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Neuroendocrine biomarkers, social relations, and the costs of cumulative stress in Taiwan

Abstract

It is thought that the cost of cumulative life stress, or allostatic load (AL), may play a role in the causal pathway between social integration and health and that positive social relations could reduce such load. While AL constructs have been linked to negative health outcomes downstream, there is much less evidence showing that baseline AL is actually a reflection of previous life stress. This paper uses a measure of primary allostatic load (PAL), which is a construct focusing on four neuroendocrine biomarkers. This paper attempts to link PAL to enduring stressors, with attention to those related to social ties. An important finding is that current, subjective stressors (as reported among women) are correlated with PAL while various other stressors of an enduring nature are not. Among other things, these results suggest that the neuroendocrine markers of AL may be more reflective of a currently stressful state than a cumulative one over the life course. Investigators using variations of the AL construct should consider the possibility of non-linear relationships between life history measures and AL.

Keywords

Neuroendocrine biomarkers, stress, primary allostatic load (PAL), Taiwan, social relations

Introduction

Some of the earliest sociological works associated certain forms of social participation with reduced mortality (Durkheim 1951). Since then numerous studies, both cross-sectional and longitudinal, have linked greater social integration as measured by marriage, number of friends, and in other ways with improved morbidity and mortality (Umberson 1987; Taylor et al. 1997; Rogers et al., 2000). The magnitude of such findings has often been found to be on par with variables that have traditionally been given more attention in the literature, like smoking and race (Rogers et al., 2000). Most population surveys have attempted to explain the mechanisms by which social integration affects health by examining what might be considered overt factors like instrumental support. Yet social interaction may directly – and in the end must – affect one's physiology. That is, social relations have to get "under the skin" to eventually cause differential health outcomes.

The analysis here uses one of a new generation of surveys that combines physiological measures, or biomarkers, with traditional social variables. This sort of data combined in one survey holds promise to clarify the biological causal links between social connection and health, phenomena previously demonstrated to only be associated with one another. A theoretical framework underlying the survey's design is that of capturing the costs of cumulative life stress, or what is termed allostatic load (AL). *Allostasis*, originally proposed by Sterling and Eyer (1988), is the idea that the body must constantly adapt itself to changing environmental demands in order to achieve *homeostasis*, an "ideal steady state" (Timiras 2003). Allostatic load (AL) develops, according to the theory, when the repeated costs of dealing with stress accumulate to cause "wear and tear" on the body (McEwen 1998). AL supposedly leads in a number of different physiological systems to dysregulation, which is represented by system operation outside of normal ranges. AL is considered a pre-cursor to disease and eventual mortality (McEwen 1998).

Appropriate operationalization of AL is a major challenge (Seplaki et al. 2004; Hale 2004; Karlamangla et al. 2002). A key feature of the AL construct is inclusion of multiple biomarkers in a single index. To date, the most commonly used index stems from the MacArthur studies which used 10 individual bioindicators. High baseline levels on the MacArthur construction of AL predicted worse physical and cognitive functioning years later (Seeman et al. 1997). The index has been shown to be more predictive than individual biomarkers alone (Seeman et al. 1997). In many ways the physiological diversity captured by the index is its strength. However, the interpretation of AL is tricky because the entire construction is something of a hodgepodge in that it includes markers representative of many different biological systems (Tom Boyce, personal communication). Thus, understanding the dynamics of the index components is also necessary.

This paper will use an abbreviated AL construct that includes only primary mediators (more in the methods section). The construct is called PAL, an acronym for primary allostatic load. Generally this paper tests whether stressful life events are linked to higher PAL. In particular, four specific hypotheses related to social relations and PAL are investigated. The hypotheses tap stress conceptualized in terms of raw life events and subjective interpretations. 1) Widowhood status at the time of the survey should correlate with higher PAL. 2) The longer one has been widowed the greater one's PAL should be. 3) Since AL purportedly captures a lifetime's worth of stressful events, reports of *current* psycho-social stress *should not* matter. 4) The *length of time* respondents report psycho-social stress *should* be associated with higher PAL.

Taiwanese context

Brief section on some cultural and historical aspects of Taiwanese society that will be useful in interpreting later results

Methods

Data

I analyze the Social Environment and Biomarkers of Aging Study (SEBAS), a population survey conducted in Taiwan in 2000 (for a more detailed description of the study consult Weinstein and Goldman 2003). The survey is nationally representative of those 54 and older and includes the institutionalized population[1]. The SEBAS drew its sub-sample of respondents from a larger, ongoing longitudinal study called the Taiwan Survey of Health and Living Status. Among other things, the interview portion of the SEBAS included questions about cognitive functioning, psychological well-being, socioeconomic status, and life stressors. The in-home interviews averaged nearly an hour. With the respondents' additional consent, an appointment for lab work and a physical exam was made for several weeks after the interview. Lab work included collection of blood and urine samples to produce a panel of physiological measurements and the physical exam recorded information such as height and weight, blood pressure, and checked for physical abnormalities.

Of those originally contacted for inclusion in the 2000 SEBAS, 92% gave interviews and 68% of these participants consented to the clinical examination, for a total of 1023 respondents. Analysis reveals that partly because those most and least healthy declined to participate in the clinical exams, with controls for age results derived from this data are unlikely to be seriously biased (Weinstein and Goldman 2003). In about 4% of all cases proxies helped answer some questions for the respondents. Most often a spouse was the proxy and the reason most frequently given for needing the proxy's assistance was hearing troubles. The survey over-sampled those 71 years and older and urban residents. Univariate and bivariate analysis use weighted data (**I NEED TO DO THIS**). The multivariate models use unweighted data, but control for age and residence.

It is not possible to conduct a longitudinal analysis using biomarkers since earlier waves of the survey did not contain them. Nevertheless, the 2000 cross-sectional SEBAS has a number of strengths. First, it is unusual to have a survey including biomarkers that is nationally representative. Second, the response rate is relatively high, at over 90% for the interview portion. Third, the age range of 54-91 is wide relative to other studies of a similar design. Lastly, the SEBAS has collected neuroendocrine biomarkers, a rarity in population surveys and key to the testing of AL.

Dependent variable

<u>Background and justification for the included biomarkers</u>

The MacArthur index can conceptually be broken down into at least two major sub-indexes, the primary mediators and secondary outcomes (McEwen and Seeman 1999). The latter is comprised of more familiar measures such as cholesterol and blood pressure and is the more

[1] The survey does exclude the aboriginal population.

thoroughly tested of the two. Primary mediators include such neuroendocrine markers as cortisol, DHEAS, epinephrine, and norepinephrine. This paper focuses solely on the primary mediators for a number of reasons. First, as was mentioned in the introduction, the AL load construction as a whole is predictive of worse health outcomes but the role of its components has been less intensively studied. Second, in the experimental literature primary mediators are more clearly linked as outcomes of the stress response. Accurate understanding of the AL construct requires knowledge about these mediators. Third, it is rare to have biomarkers in social surveys but it is rarer still to have primary mediators. Consequently, on the population level, little is known about them. Fourth, the primary mediators (like the secondary ones) are, in the MacArthur studies at least, predictive of worse health outcomes in their own right and thus seem to warrant further study (Seeman et al. 2001).

Here I focus on a physiologically coherent class of markers representative of the neuroendocrine stress response. Because these are primary mediators the measure introduced here is called PAL, for primary allostatic load. Among PAL's greatest advantages is its interpretability that stems from grouping markers of a similar level of biological abstraction. PAL includes markers related to two systems: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). The HPA axis is key in regulating homeostatic processes in the body and environmental stressors can lead it as well other regulatory systems to react. Cortisol and DHEAS are indicators of HPA axis activity. The body's "fight or flight" response is in part mobilized by the SNS and its activity can be measured by norepinephrine and epinephrine levels.

Measurement of biomarkers

The survey tried to capture basal (resting or non-stressed) levels of the biomarkers. This is in contrast, for example, to studies that deliberately stress respondents with an interest in the dynamics of immediate physiological reactions and subsequent return to baseline levels. Also, instead of taking numerous "point in time" measures throughout the day via blood or saliva, integrated measures for three of the four neuroendocrine markers were collected via urine samples. That is, for cortisol, norepinephrine, and epinephrine respondents were asked to void urine at 7pm, which was discarded, and to collect all subsequent samples until 7am the following day. Because dissimilar body size leads to differential concentration of the neuroendocrine markers in the urine, total urine was standardized using grams of creatinine. The subjects fasted from midnight onwards until a study affiliate came to their home to collect the urine sample and during the same day blood was also drawn. The amount of DHEAS in the body was determined through the blood sample. Six data points had to be dropped because of missing data on the dependent variables. Further analysis revealed one extreme cortisol value that has also been subsequently dropped[2]. All other data points for the remaining biomarkers appear not to be errors and have been retained.

Because biomarkers can vary over the day and be influenced by a host of factors a few features of the study design likely limited intra-subject variation. The first was use of an integrated measure of certain biomarkers. Also, respondents collected urine samples at home, presumably a less stressful environment than a laboratory setting. As well, the influence of exercise on the neuroendocrine markers was probably curtailed since from 7pm to 7am the respondents likely spent much of their time sleeping. Lastly, the prohibition on eating after

[2] While cortisol distributions are normally right tailed and thus outlying values are expected, this particular data point was nearly 25 SDs above the mean for all cortisol values.

midnight standardized to some extent the number of meals and meal times. Unlike some clinical studies, however, the SEBAS did not place any sort of restrictions on the following: the dinner time, type and quantity of the dinner meal, exercise, smoking tobacco, and chewing betel quid. Biomarkers were obtained for all subjects regardless of health condition or medication use.

Index scoring

The most popular approach to operationalizing AL has been to create a score that gives one point for every biomarker where the subject can be considered at higher risk (i.e. the elevated risk zone approach). The literature most often represents high risk by greater values for cortisol, epinephrine, and norepinephrine and lower values for DHEAS; this tradition will be followed here[3]. Since there is no agreed upon standard for what biomarker values represent different risk levels, it has been most common to define risk as above or below distribution percentiles (e.g. 10^{th}, 25^{th}, 75^{th}, 90^{th}). Since subjects can be assigned 1 point on four biomarkers if they have high risk values, PAL scores can range from 0-4. The PAL score is the dependent variable in a linear regression. This paper presents results using the 25^{th} and 75^{th} percentile as cut-offs, but later does sensitivity analysis using other cut-offs. Additionally, a summed z-score is created for respondents, which is the total number of standard deviations from the mean in the direction of high risk for each biomarker. Unlike the cut-off approach, an index using the z-score method allows for unequal weighting of the biomarkers (e.g. a combined z-score of 3 could stem from being 2 SDs above the mean for cortisol, 1 SD above the mean for epinephrine, and the mean for the other two measures). The combined z-score is again the dependent variable in a linear regression and can range from 0 to no pre-determined upper limit.

Independent variables

One set of variables of interest are those pertaining to life events. These include demographic characteristics like education and ethnicity. One respondent reported an ethnicity other than Hakka, Fukienese, or Mainlander and was dropped from the analysis. Other life event variables, such as marital status, participation in group activities, and whether or not the respondent lives with a married son, tap social connectedness. With the exception of marital status, information for respondents earlier than 2000 is not available. Those never married, divorced, or separated have been excluded (n = 50, 5% of sample) from the analysis. Thus, the sample includes only those who voluntarily entered a union and whose union ended involuntarily through spousal death. The main purpose for the exclusion is to minimize the number who spent time in an undesirable marriage (such as divorcees) for whom the state was more likely to be stressful.

The second set of variables of interest is psycho-social stressors. Only questions from the survey that were related to social stressors were included (e.g. stress questions concerning the respondent's own health were excluded). Respondents were asked whether certain situations made them *currently* feel stressed or anxious. In the multivariate regressions six stressors were used to form an index representing the number of times one reported experiencing the stressor. One of the six stressors asked about "getting along with family members (e.g. not getting along well, tension, conflict)". Four others probed stress over "family members' or children's" health, financial situation, job, and marital situation. The last question included in the index was open ended and allowed the respondent to mention a stressor not already asked in the survey. Of these

[3] For a number of other scoring schemes see Seplaki et al. (2004), Hale (2004), and Karlamangla et al. (2002).

responses only the ones related to social stressors were used. Proxy responses were not allowed for the psycho-social stress questions, leading to a reduction in sample size when the index variable is included in the model. If a participant answered affirmatively to currently experiencing a stressor, he or she was then also asked for how long it was felt. Another index was constructed by simply summing the years of reported stress across each of the six questions.

In this paper I control for a number of pertinent variables that have been overlooked in previous studies of this data set. Epinephrine, norepinephrine, and (especially?) cortisol levels can be influenced by a wide range of factors including diet, meal times, exercise, smoking, and medications. Particular to the Taiwanese context, betel quid chewing is known to elevate epinephrine and norepinephrine levels.

Results

Table 1 presents a comparison of mean PALs for different demographic characteristics, social connectedness variables, and psycho-social stressors. Relative to men, women have over twice the mean PAL, the largest ratio of the table. This differential must be explained by some phenomenon other than age since men are actually older in this sample. One might reasonably argue that higher levels of education might indicate or lead to greater access to resources and be linked to lower levels of lifetime adversity. This interpretation is supported by lower mean PALs. As expected, those widowed have higher PALs than the married respondents and the difference is statistically significant. Somewhat surprisingly, other social connectedness variables reveal no association to PAL. A gradient pattern is also observed for age, which is reassuring since AL theory postulates that the consequences of stress are cumulative throughout the life course.

For each psycho-social stressor examined, the PAL is higher for those who report the stressor compared to those who do not (Table 1). The ratio is highest for those who volunteered a familial stressor not asked in the survey, but the result is not statistically significant since so few persons volunteered a response. Table 2 shows the percent reporting various stressors and their lengths for each sex. Forty percent of the women in the sample are widowed and amongst the widowed of both sexes women have been in the state longer. For every familial stressor, a greater percentage of women report being stressed. Fifty percent of women report at least one of the familial stressors and the difference relative to men is statistically significant. Despite reporting more stressors than men, when controlling for number of stressors reported the total years stressed was the same for men and women.

Table 3 presents a linear regression, where sets of relevant variables are stepped in for the various models. Widowhood remains significant through model 4 where reported number of stressors and education in years are also included. Once female sex is included in the regression (Model 5), however, widowhood is no longer significant because those widowed are disproportionately female and being female is correlated with higher PAL. Model 7 includes significant interaction effects and all controls. There is no widowhood and sex interaction term since for both men and women widowhood status is not significant. Model 7 shows that for both men and women increasing age is linked to higher PAL, but that for women the slope is even greater. For women, but not for men, greater number of reported stressors is related to higher PAL.

In linear regressions not shown, the connection between lengths of time having experienced certain stressors and PAL was investigated. First, a regression for only the widowed was performed. It was identical to that in Table 3 except that years of widowhood replaced marital status. Years of widowhood were unrelated to PAL with controls for other factors and

this result held for both men and women. Including a "years of widowhood squared" term to the regression to capture any quadratic functional form did not change the results. Second, a similar analysis was carried out for total years of reported stressors. If number of reported stressors is already in the model, the term for cumulative years of stress experienced is insignificant.

The results already described are robust to alternate index constructions. Using the 15th and 85th, and the 10th and 90th, percentile cut-offs do not alter the conclusions. Nor are they altered using all of the various cut-points with a dichotomized dependent variable in a logistic regression. As well, the combined z-score method for operationalizing the dependent variable produces very similar substantive outcomes.

Discussion

This paper investigated an index of neuroendocrine markers, or primary allostatic load (PAL), in relation to life stressors and subjective reports of stress. How do the findings in this paper compare and reconcile with other published work? Two articles related to this one are papers by Seeman et al. (2004) and Goldman et al. (under review) which have examined the same data set. Seeman and others investigated the affect of a number of variables related to the social environment, including marital status, on a construction of AL. They separated the analysis by two age categories, the elderly and near-elderly. The authors did not investigate years widowed as in the paper here, but a change in state (e.g. married to widowed) from the beginning to the end of the period. For the elderly the period ranged from 1989 to 2000 and for the near elderly from 1996 to 2000. For near elderly men only, she found that the presence of a spouse between those 4 years was associated with lower AL. A comparative advantage of the paper here is its use of the actual years widowed ranging over a long span (from less than a month to 48 years) and an analysis of the relation of various functional forms to PAL. This paper found no support that in Taiwan, and for either sex, that marital status and years married correlates with a measure of the costs of cumulative stress. The findings here, then, extend and by and large strengthen the earlier findings of Seeman and others.

The paper by Goldman et al. focuses on perceived stress and an expanded construct of AL. The perceived stressors need not stem from more direct interpersonal sources (e.g. personal financial problems could be included). They examine stressors between 1996 and 2000 for all ages and only the demographic variables age and sex are used as controls. Goldman and her co-authors finds that among female Taiwanese more reported stressors in 2000 is positively associated with their construct. These results are congruent with the abbreviated PAL construction and index reflecting number of stressors used here. Goldman also finds that when a measure of stress over the period from 1996 to 2000 is also included in the model it has explanatory power in addition to that of the 2000 measure alone. They suggest that length of time one experiences perceived stress may affect biological function. This finding does not accord with the study here. There are numerous possible reasons for the discrepancy. One is that her design allowed for the possibility that respondents report stress in 1996 and 1999 but not in 2000. In the study here, respondents were first asked whether they currently experience a stressor and, if so, for how long. Amongst only those who reported a stressor in 2000, the length of time it was felt did not correlate with the PAL construct.

I now turn to a broader discussion of the findings in this paper. One can usefully categorize the results here as somewhat and not supportive of AL theory. Starting with the former category, older age was associated with greater PAL. This is a necessary but not sufficient condition in support of the construct. That is, almost by definition as one grows older

one lives through a greater number of stressful experiences, so if PAL did not increase by age that would be a serious challenge to the theory of allostasis. As expected, being a woman was associated with higher PAL. Women in Taiwanese society are held in lower esteem and have fewer advantages relative to men and such a position may very well be stressful. However, it is impossible to disentangle this explanation for their higher PAL from the possibility that women simply have higher levels of these biomarkers due to innate biological differences or that they react to similar life experiences as men in different ways.

Regarding the group of variables not supportive of AL theory, none of the life event variables that one would assume a priori are stressful were significant. For example, low education, rural residence, and being an ethnic minority were statistically insignificant variables. As well, for both sexes, widowhood status was insignificant and so too were years widowed among those without a spouse. This finding is surprising in light of research that indicates for men more so than for women loss of a spouse represents loss of the primary source of emotional support. More importantly for the theory of allostasis is that once the number of psychological stressors was considered, the length of time respondents experienced them was not significant.

A key element of allostatic theory is that the cost incurred by the body in dealing with stressors is cumulative over the entire life course. A stressor currently experienced should have negligible effects on an adult's AL. Here, however, amongst women only, the number of current stressors reported was significantly correlated with PAL. If the operationalization of AL better matched the theory the results presented in this paper would be reversed. That is, reports of current stress would not be significant whereas length of stressors would be.

It has been thought that the current biomarker measures are capturing two phenomena simultaneously. This distinction has probably been underemphasized in the literature. One component of PAL supposedly captures readjusted baseline levels that become dysregulated through the life course. The second component captures effects of more immediate events of the day and even weeks before the biomarker collection. According to AL theory, the first component should predominate and can be thought of as the "signal" whereas the second part is "noise" and should be reduced to the extent possible.

If, as seems to be the case in this paper, recent events strongly affect the PAL measure, assuming a linear relationship between PAL and a major life stressor like widowhood may be a mistake. For example, the PAL of those recently widowed may be similar to those widowed for a long time but for different reasons. There is the initial shock of losing a spouse from which one slowly recovers on one end of the spectrum (a peak in PAL) and at the other there is the widow or widower who, after many years, has coped with the loss but whose PAL has incrementally increased (another peak in PAL) because the unmarried state is presumably more stressful than the married one. In other words, the former case may capture more of the noise and the latter the signal. Testing for a quadratic relation over time, rather than a linear one where the differing phenomena would be obscured, seems prudent but this strategy appears rarely carried out in studies to date.

Figure 1 represents some of the issues described above in schematic form. The top panels present a hypothesized, non-zero stress level stemming from normal activity and then levels after exposure to a stressful shock that remains a permanent stressor (i.e. stress levels do not return to baseline). One could imagine a number of potential stressors fitting this scenario including chronic disease or widowhood. The panels on the right incorporate the idea that stressors have an acute phase and recovery period and that corresponding PAL trends are influenced by current events. The panels on the left ignore the psychological coping involved in dealing with stress as well as the observation here that one's current state of stress may affect the PAL construct. This paper posits that the panels on the right may be more accurate than their counterparts on the left.

Partly based on some of the findings of this paper, it seems that some further developments in survey design related to AL could be recommended. First, a key element of AL theory is that it purportedly captures lifetime cumulative adversity. A simple question could be posed in the mold of the global self-assessed health question that we know to be highly predictive of future morbidity and mortality. For example, "Over your entire life course (from birth until the present), would you say the stress that you have experienced is very high…moderate…very low". A variant of this question could ask the respondent to compare lifetime adversity to age peers. One would expect that the answers would highly correlate with AL measures. The respondent could also be asked overall levels of stress currently experienced which would allow a more direct comparison of the contributions of current and past stress to PAL or AL measures.

Other methodological considerations include collection of the biomarkers as soon as possible after respondents give their survey answers to whether they are currently stressed. In the SEBAS biomarkers were collected weeks after the interview. It is likely that the strength of the correlation between report of current stressors and PAL would be greater if this lapse was reduced. A further improvement in studies like the SEBAS would be a tighter correspondence between the life event and subjective measures. Stress in an elusive concept, but we can be more assured one is "stressed" if physiological measurements correspond to both life events and subjective interpretations of those events. In the case of widowhood, for instance, this study assumed a priori that it was stressful. Combining this widowhood variable with questions probing respondents' subjective stress related to the loss would be more ideal.

Lastly, in returning to the motivation of the study, to what extent has this paper made progress in the larger project of uncovering the causal mechanisms of social connectedness and health? Given the limitations of the PAL measure and the survey it is hard to say. More than anything, it seems that the results here highlight the need for future research to consider the negative side of social relations. Many respondents reported social stressors in their lives and for women the reports were linked to higher PALs, a risk factor for poorer health.

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Table 1 – Comparison of mean PAL for demographic, social connectedness, and psycho-social stressors variables[+]

Variables	Ratio of PAL means	% (N)
Demographics		
Sex		
Male	1	58 (585)
Female	2.2***	42 (431)
Age[++]		
54-64	1	37 (380)
65-79	1.5**	54 (546)
80+	2.0***	9 (90)
Education		
High (> primary)	1	59 (596)
Low (≤ primary)	1.5***	41 (420)
Ethnicity		
Mainlander	1	17 (173)
Hakka/Fukienese	1.1	83 (842)
Social connectedness		
Marital status		
Married	1	75 (721)
Widowed	1.5***	25 (245)
Lives w/married son		
Yes	1	42 (423)
No	.94	58 (593)
Lives alone		
No	1	93 (942)
Yes	.98	7 (74)
Group participation		
Yes	1	44 (449)
No	1.1	56 (567)
Psycho-social factors		
Current familial stressors		
Family's work situation		
No	1	78 (743)
Yes	1.3*	22 (211)
Family's financial situation		
No	1	75 (714)
Yes	1.2	25 (243)
Family's health		
No	1	79 (754)
Yes	1.1	21 (206)
Family's marital situation		
No	1	78 (736)
Yes	1.2	22 (209)
Familial tension/conflict		
No	1	94 (895)
Yes	1.4	6 (60)
Other familial stressor (volunteered)		
No	1	99 (989)
Yes	1.7	1 (6)

Note: *, **, and *** for .05, .01, and .001 significance level, respectively.

[+] One-tailed cut-off points either at the 10^{th} or 90^{th} percentile.
[++] Significance levels are relative to the baseline category.
To self: Redo figures using weights??

Table 2 – Percent reporting various stressors and length of the stressors in years, by sex

	% Reporting stressor		Length of stressor, for those reporting it, in years[+]			
Stressor	Men	Women	Men		Women	
			Mean	Range	Mean	Range
Life event (social)						
Widowhood	14	40***	10.3	0-39	14.6**	0-48
Psycho-social						
Family's work situation	20	25	5.5	0-30	7.2	0-50
Family's financial situation	22	30**	6.9	0-42	8.3	0-50
Family's health	20	23	10.1	0-88	9.3	0-50
Family's marital situation	19	26**	6.3	0-28	7.0	0-50
Familial tension/conflict	6	7	9.1	1-31	13.1	0-30
Other familial stressor (volunteered)	0.3	1	25.0	10-40	6.0	3-8
≥ 1 psycho-social stressor	43	50*	--	--	--	--
All psycho-social stressors combined[++]	--	--	15.0	0-146	18.0	0-150

Note: *, **, and *** for .05, .01, and .001 significance level, respectively.

[+] This analysis combines stressors as reported in years and months. In regard to the range of a stressor, a zero is one that occurred within the past year. For determining statistical significance of sex, length of stressor was the dependent variable in a linear regression with only sex and age as covariates.

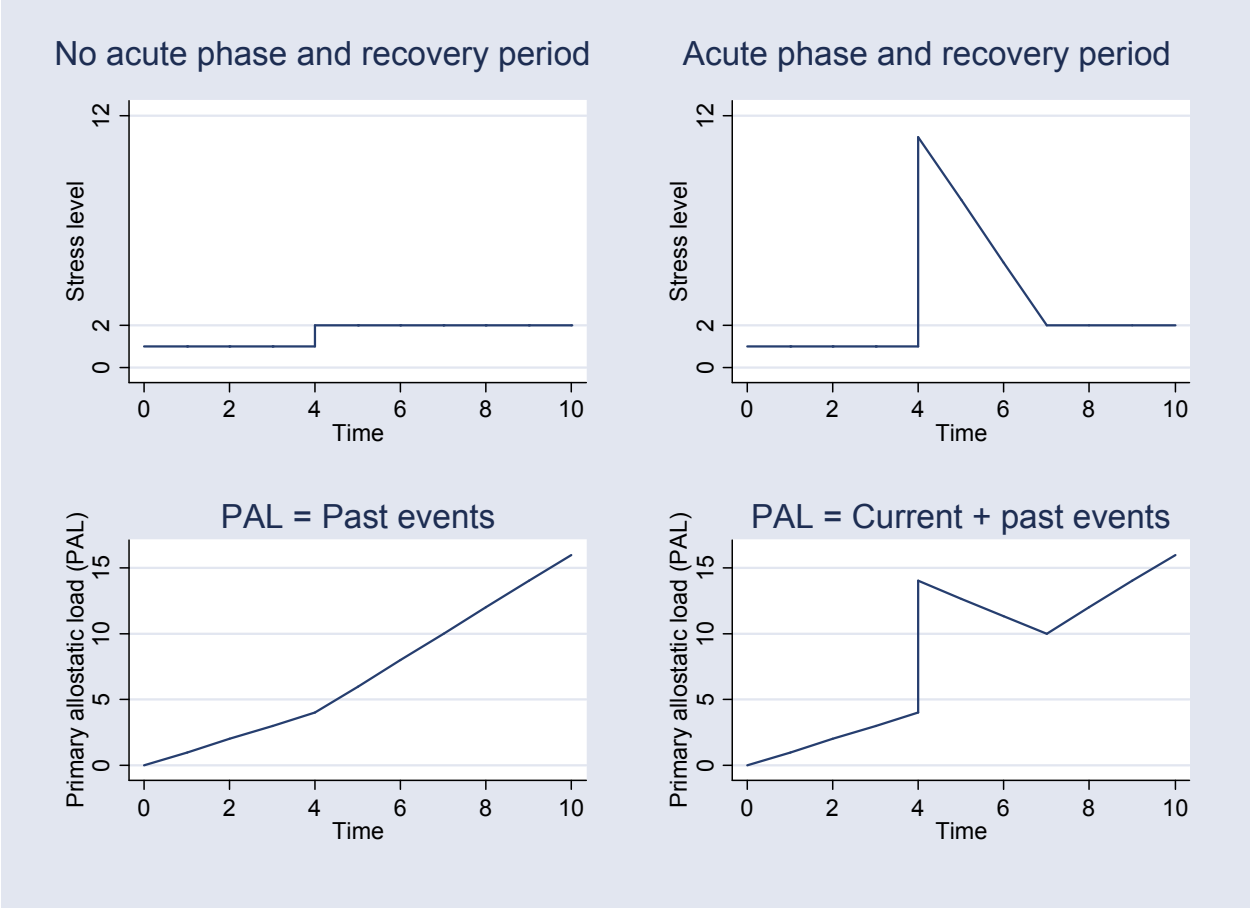
[++] For this variable only, a term for the number of stressors reported was also included in the model.

Table 3 – Theory driven stepwise linear regression with PAL (scored from 0-4) as dependent variable[+]

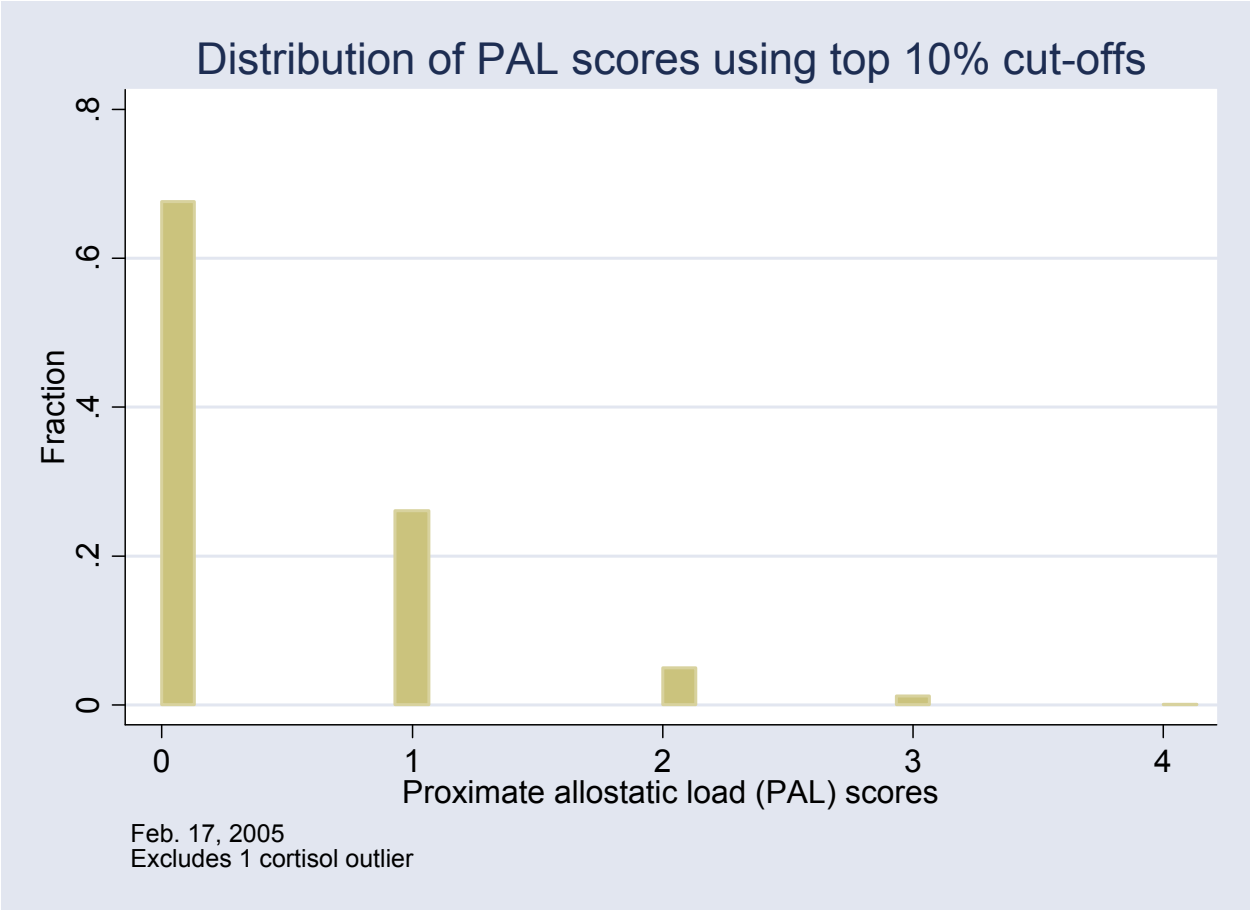
Variables	1	2	3	4	5	6	7
Widowed	.19***		.19***	.17**	.07	-.03	-.08
Lives alone	-.17		-.22	-.19	-.14	-.13	-.10
Does not live with married son	.00		-.01	.01	-.01	-.00	.01
Participates in no group activity	.03		.03	.02	.02	.01	.01
Reported family stressors (0-6)		.04*	.04*	.03	.03	.04*	-.01
Education in years				-.01*	-.00	.00	.00
Female					.34***	.38***	-.65
Age in years						.01***	.01*
Age x female							.01**
Reported stressors x female							.10**
Mainlander							not sig.
Urban residence							not sig.
Health behaviors[++]							--
N	966	931	911	911	911	911	906

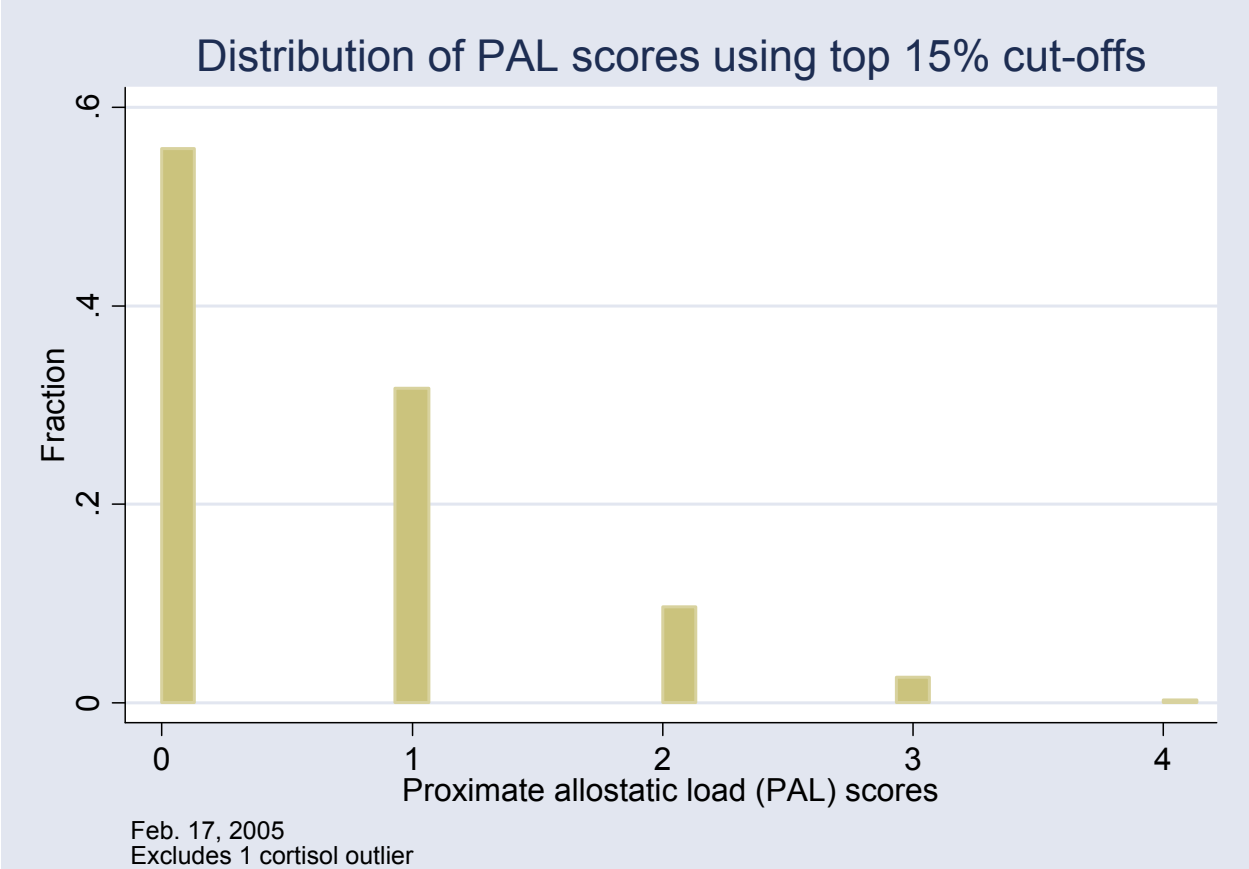
Note: *, **, and *** for .05, .01, and .001 significance levels, respectively.
[+] One-tailed cut-off points either at the 10th or 90th percentile.
[++] Controls include dummy variables for medication use, diet, exercise, betel quid chewing, and smoking.

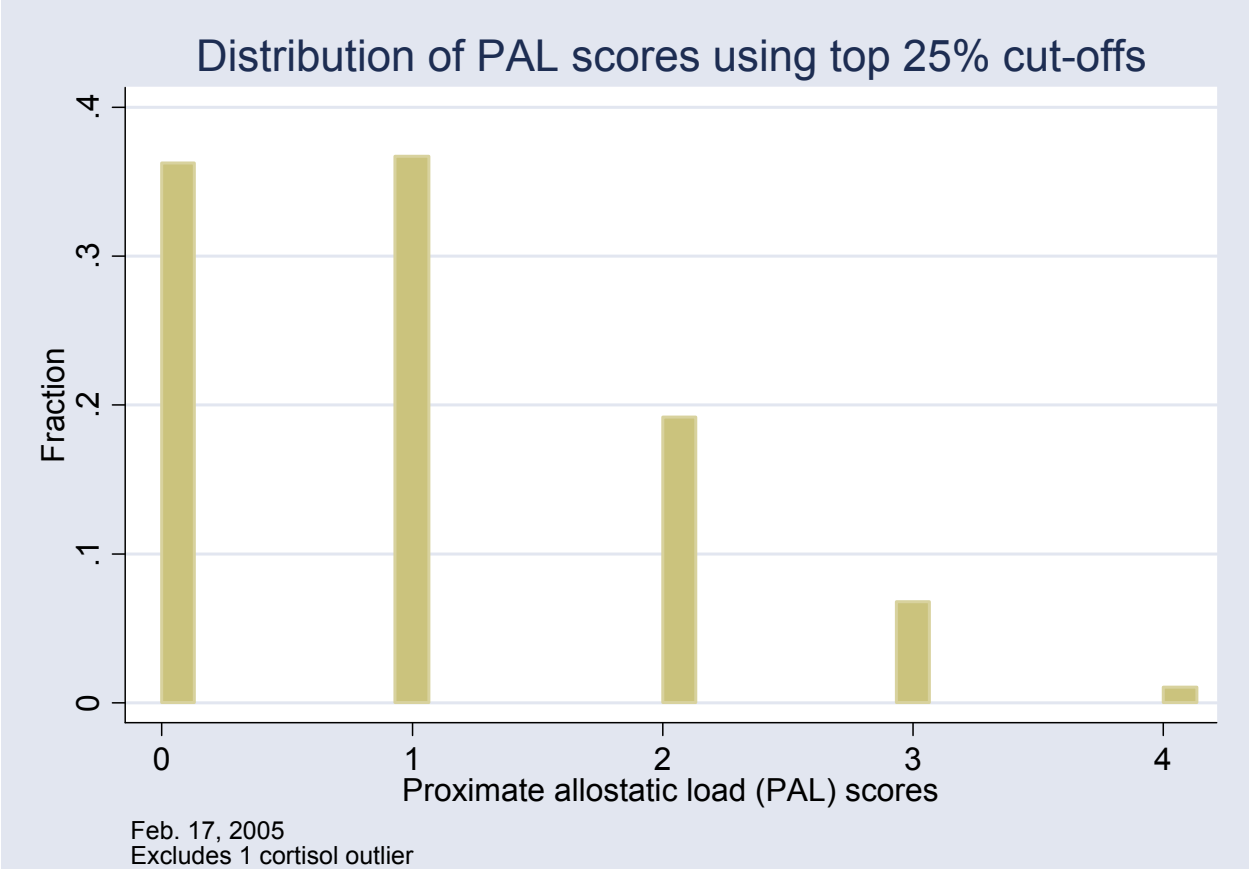
Figure 1 – Permanent stressors with and without an acute phase and recovery period and corresponding PAL trends with and without the influence of current events

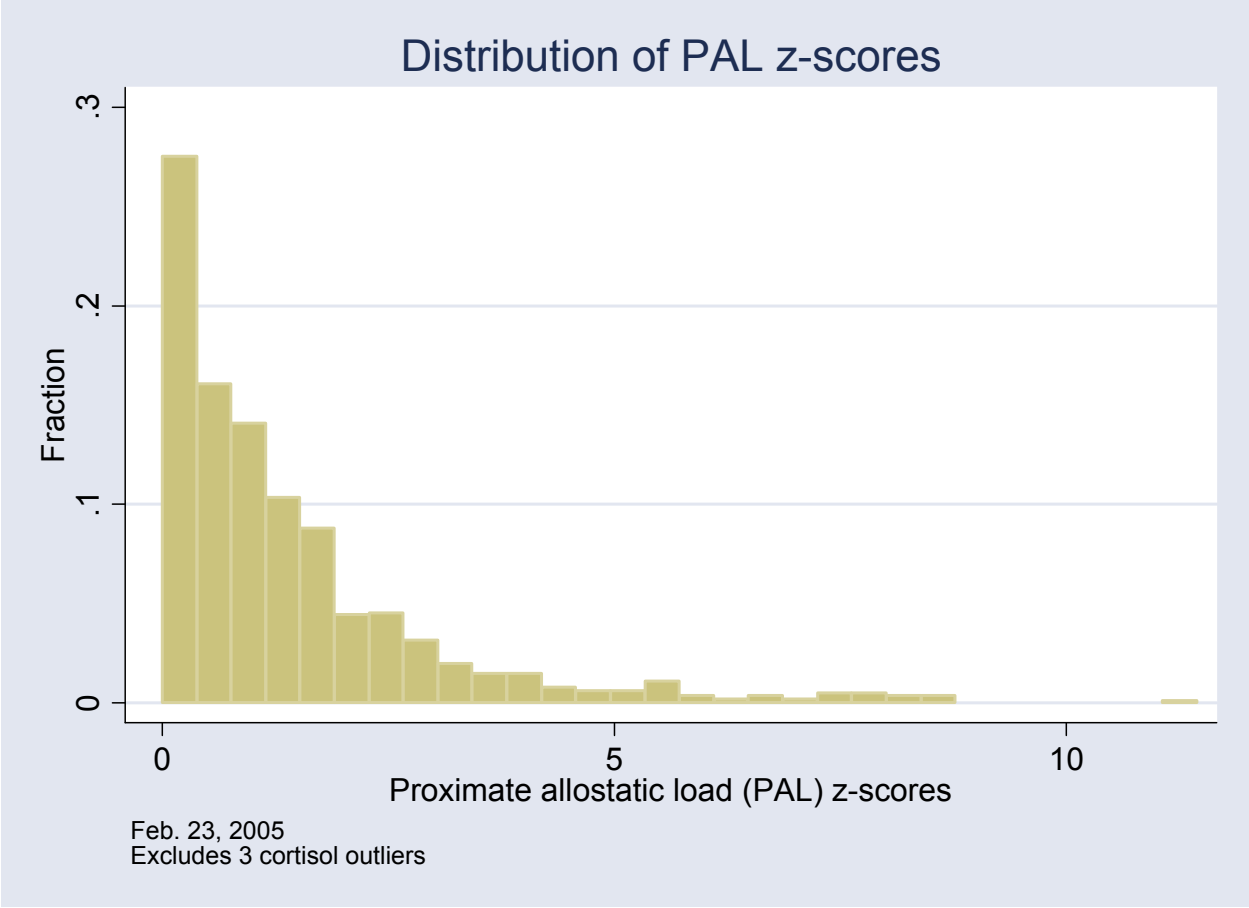


Appendix


Distribution of PAL scores using top 10% cut-offs
Fraction
0
.2
.4
.6
.8
0
1
2
3
4
Proximate allostatic load (PAL) scores
Feb. 17, 2005
Excludes 1 cortisol outlier


Distribution of PAL scores using top 15% cut-offs
Fraction
0
.2
.4
.6
0
1
2
3
4
Proximate allostatic load (PAL) scores
Feb. 17, 2005
Excludes 1 cortisol outlier


Distribution of PAL scores using top 25% cut-offs
Fraction
0
.1
.2
.3
.4
0
1
2
3
4
Proximate allostatic load (PAL) scores
Feb. 17, 2005
Excludes 1 cortisol outlier


Distribution of PAL z-scores
Fraction
0
.1
.2
.3
0
5
10
Proximate allostatic load (PAL) z-scores
Feb. 23, 2005
Excludes 3 cortisol outliers