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Perceived Stress and Physiological Dysregulation

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Noreen Goldman
Princeton University

Dana A. Glei
Georgetown University, Washington, D.C.

Christopher Seplaki
Princeton University

I-Wen Liu
Center for Population and Health Survey
Department of Health, Taiwan, ROC

Maxine Weinstein
Georgetown University, Washington, D.C.

Correspondence to: Noreen Goldman, Office of Population Research, Princeton University,
243 Wallace Hall, Princeton, New Jersey, 08544-2091. Phone: 609-258-5724. Fax: 609-248-1039.
E-mail: ngoldman@princeton.edu

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ABSTRACT

We use a population-based representative sample of older Taiwanese to investigate links between perceived stress and a broad set of biological measures. These biomarkers were collected at a single time (2000) and reflect SNS-activity, HPA-activity, immune function, cardiovascular response, and metabolic pathways. We model the relationship between measures of perceived stress and (1) both high and low values for each of 16 individual biological indicators; and (2) a measure of cumulative physiological dysregulation based on the full set of biomarkers. We consider two measures of perceived stress, one derived from the 2000 interview and a second based on data from three interviews (1996-2000). Age and sex-adjusted models reveal significant associations between measures of perceived stress and extreme values of cortisol, triglycerides, IL-6, DHEAS and fasting glucose. Numerous biomarkers examined here, including those pertaining to blood pressure and obesity, are not significantly related to perceived stress. On the other hand, the measure of cumulative physiological dysregulation is associated with both the level of perceived stress at a given time and to a longitudinal measure of perceived stress. Some results suggest that the relationship between level of perceived stress and physiological response is stronger for women than men.

INTRODUCTION

The notion that our interpretation of events is crucial to our emotional and physiological response to them has a long history. Despite the recognition that perception matters, the links between perceived stress and biological indicators of adverse health outcomes remain less well documented than those between experimental or self-reported "objective" stressors and these biological parameters.

Exposure to stress has both immediate and long-term effects on physiology. Our focus in this paper – the longer-term consequences of stressful experience – are the foundation of the theory of allostatic load (McEwen, 2002; McEwen & Stellar, 1993), which describes how an individual's biological response to stressors over time results in dysregulation of multiple interrelated physiological systems. Over the long-term, this disruption is thought to give rise to baseline levels of biological parameters that are outside of the optimal range, and ultimately to poorer health. Because the physiological systems and the resulting imbalances are interconnected, the theory implies that, in addition to examining individual biological markers, studies of the stress response need to consider a multisystem measure of physiological dysfunction or allostatic load. An initial operationalization of allostatic load based on 10 biological markers and several more recent variants have been shown to be related to diverse health outcomes, including cognitive and physical functioning, cardiovascular disease and mortality (Karlamangla *et al.*, 2002; T. E. Seeman *et al.*, 1997; T. E. Seeman *et al.*, 2001; Seplaki *et al.*, 2004b).

In most studies, the definition of stressful events is defined by the researcher without reference to the individual's interpretation of the event, yet nearly all models of stress and disease acknowledge that the individual's subjective appraisal of the event and evaluation of potential threats affect the stress response (Cohen *et al.*, 1997; Kristensen, 1996; Schwartz *et al.*, 1996). While some situations are generally viewed as threatening to almost everyone, others depend on such factors as individual personality, personal experiences, assessments of resources, coping mechanisms, and available social support (Schwartz *et al.*, 1996; Biondi & Picardi, 1999). Yet, despite the theoretical motivation for focusing on individuals' perceptions of stressful experiences, investigations of the effects of perceived stress on physiological parameters remain scarce and the findings are often conflicting.

Most studies of the cumulative effects of stress – whether perceived or objective – focus on expected *elevations* of physiological response. However, both elevated and blunted responses to stress have been documented (Biondi & Picardi, 1999; Björntorp & Rosemond, 1999; Black & Garbutt, 2002; Clauw & Chrousos, 1997; Heslop *et al.*, 2001; Suter *et al.*, 1997). Heslop et al. (2001) for example, find the expected positive association with cholesterol, but a negative association between perceived stress and both diastolic blood pressure and BMI. Other studies find blunted HPA-axis function among persons who experience long-term stress such as war veterans and those in chronic pain (Green *et al.*, 1992; Kristenson *et al.*, 1998; Yehuda *et al.*, 1991). Some investigations have failed to find any significant association between perceptions of stress and biological markers of the stress response. Suter et al. (1997) report an inverse relationship between perceived stress and systolic blood pressure but find no relationship with diastolic blood pressure, while Caputo et al. (2000) report that perceived stress did not provide additional explanatory power to a model of either systolic or diastolic blood pressure. Given theoretical, as well as empirical, arguments suggesting that either arousal or inhibition of the stress response may result from a stressor (McEwen & Stellar, 1993; Schwartz *et al.*, 1996), it is essential to consider both high and low levels of biological indicators as potential responses to stress.

Perceptions of stress and responses to them may differ between men and women (Cohen *et al.*, 1997; Coleman *et al.*, 1998; Geary & Flinn, 2002), as may baseline levels of biological markers (Biondi & Picardi, 1999). Stress-related disorders are more prominent among women than among men (Carter-Snell & Hegadoren, 2003), but there are questions as to whether this finding may be attributable to generally higher levels of morbidity among women than men (Macintyre *et al.*, 1999). Regardless of the underlying cause or structure, these results suggest that it is important to examine the role of sex in the stress response.

The analyses reported here use a population-based representative sample of elderly Taiwanese adults aged 54 and over to examine the links between reports of perceived stress and a set of 16 biological measures that have been proposed as markers that reflect the effects of stress. Biomarkers affected by stress include cortisol, epinephrine, norepinephrine, and dopamine (Gold *et al.*, 2003; Heim *et al.*, 2002; Pike *et al.*, 1997; Sluiter *et al.*, 2000; Vanitallie, 2002), glycosylated hemoglobin and fasting glucose (Goldston *et al.*, 1995; Kelly *et al.*, 1997; Konen *et al.*, 1993; Mizock, 1995), DHEA-S (Kroboth *et al.*, 1999), IL-6 (P. Black, 2003), IGF-1 (Bernton *et al.*, 1995), cholesterol (Coleman *et al.*, 1998), body mass index (BMI) and waist-to-hip ratio (Björntorp & Rosemond, 1999; Kelly *et al.*, 1997), and – although the evidence is mixed – systolic and diastolic blood pressure (Rose *et al.*, 1998; Schnall *et al.*, 1992; Steptoe *et al.*, 1999).

These biomarkers represent sympathetic nervous system (SNS) activity, hypothalamic-pituitary-adrenal (HPA) axis activity, inflammatory response, cardiovascular response, and metabolic pathways. Following McEwen's theoretical framework of allostatic load (McEwen, 2002), we organize the 16 biomarkers into primary mediators, which operate directly on tissues and organs, and secondary outcomes, which are manifest at the system level. The primary mediators in this analysis comprise: epinephrine, norepinephrine, dopamine, cortisol, IGF-1, IL-6, and DHEAS. The secondary outcomes are: systolic and diastolic blood pressure, total cholesterol, the ratio of total to HDL cholesterol, triglycerides, fasting glucose, glycosylated hemoglobin, BMI, and the waist-to-hip ratio. We use two indexes of perceived stress: the first is derived from questions that are asked of respondents several weeks prior to the physical examination; the second is based on information collected three times over the preceding four-year period. Whereas the first measure includes a wide range of potentially stressful experiences that are likely to include both short- and long-term stressors, the second measure provides us with an indicator of chronic perceived stress.

DATA

The data for this study are based on a follow-up of the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan. This longitudinal survey began in 1989 with a national sample (including the institutionalized population) of 4049 persons aged 60 and older (response rate: 92%), and was expanded in 1996 to include 2462 persons aged 50 to 66 (response rate: 81%) (Hermalin *et al.*, 1989). Both groups of respondents were re-interviewed in 1999 (response rate: 90% of survivors from the original cohorts).

In 2000, a national sub-sample of respondents who were interviewed in 1999 was selected randomly for the Social Environment and Biomarkers of Aging Study (SEBAS). Respondents aged 71 and older and residents of urban areas were oversampled. On a scheduled day several weeks after the household interview, participants collected a 12-hour overnight urine sample, fasted overnight, and visited a nearby hospital the following morning for a physical examination. During the hospital visit, medical personnel drew a blood sample and took blood pressure and anthropometric measurements. Written informed consent was obtained for participation in the interview and physical examination.

Among the 1713 respondents selected for SEBAS, 1497 provided interviews (92% of survivors) and 1023 participated in the physical examination (68% of those interviewed). Of the 474 who did not undergo the exam, 111 were not asked to participate based on specified exclusion criteria (i.e., living in an institution, seriously ill, on kidney dialysis, using a catheter or diaper). Disproportionately high non-participation rates were found among the healthiest respondents as well as the least healthy. The net impact of this pattern of non-participation is that persons who received the medical exam reported the same average health status (measured on a five-point scale) as those who did not. In addition, although respondents over age 70 were less likely than younger persons to participate, sex and measures of socioeconomic status were not significantly related to participation. These results suggest that, in the presence of controls for age, estimates derived from the medical exam portion of SEBAS are unlikely to be seriously biased (Goldman *et al.*, 2003).

Among participants, compliance with the clinical protocol was extremely high: almost all participants followed the urine protocol and provided a suitable blood sample. Ten participants were excluded from the analysis because of missing data on one of the biomarkers. Another 20 were excluded because a proxy completed the 2000 interview and four were excluded because of missing data on perceived stress in 2000. Thus, the analysis sample includes 989 participants. For analyses including longitudinal measures of perceived stress, an additional 23 cases were dropped because they were not interviewed in 1996 and 33 cases were excluded because a proxy completed either the 1996 or the 1999 interview, yielding an analysis sample of 933.

MEASURES

Biological Measures of the Stress Response

All 16 biomarkers examined in this study come from the physical examination and blood and urine collection undertaken in 2000 as part of SEBAS. Blood and urine samples were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to the routine standardization and calibration tests performed by the laboratory, duplicate samples for 10% of specimens were submitted to UCL and to Quest Diagnostics in the US for analysis. Data from these duplicates indicate high inter- and intra-lab reliability, with intraclass correlations of 0.80 or higher for duplicates sent to UCL and inter-lab correlations of 0.76 or higher between results from UCL vs. Quest Diagnostics.

Epinephrine, norepinephrine, cortisol, and dopamine measurements based on the 12-hour overnight urine sample provide integrated values of overnight secretion of these biomarkers; these biomarkers are measured in μg/g creatinine to adjust for body size. Measures of IGF-1, IL-6, DHEAS, total cholesterol, HDL cholesterol, triglycerides, glucose, and glycosylated hemoglobin were obtained from a fasting blood sample collected when the participants arrived at the health clinic for their physical examination. Information about the assays and sensitivity values used for these measures is provided in Seeman *et al.* (forthcoming).

Systolic and diastolic blood pressures (in mmHg) were calculated as the average of two seated blood pressure readings (one minute apart) that were taken at least 20 minutes after the respondent arrived at the hospital using a mercury sphygmomanometer with the respondent in a seated position. Body mass index is defined as weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). Waist/hip ratio (WHR) was calculated based on waist circumference (measured at its narrowest point between the ribs and iliac crest) and hip circumference (measured at the maximal buttocks) (Lohman *et al.*, 1988).

Because the literature suggests that low, as well as high, values of some biomarkers may be associated with health risks and with stressors, we divide biomarker values into three categories: the lowest 10%, the middle 10-90%, and above 90%. For two of these 16 biomarkers, epidemiological research identifies elevated health risk with only one end of the distribution; in these cases, we dichotomize the values to reflect the single relevant tail: DHEAS (< 10%) and the ratio of total to HDL cholesterol (> 90%). We use a common set of cutpoints for men and women and take account of sex differences in the distribution of biomarkers by adjusting for sex in the statistical models. These cutoff points are intended to capture values outside of normal operating ranges rather than clinical values (indeed, clinical cutpoints for some of the biomarkers have never been established). A recent analysis demonstrates that many of the associations between these biomarkers and profiles of health and function are robust to use of an alternative set of cutoff points (the 25^{th} and 75^{th} percentiles; Seplaki *et al.*, 2004a).

Table 1 provides the 10^{th} and 90^{th} percentile values for each biomarker. For IL-6 and epinephrine, a large number of readings fell below assay sensitivity (0.1 pg/mL for IL-6 and 2µg/L for epinephrine) so the lowest category (denoted by "B.A.S.") represents "below assay sensitivity."

Cumulative Physiological Dysregulation

In addition to analyzing individual biomarkers, we consider a measure of cumulative physiological dysregulation based on the biomarkers shown in Table 1. The conventional measure of cumulative physiological dysregulation, typically referred to as an index of *allostatic load*, is a count based on a single tail of risk for each of 10 biomarkers (Seeman *et al.*, 1997; 2001). In this paper, we use a modified version of the conventional index that (1) incorporates additional biomarkers believed to be associated with the stress response (including measures of immune function) and (2) identifies risk in both the low and high tails where appropriate. The resulting 16-item measure has been shown to predict several health outcomes better than the conventional 10-item measure (Seplaki *et al.*, 2004a).

Our measure is constructed as a count of the number of biomarkers, among the 16 presented in Table 1, for which the individual's value is below the 10th percentile (or below assay sensitivity in the case of epinephrine and Il-6) or above the 90th percentile (based on the cutpoints shown in Table 1). Although the score has a theoretical range of 0 to 16, the observed score ranges between 0 and 10, with a mean of 3.4 (Table 1).

Perceived Stress

We consider two measures of perceived stress in daily life. The first is based on detailed interview data collected in 2000 about numerous sources of perceived stress and anxiety. Although it covers what are likely to be some chronic sources of stress for the respondent, the fact that it is derived from a single round of data limits its interpretation as a measure of chronic perceived stress. The second measure is based on information in the 1996, 1999, and 2000 waves of the survey. Whereas the earlier waves of the survey have less detailed information about perceived stress than the 2000 interview, their inclusion in this second measure permits us to identify individuals who perceive moderate or high levels of stress over at least a four-year period.

The level of perceived stress in 2000 is based on the respondent's report of whether each of eight situations "makes you feel stressed or anxious." Four of these situations refer to the respondent's life (own health, financial situation, job, and getting along with family members), and an additional four items pertain to his or her family (the family's or children's health, financial situation, job, and marital situation). Each item is coded on a three-point scale: no (0), some (1), a lot of stress (2). If the respondent reported an item to be “not applicable,” it is assigned a value of 0. The index is calculated by summing across all items if there are at least six valid items: if one or two items are missing, the score is based on all valid items. The potential range for this index is 0 to 16 and the observed range is 0 to 15. Factor analysis indicates that all items load onto one primary factor (eigenvalue=2.73), with an alpha reliability of 0.79.

The measure of cumulative perceived stress is based on questions from three interviews (1996, 1999, and 2000). In 1996, respondents were asked whether work, family or daily life brings stress and worries, with response categories: “don’t feel any stress or worry at all”, “some stress and worries at times,” and “a great deal of stress and worry often.” Questions asked in 1999 were similar to those in 2000 except that there was only one question in 1999 referring to “other family members’ health, financial situation, job, marriage, etc.” making a total of five items. These items were coded and summed as described for the 2000 index (if there were at least four valid items) to create a 1999 index that varies between 0 and 10. All items load onto one primary factor (eigenvalue=1.69), with an alpha reliability of 0.72. The indexes for 1999 and 2000 were subsequently grouped into three categories with a distribution similar to that of the 1996 measure. Based on these three indexes, we constructed a dichotomous variable that is intended to capture individuals who consistently report moderate or high levels of stress over the four-year period. This measure of cumulative perceived stress identifies respondents that fall into either of the top two categories (i.e., some or a lot of stress) at all three waves (14%, n=133). If data are missing for any of the three waves, this measure is treated as missing.

Control Variables

Demographic control variables include age (in years) and sex. Age is measured as of the 2000 interview based on the respondent’s reported date of birth; the observed age range is 54 to 91 years.

STATISTICAL ANALYSIS

The statistical analysis consists of two stages. In the first, we estimate the association between the 2000 stress index and individual biomarkers. For all biomarkers except DHEAS and the cholesterol ratio, we estimate a multinomial logit model of the probability that the biomarker value falls in one of the following three categories: <10%, 10%-90%, and >90%; the middle category is the reference group. (As described above, the lowest category is "below assay sensitivity" for IL-6 and epinephrine.) For DHEAS and the cholesterol ratio, for which risk is associated with only one tail, we estimate a (binary) logit model. Each of the 16 models includes the 2000 stress index along with controls for age and sex.

In the second part of the analysis, we consider the associations between measures of perceived stress and the 16-item measure of cumulative physiological dysregulation. Here, we estimate a total of six ordinary least-squares (OLS) regression models that assess the effects of each of the two stress measures, considered separately and together, on the 16-item score. In order to determine whether the strength of these associations differs between men and women, we test interaction terms between the stress measures and sex (female). We present estimated coefficients, significance levels, R^2 values, and, where relevant, F-tests of the joint significance of the main effect and the interaction term pertaining to sex.

RESULTS

Estimated coefficients from multinomial and binomial logit models of the 16 individual biomarkers are presented in Table 2. Five of the biomarkers reveal significant associations with the 2000 stress index for at least one tail of the distribution ($p<0.05$). In all cases, the results suggest that persons with higher levels of perceived stress are more likely to have extreme (high or low) values of the biomarkers. Although much of the literature has emphasized the consequences of stress for *elevated* levels of biomarkers, only two biomarkers – cortisol and triglycerides – reveal this direction of association. Three of the biomarkers – IL-6, DHEAS, and fasting glucose – show significant associations between higher levels of perceived stress and increased relative probabilities of being in the *lowest* category. Many of the biomarkers, including those related to obesity and blood pressure, reveal no significant associations with the degree of perceived stress.

The coefficients in Table 3 are based on OLS regression models of the 16-item dysregulation score. The first two models reveal that both of the perceived stress measures are significantly related to the dysregulation index ($p<0.01$). The sizes of the respective coefficients differ substantially because of the different scales of the measures (the 2000 index ranges between 0 and 16 whereas the cumulative stress score is binary). However, estimates of standardized coefficients (not shown here) reveal similar magnitudes, whether the two stress scores are considered in a single model or in separate models. The coefficients in Model 2 indicate that individuals who perceive stress in all three waves have dysregulation scores about two-thirds of a point higher (on the 16-point scale) than their counterparts.

Models 3 and 4 reveal stronger associations between the stress measures and biological dysregulation for women than for men, but the sex difference is significant ($p<0.05$) only in the case of the 2000 stress score. In order to determine whether the two measures of perceived stress are largely redundant, Model 5 includes both variables. The results reveal that, in the presence of a given level of perceived stress in 2000, persons who also perceive stress in the earlier waves have a significantly higher dysregulation score ($p<0.05$) – by nearly half of a point. This finding persists when the 2000 stress score is specified as a set of categorical variables (results not shown). Thus, both the degree of perceived stress and the length of time during which individuals perceive stress appear to be important for biological function. The final model confirms that the sex interaction for the 2000 perceived stress score retains its significance when both stress variables are included in the model.

DISCUSSION

The results presented here identify statistically significant associations between measures of perceived stress and several biomarkers related to the stress response, including measures of HPA-activity, the immune system, cardiovascular response, and metabolic pathways. Although much of the previous literature focuses on elevated biological responses to stress, the estimates for IL-6, DHEAS and fasting glucose reveal that higher degrees of perceived stress are associated with depressed levels of these biomarkers. This inverse association with DHEAS is not surprising given a large literature relating low levels of DHEAS to poor health outcomes. However, the association between perceived stress and only very low levels of Il-6 is unexpected in light of studies that link high levels of Il-6 with stress and morbidity (Black, 2003; Anisman & Merali, 2003). At the same time, more than half of the biomarkers included in this analysis are not significantly associated with the 2000 stress index, a finding that questions the importance of many of these measures in the pathways linking stressful experiences to health. In contrast, the summary dysregulation score is significantly related to both stress measures, suggesting that the level and the duration of perceived stress relate to multisystem physiological dysregulation.

The seeming inconsistency between these two sets of results may arise for several reasons. First, despite theoretical arguments that suggest linkages between these 16 biomarkers and the stress response, only a subset of them may actually be present. There are few empirical studies that relate perceptions of stressful experience to baseline operating levels of these markers. There is a somewhat larger literature on the association between actual stressful experiences and levels of these biomarkers, but here the findings are sometimes negative or inconsistent, even in the case of well-recognized risk factors such as blood pressure and obesity (Brisson *et al.*, 2000; Caputo *et al.*, 2000; Heslop *et al.*, 2001; Rose *et al.*, 1998; Schnall *et al.*, 1992; Suter *et al.*, 1997). A second explanation relates to measurement error, which undoubtedly characterizes both the biological variables and the measures of perceived stress. Errors in the measurement of perceived stress are especially problematic because they arise from inadequacies of the survey instrument (i.e., a short battery of questions is unlikely to provide a complete assessment of anxiety in the many relevant domains of respondents' lives) as well as from inaccuracies in respondents' reports of their feelings. These measurement errors typically lead to attenuated estimates of the associations between perceived stress and the individual biomarkers. However, attenuation is less of an issue for the summary measure of physiological dysregulation, which reduces overall measurement error by combining extreme values on 16 biomarkers into a single score. A third argument derives from the theory of allostatic load, which hypothesizes that although extreme levels of individual biomarkers may fail to reveal associations with future health, the cumulative effect of these perturbations across multiple biological systems is likely to predict subsequent deteriorations in health (Karlamangla *et al.*, 2002). Similarly, one might speculate that perceived stress would have a bigger impact on multisystem dysfunction than on a single biological marker.

One of our two measures of perceived stress – the 2000 index – suggests that women are characterized by a stronger association between perceived stress and physiological response than men. There are at least two plausible explanations for this finding. The first possibility is that, among individuals who perceive a given level of stress and anxiety in their lives, women may be more likely than men to acknowledge these feelings; greater measurement error among men would attenuate the estimate of association between perceived stress and biomarkers for men. The second possibility is that women may have a greater physiological response than men to a given degree of perceived stress in their lives.

Both interpretations receive some, but far from uniform, support from earlier research. There is little discussion in the stress literature but a widespread belief in the health literature that women are more willing to report illness. Yet, Macintyre *et al.* (1999) argue that this conclusion stems largely from the absence of a gold standard for assessing the true level of symptoms and that the few studies that have attempted to compare men and women with a given health condition have found contradictory evidence for this assertion.

How likely is it that women experience a greater physiological response to perceived stress than men? Although the basic neuroendocrine stress response is believed to be essentially the same for men and women, there are undoubtedly differences that are likely to be related, in part, to sex hormone levels (Taylor *et al.*, 2000). For example, studies on laboratory rats suggest that females are more sensitive to stress and exhibit more stress-induced impairment than males because of higher estrogen levels (Shansky *et al.*, 2004). There is also some evidence suggesting that men and women respond differently to different types of stressors (e.g., women may have a greater response to emotional stress but a lesser response to achievement stress than men -- Lundberg *et al.*, 1981; Stroud *et al.*, 2002). In light of the fact that many of the perceived stress questions included in SEBAS focus on problems characterizing the family or respondents' children, it is plausible that women show greater overall physiological response. One recent study that relates high perceived stress to inhibited breathing patterns offers further support for this finding (Anderson & Chesney, 2002). This study determined that the association between perceived stress and lower breathing frequencies was more notable in women than men, a finding that suggests a potential mechanism by which chronic stress could result in hypertension, especially among women.

An important feature of the present study has been the ability to explore the associations between perceived stress and physiological responses for 1) a large set of biomarkers representing multiple physiological systems that comprise the stress response; and 2) sets of questions pertaining to perceived stress and anxiety at multiple waves. A related strength of this analysis has been the ability to examine the robustness of the findings to alternative formulations of the measures. Specifically, estimates not presented here show that the results in Table 2 remain essentially the same 1) for non-linear specifications of the 2000 perceived stress score (e.g., a set of categorical variables denoting low, moderate and high levels as well as a quadratic function); and 2) when the longitudinal measure of cumulative perceived stress, rather than the 2000 index, is tested. Other estimates reveal that the associations in Table 3 are robust to the use of alternative indexes of cumulative physiological dysfunction that are described in Seplaki *et al.* (2004a).

We have also been able to address concerns about potential endogeneity in the statistical models that stem from the possibility that the respondent's health may in itself be a potential source of stress. That is, respondents may report stress regarding their health status because they are aware of, or suffer from, their high blood pressure, cholesterol levels or obesity. The use of cross-sectional data precludes insights into the relative timing of the perceptions of stress and the respondent's physiological status. To deal with this issue, we repeated some of the analyses described above omitting respondent's health from the components of the 2000 perceived stress index (results not shown). The estimates reveal that the 2000 index remains significant in these alternative models.

There are several limitations of the present analysis. One concerns the use of medications within this older sample, many of which (e.g., hypotensive and antilipemic agents) almost certainly alter specific biological parameters. Estimates not presented here reveal that, if we exclude SEBAS respondents that report using medications for any of several cardiovascular conditions or diabetes (37% of the sample), the results for the cumulative dysregulation index and for most of the individual biomarkers remain substantively unchanged (although those for low systolic and low diastolic blood pressure become statistically significant). A second drawback is the absence of detailed data on perceived stress, particularly for earlier waves of the survey. Such information would provide a clearer distinction between acute and chronic perceptions of stress and allow us to obtain better measures of the latter. A third problem relates to measurement error in both the biological measures and the measures of perceived stress, errors which almost certainly have led to attenuated estimates of the associations. Finally, an important drawback is the restriction of the physiological measurements to a single point in time. Indeed, a possible explanation for the some of negative findings presented here is that the consequences of chronic stress may be reflected less by baseline levels of biomarkers than by the dynamics of these physiological parameters. The future availability of longitudinal information from SEBAS on biological markers will permit us to address this important issue.

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Table 1 – Descriptive Statistics* for Variables Used in Regression Models

	Mean or percent	Standard Deviation	10th percentile‡	90th percentile‡
Biological Markers				
Epinephrine (μg/g creatinine)	2.6	2.6	B.A.S.	5.6
Norepinephrine (μg/g creatinine)	21.9	9.9	11.2	34.7
Dopamine (μg/g creatinine)	221.9	1,110.2	87.4	226.7
Cortisol (μg/g creatinine)	28.6	52.6	8.7	48.0
IGF-1 (ηg/mL)	105.1	48.1	53.1	168.0
IL-6 (pg/mL)	1.8	8.2	B.A.S.	3.4
DHEAS (μg/dL)	81.2	59.1	20.9	152.4
Systolic BP (mmHg)	138.4	20.6	114	166
Diastolic BP (mmHg)	82.2	11.1	70	97
Total cholesterol (mg/dL)	200.7	39.6	153	252
Total/HDL cholesterol	4.4	1.4	2.8	6.1
Triglycerides (mg/dL)	123.4	91.0	54	204
Fasting glucose (mg/dL)	107.1	37.9	84	138
Glycosylated hemoglobin (%)	5.8	1.4	4.8	7.1
BMI	24.4	3.6	20.0	28.9
Waist-hip ratio	0.88	0.07	0.80	0.96
Cumulative physiological dysregulation score†	3.4	1.8	--	--
Measures of Perceived Stress				
Stress Index, 2000§	2	2.7	--	--
Stressed in all waves, 1996-2000 (%)	14.1	--	--	--
Control Variables				
Age in 2000	68.2	8.4	--	--
Female (%)	41.5	--	--	--

B.A.S. Denotes “below assay sensitivity”. There are a large number of values below the sensitivity of the assay for epinephrine (n=195, 20%) and IL-6 (n=321, 32%).

* All descriptive statistics are based on the sample of 989 cases, except for “stressed in all waves” which is based on the sample of 933 cases with non-missing values.

† The potential range for this summary score is 0 to 16; the observed range is 0 to 10.

‡ The cutoffs for the 10th and 90th percentile are based on the full sample of participants with valid data (ranges from 1,019 to 1,023 depending on the biomarker).

§ The potential range for this index is 0 to 16; the observed range is 0 to 15.

Table 2 – Individual Biomarkers Regressed on Perceived Stress Index (2000), Age and Sex Adjusted

	(Base category = 10th - 90th percentile)	
Coefficient for Stress Index	≤ 10th percentile	≥ 90th percentile
Primary Mediators		
Epinephrine§	0.026	-0.028
Norepinephrine	0.072+	0.064+
Dopamine	0.040	-0.019
Cortisol	0.012	0.119**
IGF-1	0.039	0.020
IL-6§	0.053*	0.008
DHEAS	0.096**	†
Secondary Outcomes		
Systolic BP	0.061+	0.035
Diastolic BP	0.027	0.029
Total cholesterol	-0.013	-0.014
Total/HDL cholesterol	‡	0.006
Triglycerides	0.065+	0.082*
Fasting glucose	0.101**	0.036
Glycosylated hemoglobin	0.004	0.030
BMI	0.027	-0.003
Waist-hip ratio	-0.006	-0.050

Note: Each row represents a separate multinomial logit model (or binary logit model for DHEAS and total/HDL cholesterol). The indicated biomarker is regressed on the 2000 stress index, age, and sex. The analysis sample includes 989 respondents from the 2000 SEBAS.
* significant at 5%; ** significant at 1%; + marginally significant at 10%
† Coded as a dichotomous variable, where 1 indicates a value ≤ 10th percentile.
‡ Coded as a dichotomous variable, where 1 indicates a value ≥ 90th percentile.
§ The <10th percentile category encompasses all values below assay sensitivity (epinephrine: 20%; IL-6: 32%).

Table 3 – Cumulative Physiological Dysregulation Score† Regressed on Measures of Perceived Stress, Age, and Sex

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Age	0.022**	0.020**	0.022**	0.020**	0.022**	0.022**
	(0.003)	(0.005)	(0.003)	(0.006)	(0.002)	(0.002)
Female	0.550**	0.562**	0.350*	0.509**	0.543**	0.352*
	(0.000)	(0.000)	(0.022)	(0.000)	(0.000)	(0.021)
Stress Index (2000)	0.090**	--	0.047	--	0.063*	0.024
	(0.000)		(0.106)		(0.010)	(0.449)
Interaction: Female X Stress Index (2000)	--	--	0.094*	--		0.090*
			(0.029)			(0.037)
Stressed in all three waves (1996-2000)	--	0.686**	--	0.509*	0.449*	0.431*
		(0.000)		(0.034)	(0.022)	(0.027)
Interaction: Female X Stressed in all three waves	--	--	--	0.362	--	--
				(0.292)		
Constant	1.568**	1.752**	1.650**	1.790**	1.518**	1.599**
	(0.002)	(0.000)	(0.001)	(0.000)	(0.003)	(0.002)
R^2	0.047	0.045	0.052	0.047	0.052	0.057
F test for both main and interaction effects			$F_{2,928}$=10.98	$F_{2,928}$=8.46		$F_{2,927}$=5.49
p-value			(0.000)	(0.0002)		(0.0042)

Note: The p-value is shown in parentheses below the coefficient. The analysis sample includes 933 respondents from the 2000 SEBAS.
* significant at 5%; ** significant at 1%
† Based on the 16 biomarkers shown in Table 2. One point is assigned for each biomarker if the value is ≤ the 10^{th} percentile or ≥ the 90^{th} percentile (exceptions: ratio of total to HDL cholesterol--only if ≥ 90^{th} percentile; DHEAS--only if ≤ 10^{th} percentile). Potential Range = 0 to 16.