussed previously (23).

**Stress Protocol.** The stress protocol lasted 75 min, consisting of a 30-min prestress baseline, when the subject sat quietly and read general interest magazines, followed by 45 min of behavioral stress. Stress included simulated public speaking (24) followed by mental arithmetic (15). The speech task (30 min) included three speeches prepared (4 min) and delivered (4 min) with no breaks before a video camera and observed by a white-coated experimenter holding a clipboard as described elsewhere (23). The subject was told that his or her speech would be shown to the laboratory staff and that they would judge the fluency of delivery of the subject and how convincing their speech was. The speech topics included recounting an article on why hair turns gray, presenting a position for or against whether homosexuals should be allowed to adopt children, and responding to an accusation that the subject was shoplifting. The order of speech topics was randomly assigned for each subject.

The 15-min mental arithmetic task consisted of three 5-min periods with no interruption other than brief instructions. At the start of each period, the subject was given a three-digit number (e.g., 298) and told to add the digits (19) and to add that total to the original number (317), to recite the new number aloud, and to proceed in that fashion for 5 min until told to stop. The experimenter monitored the answers and noted errors by telling the subject when an answer was wrong and to start back with their previous correct answer.

**Resting Control Day.** The protocol lasted 75 min, during which the subject sat and read general interest magazines or watched videotapes of nature programs lacking emotional content.

To assess subjective impact of rest and the stressors, subjects rated their moods at each saliva sample with 12 10-point visual-analogue scales adapted from Lundberg and Frankenhaeuser (25) containing a Distress subscale (impatience, irritability, distress, pleasantness, and control) and an Activation subscale (effort, tension, concentration, interest, and stimulation).

### Saliva Collection Times and Cortisol Assay

Saliva samples were collected with the Salivette device (Sarstedt, Newton, North Carolina) and taken at: awakening; arrival at the laboratory; min 10 and 20 of the baseline period; min 15, 30, and 45 of the stress protocol or continued resting protocol; 15 and 30 min after stress or rest; and bedtime. Stress reactivity as reported here was measured at min 10 and 20 of the baseline period and at min 30 and 45 of the stress period contrasted with samples taken at the same times during the extended resting protocol.

Salivettes were centrifuged at 4200 RPM for 20 min. The saliva was transferred to cryogenic storage tubes and placed into a $-20°$ C freezer until shipping. Saliva-free cortisol assays were conducted by Salimetrics (State College, Pennsylvania) with a competitive enzymatic immunoassay (26) with a sensitivity of $<.083$ μg/dL and an interassay coefficient of variation of $<6.42\%$.

In preliminary analyses on cortisol data in the women, no differences were seen in the effect of adversity between the luteal and follicular groups ($t = .71$, $p > .48$). Similarly, women using oral birth control did not differ from those not doing so ($t = .30$, $p = .76$). Menstrual cycle and oral contraceptive effects were accordingly not considered in the subsequent analyses.

### Heart Rate

Heart rate was measured from readings made every 2 min with an oscillometric monitor (Dinamap, V100, General Electric, Waukesha, Wisconsin). These were made continuously during both days during the entire period of the protocol. Heart rate data were unavailable for eight subjects due to recording failures.

### Data Analysis

Dependent variables were the cortisol and heart rate responses to stress. Cortisol response was measured as the value at the end of the stress period on the stress day minus the comparable value on the resting control day (23). Heart rate was measured as the mean heart rate during speech preparation periods minus the heart rate during the rest day protocol. This avoided confounding the heart rate data by vocal activity during the speech delivery or mental arithmetic answers. Data were analyzed with SAS software (version 9.2 for Windows, SAS Institute, Cary, North Carolina).