Stressors over the life course and physiological dysregulation in Costa Rica

Omer Gersten[1] and Will Dow[2]

March 6, 2008

Draft: Submission for 2008 PAA conference in New Orleans (Oral presentation in Session 95: Biodemographic perspectives on early life influences on later life health)
Please do not distribute/Contact first author for latest draft of paper before citing

---

Acknowledgements: This research was generously supported by a grant from the MacArthur Foundation.

[1] Author for correspondence. Institute of Sociology, Academia Sinica, Number 128, Section 2, Academia Road, Nankang, Taipei, Taiwan, 11529. E-mail: omer@gate.sinica.edu.tw. Phone: 886-2-2652-5127. Fax: 886-2-2652-5050. Web: http://idv.sinica.edu.tw/omer.
[2] School of Public Health, University of California at Berkeley.

Abstract

Allostatic load (AL) theory purports that stress experienced over the entire life course exacts a cumulative, physiological toll on the body which eventually contributes to poor health. Although mounting evidence indicates that elevated levels of AL (as measured by dysregulated physiological systems) is a risk factor for poor health, it is not yet clear whether those same elevated levels are due to stressor exposure. Thus, in order to better understand the connection between stressor exposure and AL levels, the paper here, using a new, nationally representative study conducted in Costa Rica, explores the link between a number of different potentially important life stressors (with attention to those experienced early in life) and neuroendocrine system function. The main finding of this paper is that there is little association between the life stress indicators and risky levels of the neuroendocrine biomarkers. This result is consistent with a growing literature that suggests that neuroendocrine system dysregulation stems from sources other than stressor exposure.

Keywords

Life course, stress, allostatic load (AL), neuroendocrine allostatic load (NAL), health, Costa Rica

Introduction

At least two important testable hypotheses stem from the allostatic framework. One is that physiological dysregulation (or allostatic load) is the result, over extended periods of time, of repeated activation of the body's adaptive processes in response to challenge. Another is that allostatic load (AL) is a risk factor for poor health. Of these two hypotheses, far more support has been found for the latter. For instance, using the MacArthur studies, Seeman and others (1997) found that high AL at baseline predicted greater cognitive and physical declines and earlier mortality over the study period, and work by Goldman and others (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, both Gersten (forthcoming) and Glei (working paper) were largely unsuccessful in linking various measures of stress experienced over the life course (e.g. widowhood, living alone, financial strain, subjective reports of chronic stress) to riskier AL levels. In an attempt to further investigate the level of supportive evidence for the more questionable hypothesis (i.e. that markers of life history stress are correlated with higher levels of AL), the paper here will analyze a new, nationally representative data set from Costa Rica that has incorporated biomarkers into a more traditional social survey.

The data that will be analyzed in this paper comes from the CRELES, which obtained information from older Costa Rican men and women in 2004-2006 (in the first wave of data collection). Much of the data was meant to be comparable to other studies that have investigated AL (such as the Taiwanese SEBAS), and thus the CRELES has obtained many of the same

biomarkers traditionally used to measure load. One drawback of the CRELES is the lack of questions that probe subjective levels of stress. A strength of the survey, however, is its collection of a number of indicators of stressful life events, especially those occurring in early childhood. 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 and 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 challenges over the life course (McEwen, 1988; Timiras, 2003). Further, AL is thought to develop in a number of different and important physiological systems, including those of the metabolic, cardiovascular, and neuroendocrine systems (McEwen, 1988; Timiras, 2003). The paper 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 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 construct. Second, despite the recent inclusion of neuroendocrine markers in large-scale studies, the markers have been shown to predict a number of health outcomes, including more rapid decline in physical and cognitive function, greater incidence of cardiovascular disease, and earlier mortality (Goldman et al., 2006, Karlamangla et al., 2005; Seeman et al., 2001). 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. More specifically, from a

physiological perspective, it can be difficult to interpret a score from the construct that includes such vastly different markers. Further, it is often unclear which system, if any, is driving an overall pattern of the construct. Thus, for some of the above reasons, this paper will focus on analyzing four neuroendocrine biomarkers (i.e. cortisol, DHEAS, epinephrine, and norepinephrine) that represent function at a similar level of biological abstraction.

Data and Methods

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 (working paper)). The survey is nationally representative of those 60 and older in the non-institutionalized population, and the CRELES drew its sub-sample 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 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 picked up the urine, drew blood samples, and took anthropometric (e.g. height

and weight) measures. The blood and urine samples were used to produce a panel of physiological measurements including more traditional markers such as total and HDL cholesterol and less traditional markers such as epinephrine and cortisol.

Of survivors who could be located and were initially contacted for inclusion in the 2004-2006 CRELES, 96% gave interviews. Of these participants, 95 and 92% gave blood and urine samples, respectively, for a total of XXX respondents. In about 25% of all cases a proxy (most often the respondent's son or daughter) helped answer some questions for the respondents. The survey over-sampled those 71 years and older and urban residents (**Did the CRELES oversample any group?**).

Dependent variable

The neuroendocrine biomarkers

In this paper we focus on cortisol, DHEAS, epinephrine, and norepinephrine, a physiologically coherent class of markers representative of the neuroendocrine stress response (Sapolsky 2004; Cohen et al. 1995; Crimmins and Seeman 2001). The measure used here based on these markers is called NAL, for neuroendocrine allostatic load, and has been discussed in detail elsewhere (Gersten, forthcoming). Among NAL's greatest advantages is its interpretability that stems from grouping markers of a similar level of biological abstraction. 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 (Sapolsky 2004; Cohen et al. 1995; Crimmins and Seeman 2001). 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 (Sapolsky 2004; Cohen et al. 1995; Crimmins and Seeman 2001).

Measurement of biomarkers

The survey attempted to capture basal levels of the neuroendocrine biomarkers and to this end biological materials were collected in the participants' homes under non-stress conditions. Three of the four markers were collected in urine samples and thus the samples represent integrated, in contrast to point-in-time, measures. More specifically, for cortisol, norepinephrine, and epinephrine, respondents were asked to void urine at 6pm, which was discarded, and to collect all subsequent samples until 6am the following day. 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 fasted from 6 p.m. onwards until a study affiliate came to their home to collect the urine sample, and during the same day blood was also drawn. The amount of DHEAS in the body was determined through the blood sample.

Independent variables

Most of the independent variables used are straightforward to interpret, although some of the following require explanation. Wealth is determined by first creating an index based on a number of measures that include...

Other independent variables serve as controls. Since levels of the neuroendocrine biomarkers can be influenced by a wide variety of factors independent of stress (Gersten, 2005), all models control for variables pertaining to diet, exercise, smoking, alcohol consumption, and medication use. CONTROL FOR HEALTH STATUS?

Methods

Biomarker index scoring

The most popular approach to operationalizing AL has been to create a score that gives one point for every biomarker for which the subject can be considered at higher risk (i.e. the elevated risk zone approach). The literature most often represents high risk by greater values for cortisol, epinephrine, and norepinephrine, and lower values for DHEAS; this convention is followed here. Since 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. 10^{th}, 25^{th}, 75^{th}, 90^{th}). Since subjects can be assigned 1 point on four biomarkers if they have high risk values, NAL scores can range from 0–4.

The NAL score is the dependent variable in various regressions (i.e. linear, ordered logit) and is scored using different cut-off points (i.e. 10^{th}, 15^{th}, 25^{th}, 75^{th}, 85^{th}, 90^{th}). See Table 1 for descriptive statistics and cut-points for the neuroendocrine biomarkers. Additionally, a summed z-score is created for respondents, which is the total number of standard deviations from the mean in the direction of high risk for each biomarker. Unlike the cut-off 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 measures). The combined z-score is again the dependent variable in a linear regression and can range from 0 to no pre-determined upper limit.

Software, weights, and sex stratification

All analysis is carried out using STATA version 8.0 (StataCorp 2003). The bivariate and multivariate analysis use weighted data. Because of potentially important sex differences stemming from biological, psychological, and social factors that could in the end affect biomarker levels, analysis of stress reporting, duration, and the multivariate analysis is conducted separately by sex.

Results

Table 1 depicts descriptive statistics (of the entire, unweighted sample) for variables that are used in this analysis. One of the things to note in the table is the relatively low levels of education of those in this sample, with 70% not having completed their primary education (i.e. having less than six years of schooling). Also striking is the percent of respondents who have had at least one of their children die and the percent of respondents who have grown up without a biological father (45% and 22%, respectively). Table 1 also reveals that religion is important in the lives of many older persons in Costa Rica, with nearly 45% reporting going to church one or more times a week. It is also worth observing that 39% 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.

Descriptive statistics for the childhood and adolescence economic deprivation and health status indices are presented in Table 2. As can be seen from the table, most of the respondents did not grow up in a home that had electricity and more than a majority did not wear shoes regularly while growing up. Few respondents reported having tuberculosis, rheumatic fever, or poliomyelitis when younger, but one in ten reported experiencing malaria or asthma/chronic bronchitis.

Table 3 presents estimated regression results for different models with NAL as the dependent variable. A key finding from this table is the consistency and strength of the relationship between NAL and both age and female sex. Surprisingly, practically every stressor examined was not associated with NAL in the expected way. Most congruent with expectation was the positive correlation between having at least one child who had died (controlling for number of children born) and NAL, although this relationship was not statistically significant (p-value = 0.114).

To do:

1. Create Table 4, which will present correlations between NAL and stress indices (counts of number of stressors experienced), in contrast to the correlation between NAL and individual stressors, as presented in Table 3.

2. Examine whether length of widowhood (in years) is correlated with NAL.

3. Examine whether spousal characteristics such as poor spousal health and low spousal education is correlated with NAL.

4. Experiment with whether different cutpoints in relationship to scoring NAL alters the results in any important way.

(Preliminary) Conclusion

- To date, most studies (including this one) have found little evidence linking risky baseline neuroendocrine levels with stressful life events (e.g. social status, widowhood, living alone).

- Future studies should attempt to measure stress experienced over the life course more comprehensively (e.g. major life events, traumas, perceived stress, and daily hassles).

- Future studies should also measure neuroendocrine biomarkers more comprehensively (e.g. on multiple days over the course of two or more weeks, take multiple salivary cortisol measures over a single day, measure reactivity to stressors and return to baseline levels).

References

Cohen S, Kessler RC, Gordon LU. Strategies for measuring stress of psychiatric and physical disorders. In: Measuring stress: a guide for health and social scientists. Cohen S, Kessler RC, Gordon LU, eds. 1995. New York: Oxford University Press, pp. 3-26.

Crimmins E, Seeman T. Integrating biology into the study of health disparities. In: aging, health, and public policy: demographic and economic perspectives. Linda J. Waite, editor. 2004. Population and Development Review, 30:89-107.

Crimmins E, Seeman T. Integrating biology into demographic research. In: Cells and surveys: should biological measures be included in social science research? Finch CE, Vaupel JW, Kinsella K, eds. 2001. Washington, DC: National Academy Press, pp. 9-41.

Day TA. Defining stress as a prelude to mapping its neurocircuitry: no help from allostasis. Prog Neuropsychopharmacol Biol Psychiatry. 2005 Dec;29(8):1195-200.

Gersten O. Bridging the biological and social worlds: neuroendocrine biomarkers, social relations, and the costs of cumulative stress in Taiwan. 2005. Ph.D. dissertation: UC Berkeley.

Gersten O. (forthcoming). Neuroendocrine biomarkers, social relations, and the costs of cumulative stress in Taiwan. Social Science and Medicine.

Glei, Dana A. (working paper). Do chronic stressors lead to physiological dysregulation? Testing the theory of allostatic load. Office of Population Research, Princeton University: Working paper series (working paper no. 2007-01). Accessible at: http://opr.princeton.edu/papers/

Goldman, N., Glei, D. A., Seplaki, C., Liu, I-W., & Weinstein, M. (2005). Perceived stress and physiological dysregulation in older adults. *Stress, 8*(2), 95-105.

Goldman, N., Turra, C. M., Glei, D. A., Lin, Y.-H., & Weinstein, M. (2006). Physiological dysregulation and changes in health in an older population. *Experimental Gerontology, 41*(9), 862-870.

Karlamangla AS, Singer BH, Greendale GA, Seeman TE. Increase in epinephrine excretion is associated with cognitive decline in elderly men: MacArthur studies of successful aging. Psychoneuroendocrinology. 2005 Jun;30(5):453-60.

McEwen BS. Protective and damaging effects of the mediators of stress and adaptation: allostasis and allostatic load. In: Allostasis, homeostasis, and the costs of physiological adaptation (Schulkin J, ed.). 2004. Cambridge University Press.

Rosero-Bixby, L. (working paper). Biomarkers in a survey on aging in Costa Rica.

Sapolsky RM. Why zebras don't get ulcers, 3rd edition. 2004. New York: Henry Holt & Co.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation - allostatic load and its health consequences. MacArthur studies of successful aging. *Archives of Internal Medicine, 157*(19), 2259-68.

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences of the United States of America, 98*(8), 4770-5.

Seeman, T. E., Glei, D., Goldman, N., Weinstein, M., Singer, B., & Lin, Y.-H. (2004). Social relationships and allostatic load in Taiwanese elderly and near elderly. *Social Science & Medicine, 59*(11), 2245-57.

StataCorp. Stata statistical software: release 8.0. 2003. College Station: Stata Corporation.

Timiras PS. The adrenals and pituitary. In: Physiological basis of aging and geriatrics, 3rd edition. Timiras PS, ed. 2003. Boca Raton: CRC Press, pp. 167-88.

Cassio M. Turra, Noreen Goldman, Christopher L. Seplaki, Dana A. Glei, Yu-Hsuan Lin, Maxine Weinstein. (2005). Determinants of mortality at older ages: the role of biological markers of chronic disease. Population and Development Review 31 (4), 675–698.

Table 1 Descriptive statistics for the dependent and independent variables used in the analysis -- sample population, Costa Rica (ages 60 to 110, both sexes combined, years 2004-2006)

Variables	% or Mean (SD)	Range	N
Dependent			
Neuroendocrine allostatic load (NAL)*	0.99 (1.02)	0-4	1335
Independent			
Demographic			
Age	76.5 (10.3)	60-110	2827
Female sex	54%	--	2827
Low education (< 6 years)	70%	--	2827
Urban residence (v. rural)	51%	--	2827
Immigrant (v. native born)	6%	--	2817
Economic resources			
Household wealth**	2.02 (0.62)	1-3	2780
Spousal characteristics			
Low education (< 6 years)	68%	--	2827
Serious health problem	39%	--	1402
Social deprivation			
Currently unmarried (v. curr. married)	50%	--	2817
Lives alone	12%	--	2823
Low church attendance (< weekly)	56%	--	2822
Loss			
No. of children who have died (>= 1)	45%	--	2818
Widowed (v. currently married)	39%	--	2311
Length of widowhood (years)***	15.9 (13.4)	0-70	785
Early childhood conditions			
Maternal age at death	73.9 (18.1)	17-115	2302
Low maternal education (no education)	49%	--	2827
Lived without biological father	22%	--	2114
Poor health (>= 1 health problems)	23%	--	2083
Economic deprivation index****	2.2 (1.3)	0-4	2103

Note: Tabulations based on unweighted data.
* Respondents received one point toward their neuroendocrine allostatic load (NAL) score for each biomarker which had a "high-risk" value (i.e. a value in the bottom 25% for DHEAS and top 25% for cortisol, epinephrine, and norepinephrine).
** High wealth is coded as three and low wealth is coded as one.
*** Only includes the widowed respondents.
**** More severe economic deprivation is represented by higher values on this index.
Source: Authors' tabulations based on the 2004-2006 CRELES (Rosero-Bixby, working paper).

Table 2 Descriptive statistics for the childhood and adolescent economic deprivation and health status indices – sample population, Costa Rica (ages 60 to 110, both sexes combined, years 2004-2006)

Variables	Percent %
Economic problems	
Home did not have a bathroom or latrine	28
Home did not have electricity	70
Slept on the floor or with others in a bed	54
Did not wear shoes regularly	64
Number of reported economic stressors	
0	14
1	15
2	25
3	29
4	16
Health problems	
Tuberculosis	0.38
Rheumatic fever	2
Poliomyelitis	0.24
Malaria	13
Asthma or chronic bronchitis	10
Number of reported health stressors	
0	77
1	21
2	2
3	0.10

Note: Tabulations based on unweighted data.
Source: Authors' tabulations based on the 2004-2006 CRELES (Rosero-Bixby, working paper).

Table 3 Estimated regression results from different models with neuroendocrine allostatic load (NAL) as the dependent variable, Costa Rica (ages 60 to 110, both sexes combined, years 2004-2006)*

Dependent variable: NAL**	Model 1	Model 2	Model 3	Model 4	Model 5
Independent variables					
Demographic					
Age	**0.02 (0.000)**	**0.02 (0.000)**	**0.03 (0.000)**	**0.02 (0.000)**	**0.02 (0.000)**
Female sex	**0.41 (0.000)**	**0.38 (0.000)**	**0.40 (0.000)**	**0.40 (0.000)**	**0.39 (0.000)**
Low education (< 6 years)	-0.09 (0.185)	--	--	--	-0.07 (0.334)
Household wealth	0.06 (0.143)	--	--	--	0.08 (0.264)
Urban residence (v. rural)	-0.11 (0.232)	--	--	--	-0.12 (0.206)
Immigrant (v. native born)	-0.18 (0.143)	--	--	--	-0.19 (0.162)
Social deprivation					
Currently unmarried (v. curr. married)	--	-0.10 (0.187)	--	--	-0.01 (0.915)
Lives alone	--	0.03 (0.754)	--	--	0.08 (0.493)
Low church attendance (< weekly)	--	0.01 (0.526)	--	--	-0.00 (0.974)
Loss					
No. of children who have died (>= 1)***	--	--	0.09 (0.205)	--	0.12 (0.114)
Early childhood conditions					
Maternal age at death	--	--	--	0.00 (0.153)	0.00 (0.191)
Low maternal education (no education)	--	--	--	-0.07 (0.317)	-0.10 (0.198)
Lived without biological father	--	--	--	-0.01 (0.927)	0.01 (0.905)
Poor health (>= 1 health problems)	--	--	--	-0.13 (0.084)	-0.14 (0.055)
Economic deprivation index	--	--	--	0.02 (0.557)	0.02 (0.570)
Constant	**-1.02 (0.001)**	**-0.84 (0.004)**	**-1.01 (0.000)**	**0.70 (0.000)**	**-0.96 (0.023)**
N	1320	1333	1331	932	925
R^2	0.096	0.093	0.096	0.077	0.0928

Note: * The regression coefficients are unstandardized and p-values are inside the parentheses. All regressions control for alcohol consumption, smoking, and medication use.
** NAL ranges from 0 to 4, with 4 representing highest risk.
*** Regressions with this variable in the model also control for total number of children ever born.
Source: Authors' calculations based on the 2004-2006 CRELES (Rosero-Bixby, working paper).