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Article

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Stressors Over the Life Course and Neuroendocrine System Dysregulation in Costa Rica

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Abstract

Objectives: A key aspect of the increasingly popular allostatic load (AL) framework is that stressors experienced over the entire life course result in physiological dysregulation. Although core to AL theory, this idea has been little tested, and where it has been tested, the results have been mixed. **Method:** The study analyzes the Costa Rican Study on Longevity and Healthy Aging (CRELES), a new, cross-sectional, and nationally representative survey of older Costa Rican men and women (aged between 60 and 109 years). The survey period is between 2004 and 2006, and the survey has a sample size of 2,827 individuals. This article focuses on the relationship between a variety of stressors experienced over the life course and cortisol, dehydroepiandrosterone sulfate (DHEAS), epinephrine, and norepinephrine analyzed separately and in an index. **Results:** There are some links between certain stressors and worse cortisol levels, but overall, almost all of the stressors examined are not associated with riskier neuroendocrine biomarker profiles. **Discussion:** More work is needed, in order to establish

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the connection between stressors experienced over the life course and resting levels of the neuroendocrine markers.

Keywords

stress, biomarkers, neuroendocrine allostatic load (NAL), Costa Rica, aging

At least two important testable hypotheses stem from the allostatic framework, a framework that has grown markedly in popularity and has emphasized the role of stress in illness (Gersten, 2008a; McEwen, 2004). One hypothesis is that allostatic load (AL), a measure of physiological dysregulation, is the result, over extended periods of time, of repeated activation of the body's adaptive processes in response to challenge. Another hypothesis is that AL is a risk factor for morbidity and mortality. Of these two hypotheses, far more support has been found for the latter. Using the MacArthur studies, for instance, Seeman, Singer, Rowe, Horwitz, and McEwen (1997) found that high AL at baseline predicted greater cognitive and physical declines and earlier mortality over the study period. In addition, work by Goldman, Glei, Seplaki, Liu, and Weinstein (2006), and Turra and others (2005), found that various measures of physiological dysregulation in a Taiwanese population predicted health outcomes such as depression, cognitive and physical function, and survival.

In contrast to these findings, using the same Taiwanese data set, analysis by Glei, Goldman, Chuang, and Weinstein (2007) attempting to link various stressors to riskier AL levels produced mixed results. Although an index of stressors with items such as moving, crime victimization, and the death of a child experienced between 1996 and 2000 was associated (although quite weakly) with higher AL levels, other stressors such as low socioeconomic status, low levels of emotional support, and fewer social ties with friends and relatives were not. Gersten (2008b) also analyzed the same data set as Glei and others, but with a focus on neuroendocrine markers and a different set of stressors over the (e.g., length of widowhood and subjective reports of chronic stress over family matters and work and financial issues), and found almost entirely negative results. And although negative findings have also been found by others (Babisch, Fromme, Beyer, & Ising, 2001; Powell et al., 2002), these studies typically have only examined one particular type of stressor (e.g., marital disruption or noise exposure) instead of multiple stressors that span the life course. A further limitation of these studies is that they have often investigated one particular biomarker (instead of a grouping representative of a physiological system or systems) and have been conducted on small, non–population-based samples (Babisch et al., 2001; Luecken et al., 1997; Powell et al., 2002; Wheler et al., 2006). In sum, there is a paucity of studies (the 2000 SEBAS and perhaps one or two others) that can claim to

have tested in a rigorous way the hypothesis that markers of life-course stress are correlated with higher levels of AL. In order to extend this literature, then, we will analyze a new, nationally representative data set from Costa Rica.

The data that will be analyzed in this paper come from the CRELES, which recently obtained information from older Costa Rican men and women. Much of the data were meant to be comparable to other studies that have investigated AL, such as the MacArthur studies and the Taiwanese SEBAS, and thus the CRELES has obtained many of the same biomarkers as these surveys. One drawback of the CRELES is the lack of questions that probe subjective levels of stress (e.g., "Do you feel stressed about . . . ?"). A strength of the survey, however, is its collection of a number of indicators of stressful life events, especially those occurring in early childhood (e.g., economic deprivation). Many other surveys investigating the impact of life stressors on AL have only examined stressors that have occurred in middle and later life (Goldman et al., 2005; Seeman et al., 2004), even though the allostatic framework is quite clear about the importance of using a life-course approach in analyses (Crimmins & Seeman, 2004; McEwen, 2004).

As suggested earlier, AL is the idea that the body experiences a cost, or "wear and tear," from responding to myriad acute and chronic challenges/stressors over the life course (McEwen, 1988; Timiras & Gersten, 2007). AL is also thought to develop in a number of different and important physiological systems, including the metabolic, cardiovascular, and neuroendocrine ones (McEwen, 1988; Timiras & Gersten, 2007). The article here will focus on the neuroendocrine markers of the AL construct for a number of reasons. First, in population-level studies that have been conducted to date, the neuroendocrine markers have been some of the most recently added and hence least studied (compared to, say, those markers indicative of cardiovascular and metabolic function). Biomarkers of neuroendocrine system function have been little studied, even though they are critical to the stress response and form a core component of the AL measure. Second, despite the recent inclusion of neuroendocrine markers in large-scale studies, there is convincing evidence that certain levels of the markers predict a number of health problems, including more rapid decline in physical and cognitive function, greater incidence of cardiovascular disease, and earlier mortality (Goldman, Turra, Glei, Lin, & Weinstein, 2006; Karlamangla, Singer, Greendale, & Seeman, 2005; Seeman, McEwen, Rowe, & Singer, 2001). In other words, the neuroendocrine markers make an important contribution in predicting worse health. Third, although one of the strengths of the AL construct has been measurement of different physiological systems in one index in an attempt to gauge health more holistically, such an approach is also one of the construct's weaknesses. That is, from a physiological perspective, it can be difficult to interpret

a score from the measure that includes such vastly different markers. Relatedly, it is often unclear which system, if any, is driving an overall pattern of the construct. Fourth, a focus on the neuroendocrine markers in this article allows for a more in-depth analysis of them than can usually be carried out. Such a careful treatment is important for a number of reasons, including that, as mentioned before, these markers are relatively novel and relatively little is known about them. Thus, for the aforementioned reasons, this article will focus on analyzing four biomarkers representing neuroendocrine system function (i.e., cortisol, dehydroepiandrosterone sulfate [DHEAS], epinephrine, and norepinephrine) in relation to stressors experienced over life course.

Study Hypotheses

On the basis of the general literature and that specific to Costa Rica, and following in the tradition of the "environmental stress perspective" that focuses on potentially stressful life events (Cohen, Kessler, & Gordon, 1995), we hypothesize that a number of states and experiences have likely proved challenging, and hence, have likely led to greater AL. Because life brings both good and bad, growing older can only result in exposure to more stressors. And because AL is thought to be cumulative, we hypothesize that greater age is positively correlated with greater AL. We also expect a similar relationship between female gender and AL because women generally report greater distress and depression than men (Steptoe, Tsuda, Tanaka, & Wardle, 2007; Thoits, 1995). Indicators of lesser material resources, such as lower education, lower current household wealth, and economic deprivation early in life are all expected to be associated with higher AL (Dow & Schmeer, 2003; Rosero-Bixby, Dow, & Lacle, 2005; Steptoe et al., 2007; Wolf, De Andraca, & Lozoff, 2002), and so too are indicators of lesser emotional resources, such as growing up without a biological father (Budowski & Rosero-Bixby, 2003) and earlier maternal age at death. Markers of poor health early in life, like having had malaria or asthma, might also very well indicate greater stress (and hence greater AL) that comes with dealing with illness.

Given the suggestion in the literature that some of the negative health effects of social deprivation are due to increased levels of stress (Cacioppo & Hawkley, 2003), we expect that measures of such deprivation (which in our study are whether the respondents are unmarried, live alone, and attend church infrequently or not at all) should also be associated with higher AL (Brenes-Camacho, 2008; Dow & Schmeer, 2003; Low, 1981; Rosero-Bixby et al., 2005; Wolf et al., 2002). Furthermore, we expect a similar relationship between AL and measures of personal loss, which in this study are the experience of a death of a child and length of widowhood (Low, 1981). Status as an

immigrant (in comparison to the native born) is included as a variable in our analysis because such status is potentially important, though we remain neutral in hypothesizing its directionality. On one hand, immigrants are more likely to be disconnected from family, experience more difficult working and living situations, and experience discrimination (Bolaños, Partanen, Berrocal, Alvárez, & Córdova, 2008; Sandoval-García, 2004), but on the other hand they may be healthier and more robust to these sorts of stressors than the native population because of selective migration (Herring et al., 2010). Moreover, we suspect that rural residents of Costa Rica, who compare less favorably than their urban counterparts on a number of indicators of welfare (e.g., employment rate, infant mortality, and levels of malnutrition; Bähr & Wehrhahn, 1993; Hall, 1984), will have higher ALs. Last, in analysis of only the currently married, we predict that those who report a spouse in poor health will themselves have higher AL in part because of the possibility of stress caused by caregiving responsibilities (Epel et al., 2004).

Method

Overview of the Data Set

We analyze the Costa Rican Study on Longevity and Healthy Aging (CRELES), a population survey conducted in Costa Rica in 2004-2006 (for a more detailed description of the study, consult Rosero-Bixby, 2007). The survey is nationally representative of those aged 60 and older in the noninstitutionalized population, and the CRELES drew its subsample of respondents from the 2000 census database. Among other things, the interview portion of the CRELES included questions about cognitive and physical functioning, health care utilization, nutrition and other health behaviors, social support, employment history and pensions, and a variety of life stressors. The in-home interviews averaged nearly an hour and a half, and during the same visit by survey staff, mobility tests were performed and blood pressure measurements were taken. With the respondents' additional consent, they were enrolled in the more invasive aspect of the survey's data collection efforts. After receiving relevant instructions and materials, participants collected urine and began fasting on the same day as the in-home interview, and, on the next day, the survey staff collected the urine and blood samples and took anthropometric (e.g., height and weight) measures. The blood and urine samples were used to determine traditional health indicators such as total and HDL cholesterol and less traditional indicators such as epinephrine and cortisol.

Of survivors who could be located and were initially contacted for inclusion during the CRELES survey period, between 2004 and 2006, 96% gave

interviews, yielding a sample of 2,827 participants. Of these, 95% and 92% gave blood and urine samples, respectively, and in about 25% of all cases a proxy (most often the respondent's son or daughter) helped answer some questions for the respondent. The survey oversampled those aged more than 95 years.

Dependent Variable

The neuroendocrine biomarkers. In this article, we focus on cortisol, DHEAS, epinephrine, and norepinephrine, a physiologically coherent class of markers indicative of neuroendocrine system function (Cohen et al., 1995; Crimmins & Seeman, 2001; Sapolsky, 2004). The measure used here based on these markers is called NAL, for neuroendocrine AL, and has been discussed in more detail elsewhere (Gersten, 2008b). Among NAL's greatest advantages is its interpretability that stems from grouping markers of a single physiological system. NAL includes markers related to two neuroendocrine systems: the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS). The HPA axis is key in regulating homeostatic processes in the body and environmental stressors can lead it as well other regulatory systems to react (Cohen et al., 1995; Crimmins & Seeman, 2001; Sapolsky, 2004). Cortisol and DHEAS are indicators of HPA-axis activity. The body's "fight-or-flight" response is in part mobilized by the SNS, and its activity can be measured by norepinephrine and epinephrine levels (Cohen et al., 1995; Crimmins & Seeman, 2001; Sapolsky, 2004).

Measurement of biomarkers. The CRELES attempted to capture basal levels of the neuroendocrine biomarkers, and, to this end, the blood and urine samples were collected in the participants' homes under resting conditions. Three of the four markers were collected in overnight urine samples, and when collected in this way, the samples represent integrated, in contrast to point-in-time, measures. For cortisol, norepinephrine, and epinephrine, respondents were asked to void urine at 6 p.m., which was discarded, and to collect all subsequent samples until 6 a.m. the following day. In part because dissimilar body size leads to differential concentration of the neuroendocrine markers in the urine, total urine was standardized using grams of creatinine. The subjects also fasted from 6 p.m. onwards on the day they began urine collection, until a study affiliate came to their home to collect the urine sample and draw blood. The amount of DHEAS in the body was determined through these blood samples.

The blood samples for each respondent were drawn by venipuncture by a phlebotomist and put into three tubes, one tube with EDTA (which acts as an

anticoagulant) and two serum-separating tubes (SST) with clot activators. The tubes with the clot activator were centrifuged in the field to separate the serum from the other elements and to prevent hemolysis (the breaking open of red blood cells and the release of hemoglobin into the surrounding fluid). From the point of initial blood collection, the tubes were kept in coolers for no more than 6 hr, until they were separated in various nearby labs into aliquots of 0.5 or 1.0 mL and stored at –40 °C. The serum was later used to analyze DHEAS levels and levels of some other markers. Regarding the urine samples, after they were picked up from respondents' homes they were kept in coolers and also taken to nearby labs where their volume was measured and separated into five aliquots (of either 1.0 or 2.0 mL). These aliquots of urine were also stored at –40 °C.

From the storage labs, the urine samples were initially sent to Neuroscience Laboratories at the University of Costa Rica for analysis and then to the Central American Center for the Analysis of Hormones (CENHACE), a private laboratory in San Jose, Costa Rica. Both these laboratories were certified by a national reference center of clinical chemistry, an agency under the Ministry of Health. The catecholamines were analyzed by high-performance liquid chromatography (HPLC) at Neuroscience Laboratories, and cortisol and DHEAS were analyzed by chemiluminescence immunoassay at the CENHACE laboratory. Unfortunately, for a sizable share of respondents (about 37%) who otherwise gave valid urine samples, epinephrine and norepinephrine values had to be coded as missing, as there was a problem with acidifying the urine samples properly. As far as the possibility of biased estimates from the missing values on eipinephrine and norepinephrine is concerned, the missingness is related to when respondents were surveyed during the survey cycle (i.e., between November 2004 and September 2006), which is unrelated to individual characteristics, and thus, there is no reason to suspect that the missingness is systematic.[1] It is noteworthy that no such missingness issue applies to cortisol and DHEAS for which the CRELES has quite a large sample. Also, the sample size of the CRELES for which there is complete data on all four neuroendocrine markers (i.e., including epinephrine and norepinephrine) is still larger than other similar, key studies.[2]

Independent Variables

Most of the independent variables used are straightforward to interpret, though the following require some explanation. Household wealth is determined by first creating an index based on whether the respondent's home has a kitchen, electricity or gas as cooking fuel, potable water, indoor toilet, a refrigerator or

freezer, television, a phone (either a cell or landline), and washing machine and whether the respondent owns a car. This index is then coded into high, medium, and low household-wealth categories. Economic problems early in life were determined by asking respondents whether or not in childhood and adolescence they lived in a home that had a bathroom or latrine, lived in a home that had electricity, slept on the floor or with others in a bed, and regularly wore shoes. Health problems early in life were determined by whether or not the respondent reported having in childhood and adolescence tuberculosis, rheumatic fever, poliomyelitis, malaria, and asthma/chronic bronchitis. It is worth noting here a limitation of the recall variables, and that is the possibility of negatively biased recall of childhood variables in depressed, and otherwise unhealthy, participants who are also likely to have abnormal biomarker levels.

In another finance-related question, respondents were asked to describe their present economic situation, to which they could respond "Excellent," "Very good," "Good," "Average/normal," or "Bad." Respondents were also asked to provide their total monthly income stemming from work and pensions. Respondents who did not give a precise figure but gave a range (e.g., 80,000-170,000 colones/month) were given the mean income of those reporting an exact amount within the same range. Income from pensions and work were added to that from transfers from relatives and friends to produce the final variable of total monthly income.

In drawing on an established literature of stressful life events checklists (Turner & Wheaton, 1995), we created a measure of cumulative adversity in which respondents received 1 point toward their score if they could be characterized by any of the following: less than 6 years of education; rural residence; lower household wealth; "bad" self-assessed economic situation; monthly income less than or equal to the lower 25th percentile of incomes; being currently unmarried; living alone; death of at least one child; less than weekly religious attendance; mother with no formal education; mother who died before age 50; growing up without a biological father; having reported one or more health problems early in life; and having reported three or more economic problems early in life. This cumulative adversity index can thus theoretically range from 0 to 14. It should be noted that limitations of the index include that the variable *growing up without a biological father* in the household does not make clear whether the respondent was raised by a single mom alone or with the additional help of another father figure. Also, having information on when participants' mothers died is less preferable to knowing exactly how old participants themselves were when their mothers died. Last, in addition to the cumulative adversity index, we created indices that are

subsets of the larger measure and based on the categories of socioeconomic status, social deprivation, loss, and early childhood conditions.

As levels of the neuroendocrine biomarkers can be influenced by a variety of factors independent of stress (Cohen et al., 1995; James & Brown, 1997), all models initially controlled for smoking, alcohol consumption, and medication use. We present results without these controls, however, as simpler models without the controls are nearly identical to those with them.

Analytical Procedures

Regarding extreme values, one outlier was removed for norepinephrine, two for epinephrine, and four for cortisol. These outliers were at least 11 standard deviations above the mean for their respective distributions. Concerning other data transformations, the four neuroendocrine biomarkers all had distributions that exhibited positive skewness (right tails) and have been logged, creating more normalized distributions and more normalized residuals.

In this article, we will analyze the biomarkers both individually and as part of an index. When analyzed individually, the biomarkers are kept continuous and are the dependent variables in separate OLS regressions. When analyzed in an index, we follow the most popular approach to operationalizing AL that is to create a score that gives 1 point for every biomarker for which the participant can be considered at higher risk (i.e., the elevated risk zone approach; Glei et al., 2007; Seeman et al., 1997; Singer & Ryff, 1999). The literature most often represents high risk by greater values for cortisol, epinephrine, and norepinephrine, and lower values for DHEAS (Kubzansky, Kawachi, & Sparrow, 1999; Loucks, Juster, & Pruessner, 2008; Seeman et al., 1997); this convention is followed here. As there is no agreed-upon standard for what biomarker values represent different risk levels, it has been most common to define risk as above or below distribution percentiles (e.g., the 10th, 25th, 75th, and 90th; Goldman et al., 2005; Kubzansky et al., 1999; Seeman et al., 1997). See Table 1 for descriptive statistics and cut-points for the neuroendocrine biomarkers. As participants can be assigned 1 point on each of the 4 biomarkers if they have high-risk values, NAL scores can range from 0 to 4. These scores serve as the dependent variables in OLS regressions (using Poisson regressions instead produces only minor differences in the results [not shown]). Last, all analysis is carried out using STATA version 9.0 (StataCorp, 2005), and the multivariate analysis makes use of sample weights that correct for the oversampling of the oldest-old and for some nonresponse by demographics.

Table 1. Descriptive Statistics and Cut-Points for the Neuroendocrine Biomarkers

				Percentile cutoffs			
	Mean	*SD*	*N*	10th	25th	75th	90th
System							
HPA axis							
Cortisol (logged)[a]	3.09	0.72	2252	2.21	2.62	3.53	3.96
DHEAS (logged)[b]	3.58	0.79	2621	2.34	2.98	—	—
SNS							
Epinephrine (logged)[a]	1.62	1.00	1520	—	—	2.32	2.94
Norepinephrine (logged)[a]	3.52	0.69	1571	—	—	3.96	4.36

Source: Authors' tabulations based on the 2004-2006 CRELES (Rosero-Bixby, 2007).
Note: Sample population, Costa Rica (ages 60 to 109 years, both genders combined, years 2004-2006). The tabulations are based on unweighted survey data.
a. μg/g creatinine.
b. μg/dl.

Results

Table 2 depicts descriptive statistics for variables that are used in this analysis. One of the things to note in the table is the relatively low levels of education for these Costa Ricans, with 51% not having completed their primary education (i.e., having less than 6 years of schooling). Also striking is the percentage of those who have had at least one of their children die and the percentage of those who have grown up without a biological father (36% and 21%, respectively). Table 2 also reveals that religion is important in the lives of many older persons in Costa Rica, as nearly 50% reported going to church one or more times a week. Last, it is also worth observing that 36% of those with a spouse reported that the spouse has a serious health problem, suggesting that a fair amount of married older persons provide caregiving services to their husband or wife.

Table 3 presents results from regressions in which each stressor variable is included in a separate regression with age and gender as the only controls. With regressions for age and gender also run (controlling for gender and age, respectively), each dependent variable in the table is associated with 17 different regressions. As can be seen from the table, the strongest and most consistent relationship is that for age and gender. Being female is associated with riskier levels for all the biomarkers, with the relationship most statistically significant for DHEAS and norepinephrine. Greater age is also associated

Table 2. Descriptive Statistics for the Dependent and Independent Variables Used in the Analysis

Variable	% or *M* (*SD*)	Range	*N*
Dependent			
Neuroendocrine allostatic load (NAL)[a]	0.85 (0.96)	0-4	1,332
Independent			
Demographic			
Age	70.5 (8.11)	60-109	2,827
Female gender	53%	—	2,827
Low education (< 6 years)	51%	—	2,827
Rural residence (vs. urban)	37%	—	2,827
Immigrant (vs. native born)	5%	—	2,817
Economic resources			
Household wealth[b]	2.13 (0.62)	1-3	2,780
Monthly income (colones in thousands)	190.23 (539.2)	0-10,548	2,738
Self-assessed economic situation[c]	3.6 (0.94)	1-5	2,811
Spousal characteristics			
Low education (< 6 years)	43%	—	2,827
Serious health problem	36%	—	1,402
Social deprivation			
Currently unmarried (vs. currently married)	40%	—	2,817
Lives alone	10%	—	2,823
Low church attendance (< weekly)	50%	—	2,822
Loss			
No. of children who have died (≥ 1)	36%	—	2,818
Length of widowhood (years)[d]	14.1 (12.0)	0-70	785
Early childhood conditions			
Maternal age at death	74.8 (17.1)	17-115	2,302
Low maternal education (no education)	69%	—	2,245
Lived without biological father	21%	—	2,114
Poor health (≥ 1 health problems)	22%	—	2,090
Economic deprivation index[e]	2.0 (1.3)	0-4	2,103
Cumulative adversity			
Overall stressor index	3.8 (2.3)	0-13	1,764

Source: Authors' tabulations based on the 2004-2006 CRELES (Rosero-Bixby, 2007).
Note: Sample population, Costa Rica (ages 60 to 109, both genders combined, years 2004-2006). The tabulations are based on weighted data.
a. Respondents received one point toward their neuroendocrine allostatic load (NAL) score for each biomarker which had a "high-risk" value (i.e., a value below the 25th or above the 75th percentiles).
b. High wealth is coded 3 and low wealth is coded 1.
c. "Excellent" is coded 1 and "bad" is coded 5.
d. Only includes the widowed respondents.
e. More severe economic deprivation is represented by higher values on this index.

Table 3. Estimated Regression Results From Separate Regressions for Each of the Stressor Variables and Each Biomarker, Controlling Only for Age and Gender

	Dependent variables[a]			
Independent variable	Cortisol	DHEAS	Epinephrine	Norepinephrine
Demographic				
Age	0.01 (0.002)****	−0.02 (0.002)****	0.01 (0.037)**	0.01 (0.002)**
Female gender	0.09 (0.039)**	−0.62 (0.033)****	0.16 (0.062)**	0.28 (0.040)****
Low education (< 6 years)	0.11 (0.038)***	0.15 (0.033)****	0.05 (0.064)	0.07 (0.040)*
Rural residence (vs. urban)	0.11 (0.039)***	0.17 (0.033)****	−0.00 (0.064)	0.10 (0.039)***
Immigrant (vs. native born)	−0.04 (0.076)	0.10 (0.075)	−0.10 (0.150)	−0.10 (0.070)
Economic resources				
Household wealth	−0.07 (0.032)**	−0.10 (0.026)****	−0.08 (0.052)	−0.04 (0.032)
Monthly income (colones in millions)	−0.06 (0.036)*	0.02 (0.042)	−0.16 (0.104)	−0.02 (0.072)
Self-assessed economic situation	0.01 (0.023)	0.02 (0.02)	0.022 (0.035)	0.03 (0.023)
Social deprivation				
Currently unmarried (vs. currently married)	0.03 (0.038)	0.03 (0.034)	0.07 (0.065)	0.03 (0.043)
Lives alone	−0.02 (0.054)	−0.02 (0.054)	0.15 (0.095)	0.06 (0.053)
Low church attendance (< weekly)	0.03 (0.040)	0.04 (0.033)	−0.04 (0.063)	−0.05 (0.040)
Loss				
No. of children who have died (≥ 1)[b]	0.05 (0.045)	−0.00 (0.042)	0.03 (0.080)	0.05 (0.048)
Early childhood conditions				
Maternal age at death (years)	−0.00 (0.001)	−0.00 (0.002)	0.00 (0.002)	0.00 (0.001)
Low maternal education (no education)	−0.02 (0.046)	−0.03 (0.039)	−0.09 (0.075)	−0.03 (0.043)
Lived without biological father	0.01 (0.060)	0.01 (0.043)	0.03 (0.080)	−0.02 (0.052)
Poor health (≥1 health problems)	−0.09 (0.045)*	0.05 (0.045)	−0.01 (0.077)	0.01 (0.047)
Economic deprivation index	0.02 (0.017)	0.05 (0.014)***	−0.00 (0.027)	0.01 (0.016)

Source: Authors' calculations based on the 2004-2006 CRELES (Rosero-Bixby, 2007).
Note: Sample population, Costa Rica (ages 60 to 109, both genders combined, years 2004-2006). The regression coefficients are unstandardized, and standard errors are inside the parentheses. Columns 2 to 5 represent results from 17 separate regressions. The regressions for age and gender only control for gender and age, respectively.
a. All dependent variables have been logged (as per Table 1).
b. Regressions control for total number of children ever born.
*$p < .10$. **$p < .05$. ***$p < .01$. ****$p < .001$.

with worse biomarker profiles for all biomarkers. For the stressor variables, the relationships are, by and large, far from statistically significant at the conventional threshold, inconsistent, or going in the unexpected direction. For example, as expected, low education is associated with worse biomarker profiles for cortisol and norepinephrine, but associated with a good profile for DHEAS. A similar relationship holds for rural residence. Although for cortisol, as expected, greater household wealth is linked to more favorable cortisol values, poor health (unexpectedly) is also linked to more favorable cortisol values. As regards lack of associations, none of the stressor variables is statistically significant for epinephrine, and the social deprivation and loss variables (and most of the early childhood conditions variables) are not statistically significant for the other biomarkers as well.

Table 4 presents estimated regression results for different variables and indices, with NAL as the dependent variable. A key finding from this table is the consistency and strength of the relationship between NAL and age and female gender. Also more important, most of the indices were not associated with NAL in the expected way. Most congruent with expectation is the positive correlation between the SES index and higher NAL values, significant at the .10 level. Although not significant at the .10 level, the social deprivation and loss indices do have the expected positive correlation with higher NAL levels.

We also examined only the currently married respondents to test whether having a spouse with low education or poor health was linked to worse biomarker profiles. Results (not shown) did not support the presence of these links. The last measure we analyzed was that of cumulative adversity—in contrast to the stressors singly—also in relation to individual biomarker and NAL values. In these regressions, included along with the overall stressor index variable were controls for age, gender, and children ever born. For the NAL construct, the coefficient was positive (i.e., more stressors were correlated with greater NAL values) and had a p value of .182. Regarding the biomarkers analyzed individually, for cortisol, epinephrine, and norepinephrine, riskier levels were associated with more stressors ($p = .03$, $p = .365$, $p = .221$, respectively), but for DHEAS, riskier levels were associated with fewer stressors ($p = .002$).

In addition to the results already presented and described, we ran a variety of additional analyses. These included using NAL cut-points at the 10th and 90th percentiles instead of at the 25th and 75th, and also creating a NAL measure on the basis of a summed z score for respondents in which the score is the total number of standard deviations from the mean in the direction of high risk for each biomarker.[3] We also analyzed NAL as a binary variable

Table 4. Estimated Regression Results From Different Models, With Neuroendocrine Allostatic Load (NAL) as the Dependent Variable

Dependent variable: NAL[a]	Model 1	Model 2	Model 3	Model 4	Model 5
Independent variables					
Demographic					
Age 70-79	0.18 (0.065)***	0.18 (0.065)***	0.21 (0.065)***	0.21 (0.071)***	0.21 (0.071)***
Age 80-89	0.41 (0.075)****	0.40 (0.075)****	0.45 (0.075)****	0.39 (0.092)****	0.40 (0.095)****
Age 90-99	0.76 (0.159)****	0.74 (0.161)****	0.79 (0.158)****	0.93 (0.262)****	0.86 (0.272)***
Age 100+	0.81 (0.252)***	0.75 (0.242)***	0.81 (0.241)***	1.88 (0.478)****	1.79 (0.504)****
Female gender	0.41 (0.062)****	0.41 (0.061)****	0.42 (0.062)****	0.43 (0.069)****	0.41 (0.071)****
Rural residence (vs. urban)	−0.02 (0.066)	0.01 (0.060)	0.04 (0.062)	0.06 (0.072)	0.05 (0.071)
Immigrant (vs. native born)	−0.18 (0.113)	−0.18 (0.110)	−0.16 (0.109)	−0.26 (0.128)**	−0.23 (0.127)*
SES index[b]	0.05 (0.028)*	—	—	—	0.04 (0.032)
Social deprivation index[c]	—	0.05 (0.038)	—	—	0.01 (0.045)
Loss					
No. of children who have died (≥1)[d]	—	—	0.10 (0.072)	—	0.13 (0.082)
Early childhood conditions index[e]	—	—	—	−0.01 (0.034)	−0.02 (0.034)
Constant	0.49 (0.064)****	0.47 (0.067)****	0.57 (0.067)****	0.47 (0.072)****	0.54 (0.087)****
N	1315	1329	1327	896	889
R^2	0.089	0.089	0.092	0.084	0.093

Source: Authors' calculations based on the 2004-2006 CRELES (Rosero-Bixby, 2007).

Note: Sample population, Costa Rica (ages 60 to 109 years, both genders combined, years 2004-2006). The regression coefficients are unstandardized, standard errors are inside the parentheses. All regressions control for total number of children ever born.

a. NAL ranges from 0 to 4, with 4 representing highest risk. Results are presented with NAL cut-points at the 25th and 75th percentiles.

b. One point toward index score for having low education, low wealth, low monthly income, and bad self-assessed economic situation.

c. One point toward index score for being currently unmarried, living alone, and low religious attendance.

d. Regressions with this variable in the model also control for total number of children ever born.

e. One point toward index score for having mother with no formal education, mother who died before 50 years old, for growing up without a biological father, having reported one or more health problems early in life, and having reported three or more economic problems early in life.

*$p < .10$. **$p < .05$. ***$p < .01$. ****$p < .001$.

(cut-points NAL ≥ 1 and NAL ≥ 2) and used logistic regression. These alternative methods of scoring the NAL construct produced largely the same results. The exceptions were that the relationship between NAL levels and low education, at least one child who has died, immigrant status, and the overall stressor index were considerably weaker. Separate analyses were also carried out by gender and using gender-specific biomarker cut-points, and the results remain largely unchanged compared to the already presented combined-gender analyses. Last, because there is evidence to suggest that for cortisol, not only high, but low values as well, pose risk (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Loucks et al., 2008), we reran analyses examining both tails of cortisol's distribution for the marker analyzed separately and as part of NAL constructs. The results of these analyses revealed that key associations such as those between cortisol levels and age and gender were attenuated, and in some cases especially so.

Discussion

This article investigated stressors throughout the life course—in early, middle, and later ages—in relationship to riskier neuroendocrine biomarker profiles in a new, nationally representative study of older Costa Rican men and women. The main finding is that, contrary to our hypotheses, these stressors were not associated with individual biomarker levels and levels of NAL, a measure of neuroendocrine system dysregulation. Greater age and female gender, though, were linked to riskier biomarker and NAL values.

Findings and the Wider Literature

As just suggested, age and gender were the two lone characteristics in our study consistently and strongly correlated with our measures of neuroendocrine system dysregulation. These findings are not surprising. In the case of female gender, women tend to have lower levels of DHEAS than do men (Goldman et al., 2004; Worthman, 2002), though evidence is mixed on whether they have higher resting levels than do men who used cortisol, epinephrine, and norepinephrine (Goldman et al., 2004; Hinojosa-Laborde, Chapa, Lange, & Haywood, 1999; Van Cauter, Leproult, & Kupfer, 1996; Worthman, 2002). To the extent that women's levels do differ, it seems due to some combination of greater stressor exposure, greater reactivity, and other predisposing psychological and biological factors (Goldberg, 2006; Kajantie & Phillips, 2006; Piccinelli & Wilkinson, 2000).

In the case of age, because greater age can only bring about greater exposure to stressors and the allostatic framework theorizes that the costs to the body in dealing with challenge are cumulative, we would expect a positive relationship between age and NAL. In other words, that age and NAL are correlated with one another is only a necessary, but not sufficient, condition for allostatic theory to hold. The challenge for the allostatic framework, then, is to demonstrate that when holding age constant, measures of a stressful life course are correlated with greater load.

In order to reconcile the findings here with the wider literature, we undertook an extensive literature search for articles related to linking stressors to levels of cortisol, DHEAS, epinephrine, norepinephrine, and AL. We focused on those articles that collected urinary samples to measure the catecholamines and cortisol, and blood samples to measure DHEAS. It is difficult to compare the findings in this article with this wider literature because the latter seldom set out to test the hypothesis that stressors over the life course alter baseline levels of the neuroendocrine markers. Indeed, most of the studies that have attempted to link stressors to neuroendocrine marker levels have only examined one source (or few sources) of chronic stress. For instance, a study by Babisch and others (2001) tried to link traffic noise outside of respondents' homes to catecholamine levels, and another representative study examined whether women currently undergoing a divorce or separation had higher levels of the catecholamines and urinary free cortisol (Powell et al., 2002). In addition to the paucity of studies using multiple measures of stress over the life course, many did not include as many indicators of neuroendocrine system function as in the article here and most made use of considerably smaller, non–population-based samples. Although it is difficult to summarize these varied studies, on the whole results appear mixed, with some supporting (Evans, 2003; Janicki-Deverts et al., 2007; Lemieux & Coe, 1995; Yehuda et al., 1995), some not supporting (Kubzansky, Berkman, Glass, & Seeman, 1998; Powell et al., 2002), and others providing evidence for and against (Babisch, 2003; Luecken et al., 1997; Olff, Güzelcan, de Vries, Assies, & Gersons, 2006; Wheler et al., 2006) the connection between life stress and dysregulated neuroendocrine biomarker levels.

In addition to the studies already described, one stands out for its more thorough operationalization of chronic stress and ready comparability to the study here. This study is the Social Environment and Biomarkers of Aging Study (SEBAS), and it was carried out in Taiwan in 2000. Like the CRELES, the SEBAS is a large study (>1,000 participants), is nationally representative, focuses on older persons (aged 54 and older), and has collected the catecholamines and cortisol through overnight urine samples and DHEAS through

blood samples. In one study of the SEBAS by Gersten (2008b), he operationalizes the experience of stress over the life course in part through the experience of such events as being widowed, living alone, and lack of group participation, as well as through respondents' report of stress over their family's work situation, health situation, marital situation, and other domains. Gersten fails to find a link between these stressors and the neuroendocrine markers analyzed in an index. This finding is supported by Dowd and Goldman's analysis (2006) of the association between AL biomarkers and levels of education and income in the SEBAS. Glei and others (2007) and Goldman and others (2005) also investigated the connection between types of stress and AL levels in the SEBAS and find mixed results (although key parts of their analysis do not break up the findings by individual biomarkers or physiological systems, and so it is difficult to directly compare their results to the ones in this article).

Study Limitations

One limitation of the survey analyzed here is the degree of proxy respondents (about 25%). This drawback is mitigated, however, by respondents' high response rates, both in agreeing to take part in the interview portion (96%) and further willingness to give urine and blood samples (92% and 95%, respectively). For comparison, consider that for the SEBAS survey 92% gave interviews and 68% of these participants consented to the clinical examination (Goldman et al., 2003).

As respondents in the CRELES were aged 60 and older, another limitation of the present study is respondents' ability to remember events early in life. This issue may be most relevant for the questions inquiring about health problems in childhood and adolescence. It may be the case that respondents did experience the health problems asked about by surveyors but did not know or remember the names of those problems. Imprecise recall seems less of an issue, however, for questions probing economic deprivation early in life, as it seems likely that respondents would be able to remember everyday events such as whether they grew up in a house with electricity, an indoor toilet, and whether they slept in a bed with others.

As mentioned in the beginning, a further weakness of the present study is that (except for a question about self-assessed economic situation), the study does not probe respondents' subjective interpretations of their life history. Although we assume, for instance, that living alone is likely to be more stressful than not for most of the participants living alone, this may not indeed be the case. Nevertheless, the emotional response to certain human experiences,

like the grieving involved in the loss of a child or spouse, seem close to being "universal," and so it is still surprising that a number of variables that we investigated were not associated with our measure of physiological dysregulation. In the case of losing a spouse, not only is the loss itself psychologically difficult to deal with, but the loss could very well also result in future reduced instrumental and emotional support, thereby increasing stress levels for the widow or widower further.

Because one of the main aims of using biomarkers in a study, such as the one here, is to uncover the precise physiological mechanisms that underlie associations between social factors and health, it is reasonable to ask whether the independent variables we used in the analysis are indeed correlated with important health endpoints. To shed light on this question, as well as provide some extra evidence that the independent variables we chose were indeed indicators of adversity, we ran additional analyses in which a variety of health outcomes were dependent variables and the independent variables were the ones used in this article. We investigated the following health endpoints: self-rated health, physical frailty, ability to perform activities of daily living (ADL) and instrumental activities of daily living (IADL), cognitive disability, and depressive symptoms.[4] The results of these additional analyses are clear: A number of the independent variables used in this article are consistently and strongly related to the health measures just mentioned.[5] The variable most strongly and consistently related to the health endpoints was the cumulative adversity measure that was correlated with each of the five health outcomes in the expected way (i.e., a greater number of stressors was associated with worse health) and had *p* values ranging from less than .001 to .006.[6]

To conclude, this is the first article to use data from the CRELES, a nationally representative survey of older persons in Costa Rica, to attempt to link measures of emotional, social, and material resources (as well as negative life events and demands) to measures of physiological dysregulation. The negative findings in this article raise doubts about a key assumption of the allostatic framework—that resting levels of the neuroendocrine markers become dysregulated through stress experienced over the life course.

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Notes

1. We confirmed that the missingness was not systematic by creating a dummy variable for whether respondents' urine samples met the quality standards or not (for all those who gave samples). This dummy variable was then regressed on demographic characteristics (i.e., age, gender, educational level, rural residence, and immigrant status), and we examined results for both individual variables and tests of joint significance.
2. For example, the sample size of the CRELES for those with complete data on DHEAS, cortisol, epinephrine, and norepinephrine levels is 1,332, which is larger than that of comparable data for the SEBAS (n = 1,020, approximately; Gersten, 2008) and the MacArthur studies (n = 870, approximately; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997).
3. Unlike the cutoff approach, an index using the z score method allows for unequal weighting of the biomarkers (e.g., a combined z score of 3 could stem from being 2 SDs above the mean for cortisol, 1 SD above the mean for epinephrine, and the mean for the other two markers). The combined z score is again the dependent variable in OLS regressions and can range from 0 to no predetermined upper limit.
4. We chose these measures because they represent a wide variety of health outcomes (i.e., physical, cognitive, and psychological ones) and are based on self-report (e.g., self-rated health), answers to established scales (e.g., Yesavage's symptoms of depression), and survey-administered tests (i.e., the physical-frailty measure is based on performance on five separate physical tasks, including grip strength, pulmonary peak flow, and chair stands). In operationalizing our health measures, we follow the methods outlined by Rosero-Bixby and Dow (2009), whose work also analyzes the CRELES data set.
5. For example, when using all available data and holding all other variables constant, low religious attendance was strongly related to physical frailty (p = .001), difficulty performing ADL and IADL (p = .004), poor self-rated health (p = .091), and depression (p =.001). In the same models, economic deprivation early in life was strongly associated with depression (p = .055) and poor self-rated health (p = .001). As might be expected results were similar, although attenuated when the sample was limited to those with complete data for cortisol, DHEAS, epinephrine, and norepinephrine (i.e., those respondents included in the NAL measure presented in the text).
6. Again, results were similar although attenuated for this relationship when the sample was limited to those with complete data for cortisol, DHEAS, epinephrine, and norepinephrine.

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