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Abstract

Theories of allostatic load postulate that an important pathway connecting the social environment with health involves biological responses to stressful stimuli and subsequent dysregulation of interrelated physiological systems. We formulate a new measure for cumulative physiological dysregulation using a grade of membership model estimated with biodemographic data from a national sample of older Taiwanese. We investigate associations between the measure and physical, psychological, and cognitive function. The results provide insights into the relationships between a set of biological profiles and various health outcomes, identify limitations of earlier approaches, and underscore next steps in the development of improved formulations of physiological dysregulation.

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1 Introduction

A vast literature accumulated over many years demonstrates strong associations between the social environment and health (Adler et al. 1999; Seeman and Crimmins 2001). More recently, researchers have begun to focus on the biological mechanisms through which these two sets of factors are interrelated. Theories of *allostatic load* (McEwen 1998b; McEwen and Stellar 1993) postulate that individuals' physiological responses to stressful stimuli are likely to constitute an important pathway linking social factors to health. These physiological mechanisms of the stress response involve the neuroendocrine, sympathetic nervous, immune, and cardiovascular systems, as well as metabolic pathways. Health-related manifestations of allostatic load are hypothesized to result from both cumulative exposure to levels of intense physiological activity (e.g., repeated stress responses) and chronic exposure of physiological parameters outside normal operating ranges (McEwen 1998a). Such forms of stimulation may result in dysregulation of interrelated physiological systems over time and, ultimately, in poor physical, psychological and cognitive functioning. From a demographer's perspective, physiological dysregulation can be viewed as an early indicator of more conventional measures of morbidity and mortality.

McEwen and Seeman (McEwen and Seeman 1999) and McEwen (McEwen 2002) develop a theoretical framework that organizes physiological system parameters into several groups. The groups reflect the relative position of each system in a sequence of physiological events originating with stimulation of the stress response and ending with disease. In this framework hormonal factors are defined as "primary mediators." These primary mediators include markers of stress-related sympathetic nervous system (SNS) activity (e.g., epinephrine and norepinephrine), hypothalamic-pituitary-adrenal (HPA) axis activity (e.g., cortisol), and

related inflammation (e.g., interleukin-6) and growth hormone (e.g., insulin-like growth factor-1) responses. Although the precise function of dehydroepiandrosterone sulfate (DHEA-S) is not well understood, researchers hypothesize that DHEA-S plays an important mediating role among these factors; low levels are associated with both worse mental health and poorer physical functioning (Berr et al. 1996; Mazat et al. 2001; Svec and Lopez 1989). According to this framework of allostatic load, these hormonal factors have "primary" effects on tissues and organs, leading to "secondary outcomes" at the system level. One important secondary outcome is the metabolic syndrome – i.e., "syndrome X" (Meigs 2003; Reaven 1988) – which can be assessed by several cardiovascular disease risk factors (e.g., blood pressure, sugar, and cholesterol levels, body mass index, and waist-to-hip ratio). Disease endpoints (e.g., coronary heart disease) that result from secondary outcomes are termed "tertiary outcomes." In this paper, we use this theoretical framework that underlies the concept of allostatic load, together with recently collected survey data, to develop a new approach to measuring physiological dysregulation.

The measurement of allostatic load involves identifying and combining the effects of dysregulation across multiple physiological systems related to the stress response. The original, and most frequently used, index of allostatic load (Seeman et al. 1997) is a sum of the number of biomarkers (out of 10) for which an individual falls into the "highest risk" quartile. Two alternative formulations, developed to overcome some of the limitations of the original measure, are more complex. The first uses canonical correlation analyses to determine the linear combination of biomarker scores that is maximally correlated with declines in functional status (Karlamangla et al. 2002). The second uses recursive partitioning to classify persons into categories by identifying the biomarker (and accompanying cutpoint) that best differentiates the

survival experiences among the categories; the procedure is repeated successively, drawing from a set of potential biomarkers, and results in pathways (i.e., Boolean statements) that define high, intermediate and low categories of allostatic load, typically on the basis of a subset of the biomarkers considered for inclusion (Singer, Ryff and Seeman Forthcoming). Researchers have demonstrated that these measures of allostatic load are associated with diverse health outcomes, including mortality, declines in cognitive and physical functioning, and cardiovascular disease (Karlamangla et al. 2002; Seeman et al. 2001; Seeman et al. 1997), as well as with various dimensions of the social environment (Schnorpfeil et al. 2003; Seeman et al. 2002). Recent studies have also provided evidence that both primary mediators and secondary outcomes contribute significantly to the association between these measures of allostatic load and health outcomes (Karlamangla et al. 2002; Seeman et al. 2001).

Nevertheless, the current formulations of allostatic load have several drawbacks that limit their usefulness as measures of cumulative physiological dysregulation. First, the ten-item index and canonical correlation approaches capture risk at only one end of each biomarker distribution, despite evidence that extreme high and low levels of many primary mediators and secondary outcomes are likely to be associated with adverse outcomes (Seplaki et al. 2004). Second, even though biomarker values and their effects are known to differ between men and women (e.g., Mazat et al. 2001; McEwen 2002), approaches that are based on the use of cutpoints of elevated risk (i.e., the 10-point index and recursive partitioning) have not used sex-specific values of the biomarkers. Third, the samples used in prior analyses of allostatic load are not representative of general populations: many results are based on the high-functioning sample of older individuals in the MacArthur Study of Aging (Seeman et al. 1997). Fourth, with the exception of some recent work that includes additional biomarkers in the conventional formulation (Crimmins et al.

2003; Schnorpfeil et al. 2003), most operationalizations of allostatic load have not incorporated measures of immune function. Lastly, the formulations based on canonical correlation and recursive partitioning use information on subsequent health outcomes to "optimize" the predictive power of the resulting measure. This approach is problematic when the measure is derived from and applied to the same dataset.

In this analysis we use data from a national sample of older Taiwanese to examine a new approach to the measurement of cumulative physiological dysregulation. We explore its association with five measures of physical and mental functioning that are hypothesized to result from such dysregulation and compare these findings with those based on the commonly-used ten-item index. Our formulation differentiates between the potentially distinct roles of primary mediators and secondary outcomes and overcomes many of the limitations described above. In particular, it allows for effects at both extremes of biomarker distributions (where appropriate), incorporates separate cutpoints by sex, avoids using observed outcomes of physical and mental functioning to operationalize the measure, comprises a broad array of biomarkers that includes measures of immune function, and is estimated on a national sample. We also derive the measure under two distinct sets of cutpoints in order to assess the robustness of our findings.

2 Methods

2.1 Data

We use data from the 2000 Social Environment and Biomarkers of Aging Study (SEBAS). These data are based on the Taiwan Survey of Health and Living Status, a longitudinal study of a nationally-representative probability sample that began in 1989 with persons aged 60 and over, and included follow-ups in 1993, 1996, and 1999. A new sample of middle-aged persons (age 50 to 66) was added for the 1996 wave. As part of SEBAS, a random subsample of 1,713 persons drawn from both cohorts was selected to be surveyed in 2000;

persons over age 70 in 2000 and those in urban areas were oversampled. This sampling design forms the basis for the two age groups used in this analysis (≤70 and >70). SEBAS consisted of two parts: an in-home survey (N=1,497, a 92% response rate among survivors) and a hospital medical exam conducted by a physician (N=1,023, 68% of those interviewed). Participants in the in-home survey provided data on their health and health history, while those in the medical exam subset also provided fasting blood and 12-hour overnight urine specimens as well as blood pressure and anthropometric measurements from a physical examination.

Compliance by those completing the medical exam was extremely high: all but ten individuals followed the urine protocol, provided a sufficient volume of blood suitable for analysis, and completed the medical exam. A comparison of the characteristics of nonparticipants and participants in the medical exam suggests that, in the presence of controls for age, estimates derived from clinical information are unlikely to be seriously biased (Goldman et al. 2003). Specifically, although persons over age 70 were less likely to participate in the medical exam than younger respondents, sex and various measures of socioeconomic status were not significantly related to participation. Persons who received the medical exam reported the same average self-assessed health status (five-point scale) as those who did not.

Among the 1,023 persons participating in the medical exam, ten individuals who were missing data on at least one of the biomarkers were excluded from this analysis. In addition, a small number of individuals were missing values for at least one of the self-reported functional outcomes. These modifications yield a sample of 972 individuals (571 males and 401 females) for our analysis.

2.2 Measures

A total of sixteen biological measures are used in this analysis, representing both primary mediators and secondary outcomes (Appendix Table A-1). Primary mediators comprise

epinephrine, norepinephrine, dopamine, cortisol, DHEA-S, IGF-1, and IL-6. Secondary outcomes comprise average systolic and diastolic blood pressures, total serum cholesterol, the ratio of total to high-density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose and glycosylated hemoglobin (a measure of the percentage of hemoglobin molecules in the blood that are bound to glucose), body mass index (BMI), and waist-to-hip ratio.

Measures are derived from the urine and blood specimens, as well as the physical examination. Twelve-hour urine specimens yielded measures on cortisol, norepinephrine, epinephrine, and dopamine (a 12-hour urine specimen is necessary to obtain integrated measures of these markers because of their diurnal variation). Measurements for cortisol, epinephrine, and norepinephrine are reported as "micrograms per gram creatinine" in order to adjust for body size. The fasting blood specimens yielded assays of HDL cholesterol, total cholesterol, triglycerides, fasting glucose, glycosylated hemoglobin, DHEA-S, IGF-1, and IL-6. The blood pressure and anthropometric measurements collected during the physical examination yielded systolic and diastolic blood pressures (each calculated as the average of two seated blood pressure readings, taken about one minute apart, using a mercury sphygmomanometer with the respondent in a seated position). Measures were also taken for height, weight, and hip and waist circumference—the data used to calculate BMI (defined as weight in kilograms divided by height in meters squared) and the waist/hip ratio.

Blood and urine specimens were sent to Union Clinical Laboratories (UCL) in Taipei for the assays. In addition to the routine standardization and calibration tests performed by the laboratory, duplicate samples for a 10% subset of the specimens were submitted to UCL and to Quest Diagnostics in the US for analysis. Data from these duplicates indicate good 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 and Quest Diagnostics.

We divide each biomarker measurement into three categories: low, middle, and high. The low and high categories are designed to capture values outside normal operating ranges and the potential for risk at both extremes of each biomarker distribution. Two distinct sets of cutpoints are used to define these categories: 1) values below the 10^{th} percentile, between the 10^{th} and 90th percentiles, and above the 90^{th} percentile; and 2) values below the 25^{th} percentile, between the 25^{th} and 75^{th} percentiles, and above the 75^{th} percentile. The lower cutpoints for epinephrine and IL-6 are below assay sensitivity (B.A.S.) in several instances in Appendix Table A-1; assay sensitivity for epinephrine is < 2 μg/L, while assay sensitivity for IL-6 is < 0.1 pg/mL. As noted earlier, cutpoints are defined separately by sex.

The functional outcomes examined in this analysis are selected to represent a spectrum of physical and mental functioning reflecting the multi-system dynamics of cumulative physiological dysregulation. They include: 1) self-assessed health (measured on a five-point scale, 1=poor, 2=not so good, 3=average, 4=good, 5=excellent); 2) an indicator for the presence of at least one impairment of an activity of daily living (ADL); 3) a count of mobility impairments; 4) an index of cognitive performance (a count of correct responses); and 5) a count of depressive symptoms. ADLs comprise bathing, dressing, eating, getting out of bed/standing up/sitting in chair, moving around the house, and going to the toilet. Mobility limitations comprise difficulty squatting, climbing 2-3 flights of stairs, lifting 11-12 kilograms, doing physical work at home, walking 200-300 meters, standing continuously for 15 minutes, and running a short distance (20-30 meters). Depressive symptoms are measured by a 10-item version of the original 20-item Center for Epidemiologic Studies Depression (CES-D) scale

(Radloff 1977). Previous studies have demonstrated that a shortened form of the CES-D yields similar internal consistency, factor structure, and accuracy in detecting depressive symptoms as the full 20-item CES-D among elderly Chinese (Boey 1999) as well as other populations (Kohout et al. 1993; Shrout and Yager 1989). Items forming the CES-D index used here (potential range of 0 to 30) include reports (in the past week) of no interest in eating, sleeping poorly, being in a terrible mood, feeling lonely, people not being nice, feeling anguished, having no energy to do things, feeling joyful (reverse coded), that doing anything is exhausting, and life is going well (reverse coded). The measure of cognitive function (potential range of 0 to 24) includes twelve items adapted from three tests: the modified Short Portable Mental Status Questionnaire (Pfeiffer 1975), the modified Rey Auditory Verbal Learning Test (Lezak 1983), and a modification of the Digits Backward test (Wechsler 1981).

2.3 Analysis

The analysis consists of three parts. The first stage uses a Grade of Membership (GOM) model (Manton, Woodbury and Tolley 1994) to estimate "GOM scores" for each respondent in the sample; the resulting scores measure individuals' similarity to five distinct profiles of biomarker combinations. In the second stage of the analysis, the GOM scores are used to predict each of the five health outcomes described above (in separate regression models). In the third stage of the analysis, a single GOM index is calculated from the GOM scores and is evaluated alongside the conventional ten-item index of allostatic load as predictors of the five health outcomes. All three stages are estimated for both sets of biomarker cutpoints (the 10/90 and 25/75 percentiles). These three components of the analysis are elaborated below.

GOM is an analytic technique that has been used in the past to describe the complex comorbid physical and mental health status of older populations (Berkman, Singer and Manton 1989; Seplaki et al. 2004). In the present analysis, GOM is used to depict physiological

dysregulation of the older population. The procedure synthesizes information from a large number of correlated variables – i.e., variables indicating whether each individual displays low, moderate, or high values on each of 16 biological parameters – into a small set of archetypal profiles. In this analysis, four profiles are defined to reflect alternative manifestations of elevated risk of poor health outcomes (e.g., low versus high values of primary mediators and low versus high values of secondary outcomes), while a fifth "reference" profile is defined to represent the lowest risk (e.g., moderate values on all biomarkers). The resulting estimates from the GOM model consist of 1) a collection of response probabilities corresponding to the levels of each biomarker, for each of the five profiles (known in GOM as *pure-types*), and 2) individual vectors of five GOM scores (i.e., one vector for each of the 972 respondents). Each of the GOM scores lies between zero and one and measures the similarity of the individual's biomarker values to the corresponding pure-type profile. Because the sum of the scores for a given individual is equal to one, each person's physiological status can be viewed as a weighted average of these five pure-type profiles. In principle, the pure-type profiles can either be defined exogenously (as is done here) or estimated iteratively with GOM scores. Additional details on GOM models are provided elsewhere (Berkman et al. 1989; Manton et al. 1994). All GOM analyses reported here are performed using the software by Charpentier (Charpentier 1996).

In the next stage of the analysis, the individual GOM scores, along with controls for age and sex, are used to predict each of the five health outcomes in separate regression models. An ordered probit model is used to predict self-rated health and a logit model is used for the probability of an ADL impairment. Ordinary least squares is used to predict the count of mobility limitations, CES-D score, and cognitive score. Robust variance estimates (from the Huber/White estimator) are used to correct for the potential effects of heteroskedasticity and

potential clustering by primary sampling unit. Simulated predicted values are calculated from each model to assist in the interpretation of results. For each biomarker, the simulated probabilities are obtained by: 1) sequentially assigning all individuals to the first GOM profile, followed by the second profile, and so on, while leaving age and sex at their observed values, and 2) in each case averaging the predicted values across individuals. All regression analyses are carried out using Stata 8.2 (StataCorp 2003).

In the final stage of the analysis, four of the five GOM scores (i.e., excluding the score measuring similarity to the low risk or reference profile) are summed to create a single GOM-based index. Because the five scores sum to unity, this sum measures *dissimilarity* to the low risk profile. The conventional index is calculated as the number of the following ten biomarkers for which an individual is in the highest risk quartile: cortisol, epinephrine, norepinephrine, DHEA-S, HDL cholesterol, the ratio of total-to-HDL cholesterol, glycosylated hemoglobin, systolic blood pressure, diastolic blood pressure, and the waist-hip ratio (Seeman et al. 1997). The performance of these two indices – the single GOM score and the 10-item index – is compared by considering each as a predictor in separate regression models.

3 Results

Overall, the mean age of the analysis sample is 67.7 (45% are over the age of 70) and 41% of the sample is female. This atypical, male-biased sex ratio reflects the approximately one million Nationalist military and civilian supporters who migrated to Taiwan from the Mainland in 1949 (Gates 1981; Tsai 1992). Table 1 provides descriptive information on the sample by sex. This table demonstrates that although men in the sample have a slightly higher mean age than women, they are also healthier on average. The sex-specific cutpoints used to define the risk categories for each biomarker comprising the GOM measure are given in Appendix Table A-1,

as are the overall cutpoints that define the risk categories of the ten-item index. This table reveals the extensive variation in cutpoint values between males and females for many of the biomarkers, underscoring the potential importance of conditioning cutpoints on sex.

3.1 GOM Estimation

On the basis of allostatic load theory and exploratory analyses supporting the distinction between primary mediators and secondary outcomes, we developed five pure types consisting of distinct combinations of primary mediators and secondary outcomes that are hypothesized to reflect varying levels of physiological dysregulation. Specifically, these five pure types are defined to identify the potential independent roles of both high and low values of groups of primary mediators and secondary outcomes. With some simplification (discussed below), the five pure-type profiles denote: (I) "not at risk" moderate levels of all biomarkers; (II) "at risk" *low* levels of primary mediators (with "not at risk" secondary outcome levels); (III) "at risk" *high* levels of primary mediators (with "not at risk" secondary outcomes); (IV) "at risk" *low* levels of secondary outcomes (with "not at risk" primary mediators); and (V) "at risk" *high* levels of secondary outcomes (with "not at risk" primary mediators).

The full characterizations of each pure-type profile are given in Table 2. These are more complex than indicated by the preceding summary of profiles because of the one-tailed risks associated with DHEA-S and the total-to-HDL cholesterol ratio. In contrast to evidence suggesting potential risks associated with both low and high values of most of the biomarkers included here, the medical literature suggests that only low values of DHEA-S and high values of the ratio of total-to-HDL cholesterol represent elevated risk.

Each cell entry in Table 2 defines one or more levels (low, middle, or high) for each subset of biomarkers (primary mediators and secondary outcomes). Cell entries in bold italics denote profile characteristics that are hypothesized to be associated with an elevated risk of poor

health outcomes. Entries that specify two levels (e.g., low/middle) indicate that the probability of response for the associated profile is defined to be divided evenly between those levels (1/2 for each); these combinations are selected to denote the complement of the single tail of DHEA-S or the ratio of total-to-HDL cholesterol that embodies high risk for poor health. Cell entries that reflect all levels (low/middle/high) signify that the associated pure-type is defined to have an equal probability (1/3) of being associated with each of the three possible levels (i.e., the profile can be considered neutral with respect to that biomarker).

Pure-type I is characterized by middle-level values for most biomarkers, high or middle DHEA-S, and a low or middle ratio of total-to-HDL cholesterol ratio – theoretically, this profile represents the lowest level of risk of poor health outcomes. Pure-type II is characterized by "at risk" *low values of the primary mediators*, including DHEA-S, and by "not at risk" values for the secondary outcomes (middle-level for most secondary outcomes and a low or middle cholesterol ratio). Alternatively, pure type III is characterized by "at risk" *high values for most of the primary mediators*, except DHEA-S, and by the same "not at risk" values for the secondary outcomes as pure-type II. No particular level of DHEA-S is identified with this profile. Pure-types IV and V correspond to pure-types II and III respectively, but focus on "at risk" values of the secondary outcomes instead of the primary mediators. Pure-type IV combines *low values for most secondary outcomes*, except the total-to-HDL cholesterol ratio, with "not at risk" values of the primary mediators. Pure-type V pairs *high values for all of the secondary outcomes*, including the total-to-HDL cholesterol ratio, with the same "not at risk" values for the primary mediators as in pure-type IV.

The distribution of individuals across the various mixes of the five profiles is presented in Table 3, for both sets of cutpoints. These estimates are based on the assumption that individuals

are described as a single pure-type if their GOM score for that type is at least 0.9 and that they are described as a given mix of (between two and five) pure-types if the sum of their GOM scores is at least 0.9 for that particular combination.

The results reveal that very few individuals can be described by a single biomarker profile, but that a sizeable fraction can be depicted by a combination of two or three profiles. Extreme values of both primary mediators and secondary outcomes are prominent in these profiles. In light of the fact that the 10/90 cutpoints define only one-fifth of individuals as being in an extreme category of a given biomarker in contrast to one-half for the 25/75 cutpoints, it is not surprising that the specific mixes differ considerably between these two sets of estimates. In particular, use of the 10/90 cutpoints, as compared with the 25/75 cutpoints, results in a much higher proportion of individuals being described in part by the low-risk profile (profile I). Results for the 25/75 cutpoints suggest a substantial number of persons who have low or high values of secondary outcomes –i.e., profile IV or V but not both – combined with extreme values of primary mediators – i.e., low and/or high values.

3.2 Prediction of Health Outcomes and Comparison with Existing Measure

Results from the regression models are shown in Table 4. In these models, GOM score coefficients are relative to the omitted score for pure-type I. Because larger values for self-assessed health and the cognitive function score signify better health, we anticipate negative GOM score coefficients for these two health outcomes. In contrast, we anticipate positive GOM score coefficients for the remaining three outcomes: the presence of an ADL impairment, count of mobility limitations, and CES-D score. The coefficient for the female variable represents the association between being female and the outcome *net* of biological factors that are encompassed within the sex-specific cutpoints.

These results highlight three general findings. First, extreme values for both primary mediators and secondary outcomes are significantly and independently associated with diverse measures of physical and mental functioning. Second, both tails of the biomarkers matter – i.e., high and low values are each significantly and independently associated with functioning. (Note that all of the results refer to *groups* of biomarkers rather than to individual biomarkers – i.e., although we cannot determine whether both low and high values of an individual biomarker are related to functioning, we see that low and high values of the set of primary mediators – or secondary outcomes – are related to functioning.) And third, different health outcomes appear to be associated with different sets of biomarkers.

A more detailed assessment of the coefficients in Table 4 reveals contrasts between the primary mediators and the secondary outcomes. For the secondary outcomes, high biomarker values are more often associated with adverse functioning than low values. For example, whereas scores representing high values of the secondary outcomes (score V) are significantly associated with every health outcome considered, GOM scores reflecting low values of the secondary outcomes (score IV) are significantly associated with two or three of the five outcomes (depending on the cutpoints). In contrast, significant associations resulting from extreme values of the primary mediators (GOM scores II and III) are as likely to result from low as from high values.

The estimates in Table 4 also suggest variation across the five health outcomes. For example, although most of the high-risk profile scores are significantly related to mobility limitations and to depression scores, only the profile score reflecting high secondary outcomes is significantly associated with cognitive performance.

The magnitude and pattern of these associations are illustrated by the predicted values in Table 5. The profile characterized by high values of secondary outcomes (score V) is generally associated with the poorest health outcomes, with the exception of depressive symptoms. Conversely, as hypothesized, profile I demonstrates the most favorable outcomes in all cases with the single exception of the cognitive score (for the 10/90 cutpoints).

The final set of analyses compares the associations found using the GOM-based measure of physiological dysregulation with those resulting from the conventional ten-item index of allostatic load (Table 6). This comparison is facilitated by aggregating the four "at risk" GOM profile scores (scores II through V) into a single score or index that represents the *dissimilarity* of each individual to profile I. Two versions of the GOM index are shown: one based on the 10^{th} and 90^{th} percentile cutpoints and a second based on the 25^{th} and 75^{th} percentile cutpoints; the latter operationalization is more comparable to the ten-item index, which uses quartiles to identify the high-risk categories. Three regression models are estimated for each health outcome. Each model includes controls for age and sex along with a single index (i.e., the 10-item index, the GOM index based on the 10/90 cutpoints, and the GOM index based on the 25/75 cutpoints, respectively).

The estimated coefficients in Table 6 demonstrate that the ten-item index is significantly associated ($p<0.05$) with three of the five outcomes (self-assessed health, mobility limitations and cognitive score, but not ADL limitations and the CES-D score). The GOM index based on the 10/90 cutpoints is significantly associated with four of the five outcomes (all except cognitive score), whereas the GOM index based on the 25/75 cutpoints is significantly associated with all five outcomes. Overall, the R^2 (or pseudo- R^2) values suggest that the GOM indices account for more variation in the outcomes than the ten-item index, and that the 10/90 variant accounts for

more variation than the 25/75 variant. Exploratory analyses (not presented here) suggest that the improvement of the GOM-based index relative to the conventional index results in part from the inclusion of additional biomarkers and the use of two tails of risk. Nevertheless, the R^2 values and the associated increments are generally small.

4 Discussion

This paper contributes to the existing literature on cumulative physiological dysregulation in three important ways. First, this research provides empirical support for the framework of allostatic load introduced by McEwen and Seeman (McEwen and Seeman 1999) and McEwen (McEwen 2002). Specifically, the results confirm the utility of distinguishing between groups of primary mediators and secondary outcomes—each subset of biomarkers is significantly and independently related to a broad range of outcomes. The findings also corroborate previous research demonstrating that measures of cumulative physiological dysregulation may be significantly associated with health outcomes, even though individual biomarkers may not demonstrate significant associations with such outcomes. (See Seplaki et al. (2004) for an analysis of the association between individual biomarkers and health outcomes, based on the SEBAS sample.)

The second contribution of this work is the development of a measure of cumulative physiological dysregulation that embodies several improvements over prior measures. The new measure recognizes both high and low biomarker values and incorporates more biomarkers than the conventional measure. As a consequence, the new measure reveals somewhat stronger associations with a broad set of health outcomes hypothesized to result from physiological dysregulation. Despite the fact that alternative sets of cutpoints produce very different profile descriptions of the sample, the associations between the GOM-based measure and the health

outcomes are generally robust to the two sets of cutpoints explored here. In addition, because the new measure does not rely on information on "downstream" physical and mental functioning, it is not subject to the endogeneity concerns that characterize some of the other formulations.

The third contribution of this research is the derivation of a measure that encompasses distinct and biologically meaningful *components* of physiological dysregulation. Although the measure can be represented as a single index, it was developed theoretically as a set of four related indices that quantify the similarity of an individual to different configurations of primary mediators and secondary outcomes. Because these profiles reflect different types and stages of dysregulation, the full set of GOM scores may provide more insights than current formulations into mechanisms that link the social environment with poor health, while still capturing the cumulative aspects of dysregulation across multiple systems.

There are several limitations of this study. First, these analyses are cross-sectional, so inferences cannot be made regarding the direction of the association between the biomarker profile scores and health outcomes. For example, although it is tempting to suggest, as much of the scientific and popular literature does, that low levels of DHEA-S lead to poor health and a short life span, it is also possible that certain illnesses reduce the levels of DHEA-S (Berr et al. 1996; Yaffe et al. 1998). Second, although almost all of the findings discussed in this analysis are robust to the use of the two sets of cutpoints, several of the coefficients and associated z-statistics are sensitive to the alternative specifications. This is especially problematic because the selection of these two sets of cutpoints is largely arbitrary. A third limitation is that the results presented here focus on associations involving single biological profiles (i.e., the five pure types) rather than the complex mixes among profiles that characterize most individuals.

These drawbacks underscore the need for future research in two domains. One important task is the establishment of systematic criteria for defining what is outside a "normal" or "low risk" range for measurements of biological dysregulation. Clinically-defined cutpoints do not exist for many of these biomarkers and would, in any case, not be suitable for this endeavor given the emphasis of allostatic load on providing "early warnings" for future negative health outcomes. Another needed area of research is an examination of how more complex combinations (sets) of biomarkers are related to health outcomes. The results in Table 3 provide a useful starting point for such an endeavor. For example, preliminary estimates (not presented here) reveal that individuals whose biological profiles can be described as a mix of low primary mediators and high secondary outcomes, or as a mix of high primary mediators and high secondary outcomes, are generally characterized by poorer health outcomes than others. The challenge here is to define all persons in the sample by a relatively simple, exhaustive, mutually exclusive, and meaningful set of profile combinations. The ultimate objective would be to provide a new measure of allostatic load that takes advantage of the richness of the GOM-estimates and outperforms the simple aggregated GOM-score introduced in this paper as well as other current formulations.

During the past few years, social scientists and epidemiologists have been expending considerable effort to design and field population-based surveys that incorporate rich social and biological information along with longitudinal information on health and survival. The future availability of several data sets of this type will permit researchers to accomplish the proposed tasks described above. These data would provide the opportunity to (1) identify meaningful cutpoints for biomarkers and develop improved measures of physiological dysregulation on a given longitudinal data set; and (2) use a distinct longitudinal data set to validate the resulting

measures and compare them with currently available formulations. The second part of this exercise could entail using the measures of physiological dysregulation as predictors of future health and survival and as outcomes in models that examine the consequences of chronic stressful experiences. Research on the measurement of physiological dysregulation has been greatly hampered by the dearth of such validation efforts.

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Table 1: Descriptive Sample Information

	Males (N=571)				Females (N=401)			
	Mean	*S.D.*	*Min*	*Max*	*Mean*	*S.D.*	*Min*	*Max*
Age	68.2	8.3	54	90	67.1	8.6	54	90
Self-assessed Health	3.17	1.0	1	5	2.94	1.0	1	5
Any ADL Impairment	0.03	0.2	0	1	0.05	0.2	0	1
Count of Mobility Limitations	1.17	1.9	0	7	2.41	2.4	0	7
CES-D Score	4.89	4.9	0	27	6.32	6.0	0	28
Cognitive Performance Score	17.1	3.0	2	24	15.9	4.1	1	24
Allostatic Load 10-item Index	2.38	1.6	0	7	2.84	1.6	0	7

Table 2: GOM Model Pure-type Definitions[a]

Pure-type	Primary Mediators	Secondary Outcomes
I	Middle (with high/middle DHEA-S) [b]	Middle (with low/middle Cholesterol Ratio) [b]
II	***Low (with low DHEA-S)***	Middle (with low/middle Cholesterol Ratio) [b]
III	***High*** (with low/middle/high DHEA-S)[c]	Middle (with low/middle Cholesterol Ratio) [b]
IV	Middle (with high/middle DHEA-S) [b]	***Low*** (with low/middle/high Cholesterol Ratio)[c]
V	Middle (with high/middle DHEA-S) [b]	***High (with high Cholesterol Ratio)***

[a]Cell entries in bold italics denote profile characteristics that are hypothesized to be associated with elevated risk of poor health outcomes. [b]Descriptions that include two levels (e.g., low/middle) signify that the pure-type has a probability of response that is split evenly between those levels (1/2 for each). [c]Descriptions that include all levels (e.g. low/middle/high) signify that the pure-type has an equal probability of being associated with the three possible levels (1/3 for each).

Table 3: Distribution of Individuals Across Pure-type Mixes[a,b,c]

	10th and 90th Percentile Cutpoints				25th and 75th Percentile Cutpoints			
	Males	**% Males**	**Females**	**% Females**	**Males**	**% Males**	**Females**	**% Females**
Pure-types								
I	17	3.0%	8	2.0%	1	0.2%	1	0.2%
Total	17	3.0%	8	2.0%	1	0.2%	1	0.2%
Two-type mixes								
I & II	47	8.2%	31	7.7%	0		0	
I & III	19	3.3%	17	4.2%	0		0	
I & IV	38	6.7%	25	6.2%	2	0.4%	1	0.2%
I & V	29	5.1%	16	4.0%	2	0.4%	0	
II & IV	2	0.4%	0		9	1.6%	1	0.2%
II & V	1	0.2%	3	0.7%	11	1.9%	8	2.0%
III & IV	2	0.4%	3	0.7%	13	2.3%	10	2.5%
III & V	2	0.4%	0		8	1.4%	4	1.0%
Total	140	24.5%	95	23.7%	45	7.9%	24	6.0%
Three-type mixes								
I & II & III	33	5.8%	14	3.5%	4	0.7%	2	0.5%
I & II & IV	59	10.3%	44	11.0%	11	1.9%	11	2.7%
I & II & V	67	11.7%	47	11.7%	9	1.6%	9	2.2%
I & III & IV	30	5.3%	29	7.2%	8	1.4%	14	3.5%
I & III & V	35	6.1%	14	3.5%	8	1.4%	9	2.2%
I & IV & V	9	1.6%	19	4.7%	2	0.4%	3	0.7%
II & III & IV	6	1.1%	2	0.5%	80	14.0%	47	11.7%
II & III & V	4	0.7%	4	1.0%	62	10.9%	46	11.5%
II & IV & V	1	0.2%	3	0.7%	28	4.9%	25	6.2%
III & IV & V	1	0.2%	0		29	5.1%	20	5.0%
Total	245	42.9%	176	43.9%	241	42.2%	186	46.4%
Four-type mixes								
I & II & III & IV	49	8.6%	29	7.2%	27	4.7%	13	3.2%
I & II & III & V	38	6.7%	40	10.0%	23	4.0%	14	3.5%
I & II & IV & V	36	6.3%	18	4.5%	29	5.1%	13	3.2%
I & III & IV & V	17	3.0%	11	2.7%	22	3.9%	17	4.2%
II & III & IV & V	5	0.9%	6	1.5%	134	23.5%	104	25.9%
Total	145	25.4%	104	25.9%	235	41.2%	161	40.1%
Five-type Mixes	24	4.2%	18	4.5%	49	8.6%	29	7.2%
Total	24	4.2%	18	4.5%	49	8.6%	29	7.2%

[a]Male N = 571, Female N = 401

[b]Individuals are defined as a pure type if any one of their GOM scores equals or exceeds 0.9. Individuals are defined as a two- (or three- or four-) type mix if the respective sum of their GOM scores equals or exceeds 0.9. The balance of the sample, by definition, reflect mixes among all five of the pure-types. In the event of ambiguity between two potential classifications for a given individual, he or she is assigned randomly to an eligible group (this occurred for one individual under the 10^{th} and 90^{th} percentile cutpoints and for six individuals under the 25^{th} and 75^{th} percentile cutpoints).

[c]See Table 2 for profile descriptions.

Table 4: Regression results[a] predicting health outcomes as a function of GOM profile scores, age and sex

	Regression models based on 10% & 90% cutpoints					Regression models based on 25% & 75% cutpoints				
	Self-Assessed Health (Ordered Probit)	Any ADL Impairment (Logit)	Count of Mobility Limitations (OLS)	CES-D Score (OLS)	Cognitive Performance Score (OLS)	Self-Assessed Health (Ordered Probit)	Any ADL Impairment (Logit)	Count of Mobility Limitations (OLS)	CES-D Score (OLS)	Cognitive Performance Score (OLS)
Age > 70	-0.15*	0.69*	1.38**	0.73*	-1.79**	-0.15*	0.73*	1.39**	0.79*	-1.75**
	[2.16]	[1.96]	[10.70]	[2.06]	[8.03]	[2.21]	[2.03]	[10.57]	[2.17]	[7.78]
Female	-0.26**	0.74*	1.34**	1.42**	-1.40**	-0.27**	0.78*	1.37**	1.52**	-1.38**
	[3.66]	[2.13]	[10.27]	[3.94]	[6.02]	[3.83]	[2.31]	[10.44]	[4.17]	[5.93]
GOM score II: Low primary mediators, Middle secondary outcomes[b]	-0.64**	1.63	1.16*	2.51*	0.76	-0.64*	3.2	1.20*	2.67	-1
	[2.68]	[1.17]	[2.41]	[2.00]	[0.94]	[2.40]	[1.70]	[2.39]	[1.91]	[1.16]
GOM score III: High primary mediators, Middle secondary outcomes[b]	-0.37	2.3	1.40**	4.72**	-0.96	-0.17	2.82	1.36**	3.17*	-1.41
	[1.22]	[1.72]	[2.81]	[3.36]	[0.96]	[0.62]	[1.40]	[2.83]	[2.42]	[1.67]
GOM score IV: Middle primary mediators, Low secondary outcomes[b]	-0.27	2.46*	0.93	2.74*	0.36	-0.57*	3.92*	0.69	3.58**	-0.73
	[1.09]	[2.16]	[1.90]	[2.14]	[0.48]	[2.21]	[2.29]	[1.51]	[2.91]	[0.94]
GOM score V: Middle primary mediators, High secondary outcomes[b]	-0.93**	4.57**	2.39**	4.10**	-2.45**	-0.90**	4.91*	1.68**	2.91*	-1.82*
	[3.19]	[4.49]	[4.36]	[2.78]	[2.64]	[3.38]	[2.56]	[3.67]	[2.27]	[2.35]
Constant		-5.37**	-0.14	3.03**	18.21**		-7.46**	-0.6	1.75*	19.10**
		[9.94]	[1.00]	[7.74]	[71.08]		[4.55]	[1.95]	[2.14]	[35.22]
Test for joint significance of GOM scores										
Wald χ^2 Statistic[c]	17.85	21.25	-	-	-	14.91	8.25	-	-	-
F-Statistic[c]	-	-	7.75	5.94	2.67	-	-	4.69	3.04	1.86
p-value	< 0.01	< 0.01	< 0.01	< 0.01	0.03	< 0.01	0.08	< 0.01	0.02	0.12

[a]Huber-White robust z statistics in brackets; each profile coefficient is relative to Profile I; * significant at 5%; **significant at 1%.
[b]See Table 2 for additional characterizations of the profile descriptions.
[c]Wald and F-statistics are used to conduct the joint hypothesis test for the significance of the GOM scores. The Wald statistic applies to the likelihood-based models (ordered probit and logit) while the F-statistic applies to the linear regression models.

Table 5: Simulated Predicted Values for Each of the Five Pure-types by Health Outcomes[a,b]

Outcome	Regression models based on 10% & 90% cutpoints	Regression models based on 25% & 75% cutpoints
Probability that Self-assessed Health is Poor or Not So Good		
All assigned to pure-type I	0.19	0.13
All assigned to pure-type II	**0.41**	**0.31**
All assigned to pure-type III	0.31	0.17
All assigned to pure-type IV	0.27	**0.28**
All assigned to pure-type V	**0.51**	**0.40**
Probability of any ADL Limitations		
All assigned to pure-type I	0.01	0.00
All assigned to pure-type II	0.05	0.03
All assigned to pure-type III	0.09	0.02
All assigned to pure-type IV	**0.10**	**0.06**
All assigned to pure-type V	**0.45**	**0.14**
Expected Number of Mobility Limitations		
All assigned to pure-type I	1.03	0.59
All assigned to pure-type II	**2.19**	**1.78**
All assigned to pure-type III	**2.43**	**1.95**
All assigned to pure-type IV	1.97	1.28
All assigned to pure-type V	**3.42**	**2.27**
Expected Number of Depressive Symptoms (CES-D Score)		
All assigned to pure-type I	3.94	2.73
All assigned to pure-type II	**6.45**	5.40
All assigned to pure-type III	**8.66**	**5.89**
All assigned to pure-type IV	**6.68**	**6.31**
All assigned to pure-type V	**8.04**	**5.63**
Predicted Cognitive Performance Score		
All assigned to pure-type I	16.84	17.75
All assigned to pure-type II	17.59	16.75
All assigned to pure-type III	15.87	16.33
All assigned to pure-type IV	17.19	17.02
All assigned to pure-type V	**14.39**	**15.93**

[a]Boldface indicates values significantly different from pure-type I ($p<0.05$), as given in Table 4.
[b]Predicted values are obtained by assigning all individuals to a given GOM profile (leaving age and sex at their observed values) and averaging the resulting predicted values across individuals.

Table 6: Comparison of Single GOM Score with Ten-item Allostatic Load Measure[a]

	Self-Assessed Health (Ordered Probit)			Any ADL Impairment (Logit)			Count of Mobility Limitations (OLS)		
Age > 70	-0.16*	-0.15*	-0.16*	0.71*	0.66	0.71*	1.37**	1.38**	1.40**
	[2.24]	[2.22]	[2.30]	[2.07]	[1.93]	[2.09]	[10.56]	[10.67]	[10.80]
Female	-0.24**	-0.25**	-0.27**	0.70*	0.70*	0.77*	1.29**	1.33**	1.37**
	[3.46]	[3.61]	[3.84]	[2.01]	[2.07]	[2.29]	[9.71]	[10.15]	[10.39]
Ten-item Allostatic Load[c] Index	-0.05*			0.14			0.18**		
	[2.10]			[1.52]			[4.48]		
Sum of GOM scores II to V, 10/90th percentile cutpoints[b]		-0.54**			2.78**			1.44**	
		[3.64]			[3.64]			[5.11]	
Sum of GOM scores II to V, 25/75th percentile cutpoints[b]			-0.58**			3.83*			1.25**
			[2.93]			[2.26]			[3.60]
Constant				-4.31**	-5.37**	-7.50**	0.08	-0.13	-0.62*
				[11.00]	[9.95]	[4.57]	[0.69]	[0.96]	[2.03]
R^2 or Pseudo-R^2	0.009	0.013	0.010	0.036	0.080	0.052	0.199	0.207	0.191
Change in R^2 from restricted model (age & sex)	0.002	0.006	0.003	0.006	0.050	0.022	0.016	0.024	0.008

[a]Huber-White robust z statistics in brackets; * significant at 5%; ** significant at 1%.

[b]The sum of GOM scores II through V represents *dissimilarity* to pure-type I (based on either the 10th and 90th percentile cutpoints or the 25th and 75th percentile cutpoints, as noted).

[c]The ten-item index uses HDL cholesterol in place of the ratio of total to HDL cholesterol, and cutpoints at the 75th (or 25th) percentile that are the same for men and women.

Table 6 (continued): Comparison of Single GOM Score with Ten-item Allostatic Load Measure[a]

	CES-D Score (OLS)			Cognitive Performance Score (OLS)		
Age > 70	0.76*	0.71*	0.76*	-1.72**	-1.76**	-1.75**
	[2.16]	[2.01]	[2.15]	[7.73]	[7.95]	[7.91]
Female	1.42**	1.40**	1.51**	-1.29**	-1.37**	-1.38**
	[3.87]	[3.89]	[4.15]	[5.52]	[5.88]	[5.94]
Ten-item Allostatic Load[c] Index	0.19			-0.19**		
	[1.65]			[2.63]		
Sum of GOM scores II to V, 10/90th percentile cutpoints[b]		3.46**			-0.48	
		[4.69]			[0.98]	
Sum of GOM scores II to V, 25/75th percentile cutpoints[b]			3.08**			-1.26*
			[3.37]			[2.10]
Constant	4.07**	3.02**	1.77*	18.44**	18.21**	19.12**
	[11.14]	[7.73]	[2.17]	[87.37]	[70.55]	[35.37]
R^2 or Pseudo-R^2	0.026	0.045	0.031	0.098	0.092	0.094
Change in R^2 from restricted model (age & sex)	0.003	0.022	0.008	0.007	0.001	0.003

[a]Huber-White robust z statistics in brackets; * significant at 5%; ** significant at 1%.

[b]The sum of GOM scores II through V represents *dissimilarity* to pure-type I (based on either the 10th and 90th percentile cutpoints or the 25th and 75th percentile cutpoints, as noted).

[c]The ten-item index uses HDL cholesterol in place of the ratio of total to HDL cholesterol, and cutpoints at the 75th (or 25th) percentile that are the same for men and women.

Appendix Table A-1: Biomarker Cutpoint Values[a]

Biomarker Category	*Biomarker*	*Percentile (N=1023[c])*	
Cutpoints (sexes combined)		*25th*	*75th*
Primary Mediators	Epinephrine (μg/g creatinine)[b]	0.78	3.67
	Norepinephrine (μg/g creatinine)	15.02	27.09
	Cortisol (μg/g creatinine)	12.53	29.98
	DHEA-S (μg/dL)	40.80	107.90
Secondary Outcomes	Systolic Blood Pressure (mmHG)	123.00	150.00
	Diastolic Blood Pressure (mmHG)	75.00	90.00
	Ratio of Total Cholesterol to HDL	3.40	5.11
	HDL Cholesterol (mg/dL)	39.00	57.00
	Glycosylated Hemoglobin	5.10	5.80
	Waist/Hip Ratio	0.84	0.93

Cutpoints by Sex		*Males (N=590[c])*				*Females (N=433[c])*			
		10th	*25th*	*75th*	*90th*	*10th*	*25th*	*75th*	*90th*
Primary Mediators	Epinephrine (μg/g creatinine)[b]	B.A.S.	0.85	3.41	4.90	B.A.S.	0.63	4.09	6.65
	Norepinephrine (μg/g creatinine)	10.42	13.89	24.23	32.91	12.88	17.71	30.30	36.16
	Dopamine (μg/L)	46.20	72.25	178.15	264.70	41.70	61.20	162.20	258.70
	Cortisol (μg/g creatinine)	7.87	11.47	25.40	43.04	10.06	14.51	34.35	53.61
	DHEA-S (μg/dL)	32.00	53.45	125.30	172.10	13.00	29.20	78.20	118.00
	IGF-1 (ng/mL)	54.30	73.45	137.15	173.70	49.80	66.80	121.30	151.90
	IL-6 (pg/mL)[b]	B.A.S.	B.A.S.	1.40	3.10	B.A.S.	B.A.S.	1.50	3.80
Secondary Outcomes	Systolic Blood Pressure (mmHG)	113.00	123.00	149.00	164.00	114.00	125.00	152.00	170.00
	Diastolic Blood Pressue (mmHG)	69.50	75.00	90.00	96.00	70.00	74.00	90.00	97.00
	Total Cholesterol (mg/dL)	148.00	170.00	218.00	242.00	163.00	182.00	232.00	263.00
	Ratio of Total Cholesterol to HDL	2.77	3.40	5.21	6.19	2.86	3.35	4.98	5.98
	Triglycerides (mg/dL)	52.00	67.00	139.00	199.00	60.00	79.00	155.00	209.00
	Fasting Glucose (mg/dL)	84.00	88.00	105.00	127.00	85.00	89.00	113.00	164.00
	Glycosylated Hemoglobin	4.80	5.10	5.70	6.50	4.90	5.10	6.10	8.10
	BMI	19.66	21.78	26.03	28.20	20.44	22.37	27.11	30.38
	Waist/Hip Ratio	0.84	0.87	0.94	0.97	0.78	0.81	0.90	0.94

[a]Percentile calculations based on all nonmissing observations from the full sample.
[b]Threshold values for epinephrine and IL-6 are below assay sensitivity (B.A.S.); assay sensitivity for epinephrine is < 2 μg/L, while assay sensitivity for IL-6 is < 0.1 pg/mL.
[c]Counts represent the maximum number of observations over which the percentiles for any one of the biomarkers are calculated; the number of missing observations varies across the biomarkers.