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DOES EXPOSURE TO STRESSORS PREDICT CHANGES IN PHYSIOLOGICAL DYSREGULATION?

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Abstract

Background—The allostatic load framework implies that cumulative exposure to stressors results in multi-system physiological dysregulation.

Purpose—To investigate the effect of stress burden on subsequent changes (2000-2006) in physiological dysregulation.

Methods—Data came from a population-based cohort study in Taiwan (n=521, aged 54+ in 2000, re-examined in 2006). Measures of stressful events and chronic strain were based on questions asked in 1996, 1999, and 2000. A measure of trauma was based on exposure to the 1999 earthquake. Dysregulation was based on 17 biomarkers (e.g., metabolic, inflammatory, neuroendocrine).

Results—There were some small effects among men: chronic strain was associated with subsequent increases in dysregulation (standardized β=0.08, 95% CI = 0.01 to 0.20), particularly inflammation; life events were also associated with increased inflammation (β=0.10, CI = 0.01 to 0.26). There were no significant effects in women.

Conclusions—We found weak evidence that stress burden is associated with changes in dysregulation.

Keywords

stressors; psychological stress; life challenges; allostatic load; physiological dysregulation; biological markers

INTRODUCTION

The allostatic load framework proposes that repeated exposure to environmental challenges creates a cumulative cost represented by dysregulation of multiple interrelated physiological systems, which may in turn result in deterioration of health (1, 2). Although measures of allostatic load have been shown to predict mortality and other health outcomes (3), studies that have examined directly the purported link between stress burden (both life events and

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CONFLICT OF INTEREST STATEMENT

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perceived chronic strain) and multi-system physiological dysregulation (allostatic load) have yielded evidence of only a modest association (4-11).

Most of these studies evaluated physiological parameters at only one time, and none has investigated the effects of stressors on changes in physiological dysregulation over time. Cross sectional differences in physiological dysregulation are likely to be a function of numerous factors, many of which may be unobserved, that differ between individuals. Longitudinal data allow us to eliminate some of this "noise" by isolating the effect of exposure to selected stressors on subsequent within-individual physiological changes. This strategy implicitly controls for any characteristics that are stable over the period of observation (e.g., genetics, influences earlier in life) and allows us to take advantage of temporal ordering to minimize potential reverse causality.

The stress process model (12) posits that personal and social factors may have direct effects on exposure to stressors and stress-related outcomes and may also moderate the impact of stressors on outcomes. For example, social support and personal mastery may have both main effects and "stress-buffering" effects (13-15). Sex and other characteristics that reflect social status may also affect all stages of the stress process: the type and severity of stressors to which one is exposed, the availability of coping resources, and the effect of stressors on outcomes (12). Levels of biomarkers and changes in those levels with age often differ by sex, so it is important to consider whether the relationship between exposure to stressors and dysregulation varies by sex.

In this paper, we used a cohort study of older Taiwanese to investigate the effects of stressful events, trauma, and chronic strain on subsequent changes in physiological dysregulation over a six-year period. Specifically, we sought to: 1) estimate the main effect of stressors controlling for personal and social factors; 2) test whether personal and social resources moderated the effect of stressors; and 3) evaluate whether the effects differed across physiological systems (metabolic, inflammatory, neuroendocrine).

METHODS

Data

The data came from a cohort study in Taiwan, the Social Environment and Biomarkers of Aging Study (SEBAS), augmented by the 1996 and 1999 waves of its parent study, the Taiwan Longitudinal Study of Aging (TLSA). The cohort is based on a nationally representative sample, selected randomly using a multi-stage sampling design. The study is described in detail elsewhere (16, 17).

The analysis was based on 639 Taiwanese aged 54 and older in 2000 who completed a home interview and hospital-based physical examination in both 2000 and 2006; see Electronic Supplementary Material (ESM), Figure S1 for details regarding attrition. A biomarker collection in both waves included a fasting blood sample, anthropometry, blood pressure measurements, and a 12h overnight urine sample (7pm to 7am) for measurement of neuroendocrine markers.

Measures

Physiological Dysregulation—Outcome measures were based on 17 biomarkers that have been included in previous formulations of allostatic load (3, 18, 19) and have been shown by prior studies to be associated with all-cause mortality. We calculated an overall score and subscores for: 1) five risk factors that comprise the clinical criteria for metabolic syndrome—hypertension, high-density lipoprotein (HDL) cholesterol, triglycerides, waist circumference, and fasting glucose; 2) four inflammatory markers—interleukin-6, C reactive

protein (CRP), soluble intercellular adhesion molecule 1, soluble E-selectin; and 3) four neuroendocrine markers— dehydroepiandrosterone sulfate (DHEAS), cortisol, epinephrine, norepinephrine. The remaining four markers—insulin-like growth factor 1 (IGF-1), creatinine clearance, albumin, homocysteine—do not represent a common biological subsystem and thus, are not analyzed as a separate subscore.

Scores were calculated by counting the number of markers for which the respondent exhibited a high-risk level. High-risk was defined by established cutoffs for the metabolic factors and CRP (see ESM Table S1 for a list of markers and cutoffs). For all other markers —which have no generally accepted clinical cutoffs—we defined high risk based on the weighted distribution of the 2000 sample: bottom quartile for DHEAS, IGF-1, creatinine clearance and albumin; top quartile for other markers. Given the various operationalizations of allostatic load (3), we also explored the robustness of the findings to several alternative formulations.

Stress Burden—Measures of stressful life events and chronic strain were based on questions asked in 1996, 1999, and 2000. We included four potentially stressful life events (i.e., marital disruption, child death, residential move, crime/fraud victimization) and summed the number of events across all waves. The index of chronic strain was based on more subjective measures related to financial and family-related perceived stress. We computed separate indices for these two domains and summed them to get a measure of overall chronic strain. Finally, we included a measure of trauma based on exposure to the 1999 earthquake. (See ESM Table S2 for details regarding the construction of stress measures.)

Potential Confounders—Factors considered as potential confounders were sex, age, urban residence, years of education, social integration, perceived availability of social support, and personal mastery. Our index of social integration was constructed following the strategy used by Cornwell & Waite (20) to develop a social disconnectedness scale. Using 11 indicators from the 1999 interview (e.g., network size, network range, marital status, participation in social organizations; see ESM Table S3 for details), we standardized each item and calculated the mean across valid items if at least 9 items were valid (α=0.73). The index of perceived social support was based on four questions (coded 0-4) from the 1999 interview: family/friends willing to listen; family/friends make you feel cared for; satisfaction with emotional support received from family; can count on family to take care of you when you are ill. We calculated the mean across valid items if at least 3 items were valid (α=0.87). Personal mastery was based on five items (coded 0-3) from the Pearlin scale (21) asked in the 2000 interview. We calculated the mean score across valid items if at least 3 items were valid (α=0.73).

Analytical Strategy

Among the 639 respondents who were examined in both 2000 and 2006, 11% were missing at least one of the biomarkers and another 5% were missing one of the predictors, leaving an analysis sample of 539 respondents. We used multiple imputation to assess how the results might have been affected by the loss of these cases.

We examined change in physiological dysregulation using a lagged dependent variable model that regressed dysregulation in 2006 on dysregulation in 2000. This modeling strategy has the advantage of allowing the change to depend on the starting level at baseline, thus it permits floor and ceiling effects that often occur for dependent variables with a limited range. The linear regression models included a random effect for the primary sampling unit to account for the multi-stage sampling design. The unadjusted model included only the

measures of stress burden and the lagged dependent variable; the adjusted model controlled for potential confounders. Sex was tested as a potential effect modifier for the measures of stress burden in the adjusted model; we retained only interactions that were significant ($p<0.05$). Finally, to assess potential stress-buffering, we tested interactions between each stress indicator and the other personal/social variables, one at a time, in models predicting overall dysregulation.

RESULTS

The average duration between the 2000 and 2006 exam was 6.1 years. Mean levels of overall physiological dysregulation increased for men ($p<0.05$, paired t test) as the cohort aged six years, but did not change significantly for women (see ESM Table S4 for descriptive statistics). Nonetheless, the changes in dysregulation varied considerably across individuals of both sexes: about half showed at least a two point increase (31% of both men and women) or decrease (15% of men, 21% of women) in overall dysregulation. Similarly, the majority of both sexes exhibited a change in each of the dysregulation subscores.

In unadjusted models (Table 1), a larger number of life events was weakly but significantly associated with a subsequent increase in overall dysregulation, but neither earthquake exposure nor chronic strain was significant. In the adjusted model, life events and earthquake exposure were not significant, but chronic strain was weakly associated with increased dysregulation for men (standardized $\beta=0.08$, 95% CI = 0.01 to 0.20), but not for women.

Tests for stress-buffering (not shown) yielded no significant interactions: there was no evidence that education, social integration, perceived social support, or personal mastery moderated the impact of any of the stress measures on changes in overall dysregulation.

The estimates for system-level subscores (Table 1, cols. 2-5) revealed that the association between changes in dysregulation and chronic strain among men was driven primarily by effects on inflammation. Chronic strain had no significant effect on changes in metabolic or neuroendocrine dysregulation. Life events were also associated with increased inflammation, but again only in men.

We tested the robustness of the final models to the inclusion of controls for baseline health status and changes in medication use, but found little effect on the magnitude of the coefficients (see ESM). We also explored five alternative formulations for measuring dysregulation that varied in terms of the biomarkers included and the scoring method (see ESM for details). As in Table 1, the association between the measures of stress burden and changes in overall dysregulation was weak for all formulations. Regardless of the operationalization of dysregulation, the indicators of stress burden accounted for, at most, 1.4% of the variability. Finally, we used multiple imputation to re-estimate the models for the entire sample (n=639); the results were consistent with those presented here.

DISCUSSION

This study is the first to examine the determinants of *change* in physiological dysregulation, although several studies have shown a modest association between exposure to stressors and physiological dysregulation. Among older Taiwanese, chronic strain was weakly associated with subsequent changes in physiological dysregulation, but only for men. Overall, the measures of stress burden accounted for very little of the variability in dysregulation.

Allostatic-load type measures have the advantage of capturing dysregulation across multiple inter-related systems with a simple summary score; the disadvantage is that the results may

hide variation in the effects across systems (22). Most previous studies have not examined the effect of stressors on different components of overall dysregulation. Our results revealed that life events and chronic strain were associated with increased inflammation in men. None of the indicators of stress burden was significantly associated with changes in metabolic or neuroendocrine dysregulation. Given increasing recognition of the role that inflammation plays in the development of many diseases, our finding that stressors are associated with increases in inflammation among men suggests that exposure to stressors may have greater implications for the development of chronic conditions such as cardiovascular disease in men than in women.

There are several possible explanations for the weak association between stress burden and changes in dysregulation: 1) incomplete measurement of stress burden; 2) it may not be stress exposure *per se*, but how an individual reacts that matters; 3) effects are short-term and thus not observed at the end of a six-year interval; 4) other factors play a more important role. First, our measures of exposure to stressors were far from exhaustive and do not fully capture cumulative "wear and tear" over a lifetime. For example, the lack of association among women may reflect the inadequacy of our measures in capturing what may be common life challenges for women in this cohort. Given highly stratified gender roles among older generations in Taiwan, salient stressors for these women may revolve around activities related to caring for their family.

Second, the extent of exposure to stressors may be less important than other factors that determine how one responds to life challenges. Bonnano (23) argues that although a few people experience chronic effects in response to trauma or loss, others follow different trajectories such as recovery after a short-term effect, a delayed response, or in many cases, resilience. Although we did not find evidence of stress-buffering, we may not have adequately captured the personal, social, or environmental factors (or combination thereof) that predict which trajectory an individual will follow. It may be that the important issues relate to what distinguishes people who are resilient from those who exhibit adverse effects, and what strategies permit us to discriminate between different patterns of response. We measured exposure to particular life events, but not the respondent's subjective appraisal of the event (i.e., whether or not s/he considered the experience to be "stressful" or if s/he felt "worried" or "threatened" by it). Nonetheless, our measures of chronic strain represent a subjective assessment regarding the respondent's level of perceived stress related to financial and family-related issues. If it is not exposure, but rather stress appraisal that matters, then we would expect a stronger association with these measures of perceived stress yet we found that association to be weak as well. Thus, one might ask whether perceptions (subjective stress) and physiological response necessarily coincide. Is it possible for a person to show a physiological response to stressors even if s/he does not perceive him/herself to be "stressed" (or vice versa)? If so, then reports of neither the extent of exposure to stressors nor perceived levels of stress may adequately predict physiological dysregulation.

A third possibility is that stressors have only a short-term effect, at least for the biomarkers we measure. If there is no lingering effect on the long-term trajectory, then stressors prior to 2000 may have little or no incremental effect on the change in dysregulation over the subsequent six years. In fact, if the respondent is beginning to "recover," we may see a subsequent decrease in dysregulation. In the case of chronic strain, the perceived stress is likely to persist over time, but the physiological effects could be concentrated in an initial acute period. For example, economic difficulties may have a strong initial effect but as they persist over time the incremental effect may be negligible. If so, then the effect of chronic strain on subsequent dysregulation would be stronger for a person who initially had low levels of dysregulation. In auxiliary models (not shown), we tested an interaction between chronic strain and the level of dysregulation at baseline, but it was not significant.

Fourth, we must consider the possibility that something else, which may be unrelated to stress exposure, plays a crucial role. Despite claims in the allostatic load literature that chronic stressors lead to multi-system dysregulation (1-3), the contribution from stressors may be only a small part of a much broader range of individual and contextual factors.

We note several additional limitations to this study. First, our analysis was restricted to older individuals who survived to the follow-up survey. Auxiliary analyses showed no evidence that the indicators of stress burden were associated with attrition (see ESM), but it is possible that the effects of stressors would be more evident in a younger population. Second, our results may not generalize to other populations with greater exposure to stressors or weaker social networks. Third, although they reflect several major physiological systems, 17 biomarkers measured six years apart capture only a glimpse of changes in complex biological processes. In addition, levels of many of these markers vary from day to day or even hour to hour, and thus observed changes may reflect measurement error and random variation that is not substantively meaningful. Furthermore, changes in biomarker levels may be smaller or less meaningful at older ages.

Unfortunately, there is no consensus regarding the best way to operationalize allostatic load. Since the original 10-marker parameterization of allostatic load (24), new markers have been incorporated and alternative formulations have been developed in an attempt to improve the measure. For example, the formulation presented here incorporates a broader range of inflammatory markers than the measure used in a previous study based on this cohort (5). Moreover, we use established clinical cutoffs wherever available, whereas many prior studies have relied solely on distribution-based cutoffs. Such differences in operationalization make it difficult to directly compare results across studies. Thus, we explored several alternative formulations that are comparable with measures used in previous research. The main result was robust: the link between stress exposure (as measured here) and changes in physiological dysregulation was weak across each of the measures of dysregulation.

In future research, it will be important to investigate whether changes in dysregulation predict subsequent health decline. Despite ample evidence that physiological dysregulation predicts mortality and health decline, little is known regarding whether changes over time have predictive ability. For example, the finding that stressors have a stronger effect on inflammation than other markers in men (but not women) leads us to question whether changes in inflammation are better predictors of subsequent mortality in men than women and whether their prognostic value is greater than that of standard cardiovascular/metabolic and neuroendocrine markers. If such changes do have prognostic value, then identifying the causal factors that determine the trajectory of dysregulation is crucial to any prevention effort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Standardized Coefficients (95% C.I.) from Linear Regression Models Predicting Change in Physiological Dysregulation (N=539)

	Overall	Metabolic	Inflammation	Neuroendocrine
Unadjusted				
Number of life events	0.11 (0.05, 0.21)	0.06 (-0.02, 0.15)	0.05 (-0.03, 0.15)	0.04 (-0.04, 0.14)
Earthquake exposure	0.03 (-0.09, 0.25)	0.02 (-0.13, 0.18)	0.04 (-0.08, 0.27)	0.03 (-0.12, 0.27)
Chronic strain	0.00 (-0.07, 0.08)	-0.05 (-0.12, 0.01)	0.06 (-0.02, 0.14)	-0.01 (-0.09, 0.07)
Overall R^2	0.320	0.394	0.206	0.145
Change in overall R^2,[a]	0.015	0.007	0.009	0.002
Adjusted[b]				
Number of life events	0.05 (-0.02, 0.15)	0.06 (-0.02, 0.14)	*c*	-0.02 (-0.11, 0.07)
Male * life events			0.10 (0.01, 0.26)	
Female * life events			-0.05 (-0.20, 0.06)	
Earthquake exposure	0.04 (-0.06, 0.27)	0.01 (-0.15, 0.17)	0.06 (-0.03, 0.33)	*c*
Male * earthquake exposure				0.07 (-0.02, 0.45)
Female * earthquake exposure				-0.05 (-0.41, 0.12)
Chronic strain	*c*	-0.05 (-0.13, 0.03)	*c*	0.04 (-0.05, 0.13)
Male * chronic strain	0.08 (0.01, 0.20)		0.10 (0.03, 0.24)	
Female * chronic strain	-0.05 (-0.20, 0.04)		-0.02 (-0.16, 0.10)	
Overall R^2	0.373	0.409	0.244	0.246
Change in overall R^2,[a]	0.014	0.005	0.025	0.008

[a] Change in R^2 associated with the addition of the three measures of stress burden.

[b] Model adjusts for sex, age, urban residence, education, social integration, perceived social support, and personal mastery.

[c] Coefficient differs significantly by sex.