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

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Abstract

Allostatic load (AL) is thought to represent the physiological toll that builds up over the life course as a consequence of the body's response to stress. An important aim of this paper is to test this widely held – but little investigated – understanding of what AL represents. More specifically, using the Social Environment and Biomarkers of Aging Study (SEBAS), a nationally representative survey of Taiwan conducted in year 2000, this paper scrutinizes the connection between stressful life histories and neuroendocrine allostatic load (NAL). The 2000 SEBAS is a cross-sectional survey with over 1,000 participants (of men and women) age 54-91 and contains both traditional social variables and a number of physiological measures. Stressful life histories are operationalized through the use of two sets of indicators: one set makes use of respondents' subjective interpretations of various life domains and the other makes use of non-subjective data about conditions that are expected to be stressful (e.g., widowhood, living alone, low education). NAL is an index of four neuroendocrine biomarkers (cortisol, DHEAS, epinephrine, norepinephrine) collected in blood and urine samples under resting, basal states.

The major findings of this paper are twofold. First, there is little evidence to support the hypothesis that baseline levels of the neuroendocrine markers stem from stressful life histories. Second, report of current stress (among women only) is positively correlated with higher NAL levels. Taken together, these findings question whether the neuroendocrine markers of the AL construct reflect long-term processes over the life course. Indeed, evidence here suggests that the neuroendocrine markers may reflect the exact opposite – a transient state at the time of the study.

Keywords

Neuroendocrine biomarkers, stress, neuroendocrine allostatic load (NAL), Taiwan, social relations, health

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Introduction

Numerous studies, both cross-sectional and longitudinal, have linked greater social integration as measured by marriage, number of friends, and in other ways to improved morbidity and mortality (Berkman & Glass, 2000; Rogers, Hummer, & Nam, 2000; Taylor, Repetti, & Seeman, 1997). One of many hypothesized pathways by which greater social integration is thought to lead to better health is that those who are more integrated may experience reduced levels of stress. Reduced stress among the socially connected may come about, in part, through the avoidance of stress-inducing social isolation and a social network that can provide assistance in times of need (e.g., during emotional, health, financial problems) (Cacioppo & Hawkley, 2003; Kawachi & Berkman, 2000; Thoits, 1995). Indeed, a number of experimental studies have documented the salutary impact of friends and other supporters on study subjects exposed to stressful laboratory situations. Supported subjects often exhibited less risky levels on a variety of physiological parameters (e.g., blood pressure, heart rate, cortisol levels) potentially important in causing a number of major health problems (Knox & Uvnäs-Moberg, 1998; Uchino, Cacioppo, & Kiecolt-Glaser, 1996).

To date, in population studies (in contrast to much smaller and controlled experimental ones), the hypothesis that greater social integration is linked to more favorable biomarker profiles (thus providing specific biological evidence of how the social world can get "under the skin" to affect health outcomes) has not been much tested. The dearth of studies investigating an underlying biological mechanism to explain the association between social connection and health stems in large part from the heretofore relative lack of inclusion of biomarkers in large-scale population surveys. Partly to address this gap in the literature, the analysis here uses a nationally representative study conducted in Taiwan (the Social Environment and Biomarkers of Aging Study) that has collected physiological measures, along with traditional social ones. Using this survey, I test the hypothesis that indicators of greater social integration (and lower levels of life history stress more generally) yield more favorable biomarker profiles. The paper here focuses on the neuroendocrine markers of a construct (growing in use) that purportedly measures the costs the body incurs in responding to stress (more below).

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; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). AL supposedly accumulates throughout the life course and eventually leads in a number of different physiological systems to dysregulation, which is represented by system operation outside of typical ranges (McEwen, 1998; Seeman et al., 1997). AL is considered a pre-cursor to later morbidity and mortality (McEwen, 1998; Seeman et al., 1997).

At least two important questions can be asked about AL. First, how predictive is the construct of negative health outcomes? Second, to what extent is AL representative of a life history of stressful insults? Regarding the first question, mounting evidence indicates that high AL is a risk factor for later cognitive and functional decline (Seeman et al., 1997) and mortality (Goldman, Turra, Glei, Lin, & Weinstein, 2006; Seeman, McEwen, Rowe, & Singer, 2001). These results seem to hold whether biomarkers indicative of the metabolic syndrome (e.g., cholesterol, blood pressure, waist-to-hip ratio) or biomarkers indicative of neuroendocrine function (e.g., cortisol, norepinephrine, epinephrine, DHEAS) are examined separately (Seeman et al., 2001).

Regarding the second (and arguably harder to resolve) question, an analysis of the MacArthur Studies has been able to link positive social experiences to lower AL (Seeman et al., 2002) and two analyses of a small sample of the Wisconsin Longitudinal Study have been able to link positive economic and relationship histories to lower AL (Seeman et al., 2002; Singer and Ryff, 1999). Similar types of investigations have been carried out in an eastern context. A pilot study in Taiwan suggested a positive connection between demands placed on respondents and higher AL (Weinstein et al., 2003), whereas a larger study also in Taiwan found only modest relationships between indicators of greater quantity and quality of social connection and higher levels of AL (Seeman et al., 2004). Lastly, Goldman and others (2005) analyzed a measure of perceived stress in 2000 and over a four-year period (in the same Taiwanese data set) found that the perceived stress measures only correlated in a limited way to biomarkers analyzed individually, but that the perceived stress measures did positively correlate to higher levels of an AL construct in which the biomarkers were combined.

Like the papers just described, the paper here investigates the relationship between stressful life histories and an AL measure. I seek to extend our understanding of this relationship by, among other things, examining a large data set (1,000+ persons) and focusing on hitherto unused measures of stress duration that allow for open-ended responses. Further, the paper here focuses on a key component of the AL construct, the neuroendocrine markers. This focus is important because, as mentioned before, high levels of the neuroendocrine markers appear to be risky. Yet, as suggested in the preceding discussion, it remains unclear whether a stressful life history is linked to levels of this integral component of the larger AL measure.

Taiwanese context

China regained control of Taiwan, named “beautiful island” by early sailors, with Japan's World War II defeat (Greenhalgh, 1984; Weiming, 1996). Shortly thereafter, conflict on the Mainland precipitated an emigration of approximately one million military and civilian supporters of the Nationalist (Koumintang) army to the island. The new arrivals, who were mainly younger and male, assumed positions of power vacated by the Japanese (Mason & Lee, 2004; Weiming, 1996). To this day, “Mainlanders” (these Chinese immigrants and their descendents) are overrepresented in higher status professions and until very recently maintained political power (Gold, 1996; Goldman, Cornman, & Chang, 2006; Greenhalgh, 1984). Mainlanders are also more likely to live in urban areas, have higher levels of education, and, since they tended to arrive without other kin, less likely to live in extended family arrangements and more likely to rely on formal sources of support (Beckett, Goldman, Weinstein, Lin, & Chuang, 2002). The other main ethnic group is the Taiwanese, having arrived in Taiwan nearly 150 years before the Mainlanders.

Despite changing norms, the preferred living arrangement for Taiwanese parents is still with their children and grandchildren, where “three generations live under the same roof” (Lin et al., 2003). Coresidence with married sons is considered ideal, and it is not uncommon for parents with more than one son to rotate among their sons' residences (Lin et al., 2003). Although there are increasingly state-funded institutions to provide support for the aged, it is still very much expected that children personally care for their parents and provide financial assistance (Kao & Stuifbergen, 1999). Sons, and especially the oldest ones, provide most of the various types of support, but daughters will do so if sons are not able to (Lee, Parish, & Willis, 1994).

Chinese culture has been heavily influenced by Buddhism, Taoism, and especially Confucianism, with these philosophies/religions affecting, among other phenomena, notions of the self in relation to others. The importance of a lack of self-centeredness and the importance of connection to others, self-sacrifice for the group and collectivity, as well as social harmony has been emphasized by these teachings (Chen, 2001; Smith, 1991). It has been hypothesized that this general sense of interdependence and collectivism mitigates the deleterious effects for the "socially impoverished," as based on Western measures (Liang et al., 1999; Cornman, Goldman, Glei, Weinstein, & Chang, 2003; Seeman et al., 2004).

Another important feature of Taiwanese society is the role of age and generation. Growing old is considered "one of the five great blessings" of life, and respect and deference to the elderly is the norm (Silverman, Hecht, & McMillan, 2000). Increasing age is associated with greater authority, decision-making power, and improved treatment by children and others (Beckett et al., 2002). Chinese culture has also placed great value on education, and in modern-day Taiwan educational attainment remains a critical component of social status and a vehicle for upward mobility (Smith, 1991; Weinstein et al., 2003).

Research hypotheses

Based on knowledge of the Taiwanese context, knowledge of the social relations and health literature, and available survey data, I chose certain variables to indicate (roughly) levels of social integration. Since the expectation is that indicators of a lack of social integration represent more stressful states, all of the following should lead to worse biomarker profiles: widowhood, not living with a married son, living alone, and not participating in groups. In regard to other demographic characteristics, I expect low education and increasing age to be associated with higher load. Low education is likely a good indicator of low socioeconomic status which, compared to its opposite, likely results in more stressors and less resources to deal with them once they occur (Liu, Hermalin, Chuang, 1998; Zimmer, Lin, Hermalin, & Chuang, 1998). Since AL purportedly represents the accumulated costs to the body in dealing with stress and exposure to stress can only accumulate with time, greater age should be correlated with greater load. This relationship between age and load should hold despite the increased deference and respect accorded to the Taiwanese elderly. The directionality of ethnicity is unclear. Mainlanders, for instance, have had experiences suggestive of both a less stressful life history (e.g., traditionally holding positions of power) and a more stressful this life history (e.g., living through uncertain and disruptive wartime conditions, leaving behind family in their migration to Taiwan) (Zimmer, Martin, & Lin, 2005; Zimmer et al., 1998). The hypothesized directionality of urban or rural residence is also uncertain, but area of residence is potentially important (Greenhalgh, 1984; Wang, Snyder, & Kaas, 2001; Zimmer, Natividad, Lin, & Chayovan, 2000) and is thus included in the models.

I also analyze subjective reports of stress. From the perspective of AL theory, when only the number of currently reported stressors is in the models, its expected correlation with load is uncertain. On the one hand, reports of current stress should not affect load because a whole life history of stress should dwarf the effect of any current condition. On the other hand, a report of current stress may be indicative of having also experienced stress in earlier periods. In the case where number of currently reported stressors and duration of those stressors are both in the models, the expectation is clear: duration should be significant, while the number of reported stressors should be insignificant.

Data

Overview of the data set

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 Goldman et al., 2003). The survey is nationally representative of those 54 and older and includes the institutionalized population. The SEBAS drew its sub-sample of respondents from a larger, ongoing longitudinal study called the Survey of Health and Living Status of the Elderly in Taiwan. The interview portion of the SEBAS included questions about cognitive and physical functioning, psychological well-being, socioeconomic status, and life stressors. The in-home interviews averaged nearly an hour. With the respondents' additional consent, they were scheduled for lab work and a physical exam 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 a number of health problems.

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 1,023 respondents. Analysis reveals that partly because those most and least healthy declined to participate in the clinical exams, with controls for age, estimates derived from the clinical information are unlikely to be seriously biased (Goldman et al., 2003). Of those respondents who participated in the clinical examination, only 10 failed to fully comply (by not following the urine protocol, by not providing a sufficient volume of blood suitable for analysis, or by not completing the medical exam). 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.

Dependent variable

The neuroendocrine biomarkers

In this paper I focus on cortisol, DHEAS, epinephrine, and norepinephrine, a physiologically coherent class of markers representative of the neuroendocrine stress response (Cohen, Kessler, & Gordon, 1995; Crimmins & Seeman, 2001; Sapolsky, 2004). The measure introduced here based on these markers is called NAL, for neuroendocrine allostatic load[1]. Among NAL's greatest advantages is its interpretability that stems from grouping markers of a similar level of biological abstraction. Additionally, although the neuroendocrine biomarkers are core to the body's stress response, relative to other typical AL markers (e.g., cholesterol, blood pressure, waist-to-hip ratio), we know relatively little about them (Gersten, 2006). NAL includes markers related to two neuroendocrine systems: the hypothalamic-pituitary-adrenal (HPA) axis

[1] In other work, these four neuroendocrine biomarkers have been referred to as non-syndrome X markers. For this analysis, this seems like a poor name since it highlights what the markers are not, rather than what they are. In previous research, neuroendocrine markers have also been referred to as primary mediators. Besides being a vague term, primary mediators can also include a number of other biomarkers in addition to the neuroendocrine ones. As far as I know, then, I am the first to use the term neuroendocrine allostatic load, although I follow other researchers in analyzing them collectively.

and the sympathetic nervous system (SNS). The HPA axis is key in regulating homeostatic processes in the body, and environmental stressors can lead the axis as well other regulatory systems to react (Cohen et al., 1995; Crimmins & Seeman, 2001; Sapolsky, 2004). 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 (Cohen et al., 1995; Crimmins & Seeman, 2001; Sapolsky, 2004).

Measurement of biomarkers

The survey tried to capture basal (resting or non-stressed) levels of the neuroendocrine biomarkers. Additionally, "integrated measures" for three of the four markers were collected in 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 samples, and during the same day blood was also drawn. The amount of DHEAS in the body was determined through the blood sample.

Blood and urine specimens were sent to Union Clinical Laboratories (UCL) in Taipei. In addition to routine standardization and calibration tests performed by the laboratory, blind duplicate samples were submitted to UCL periodically throughout the fieldwork and a further set of duplicates were sent to Quest Diagnostics in the United States for analysis. Data from duplicate samples indicate intra-lab correlations (UCL and UCL) of 0.80 or higher and inter-lab correlations (UCL and Quest Diagnostics) of 0.76 or higher. Despite the high intra- and inter-lab reliability, some measurement error in the markers is likely because the blood and urine samples were taken either at one point in time or over a narrow time span.

Independent variables

Demographic and life event variables are one set by which a stressful life history is operationalized. Variables such as marital status, participation in group activities, and coresidence with a married son tap social connectedness. With the exception of marital status, information for respondents earlier than 2000 is not available. Those divorced, separated, or never married have been excluded (n = 50, 5% of sample) from the analysis mainly to better ensure that the analysis compares two distinct groups in which one is more likely to have experienced less stress than the other (i.e., the currently married compared to the widowed).

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. If, and only if, a participant answered affirmatively to currently experiencing a stressor was he asked about its duration (to which he could give an open-ended answer in years and months). 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 was open ended and allowed the respondent to mention a stressor not already asked about in the survey.

Other independent variables serve as controls, since levels of the neuroendocrine biomarkers can be influenced by a wide variety of factors independent of stress (Gersten, 2006). Control variables include those pertaining to diet, exercise, smoking, and medication use.

Table 1 presents descriptive statistics for the main independent variables used in the analysis. Most of the exclusions from the effective sample stem from disallowing proxy respondents from answering subjective stress questions for study participants. As shown in the table, respondents are in part characterized by relatively low levels of urban residence and formal education, an indication that most of the Taiwanese in the survey were born before the rapid economic and social changes that took place after World War II. Also, as might be expected because of the Nationalist army's migration from mainland China shortly after the war, men outnumber women in the sample. A large number of respondents (44%) live with a married son and nearly half of respondents participate in some form of group activity.

Methods

Biomarker index scoring and statistical procedures

The literature has most often represented high risk by greater values for cortisol, epinephrine, and norepinephrine, and lower values for DHEAS (Seeman et al., 1997; Seeman et al., 2004; Singer and Ryff, 1999); this convention is followed here. Additionally, since it is unclear what precise biomarker levels correspond to varying levels of risk, it has been most common to define risk as above or below distribution percentiles (e.g., 10^{th}, 25^{th}, 75^{th}, 90^{th}). Further, distribution percentiles have most commonly been based on entire sample populations (i.e., those in which both sexes have been combined) (Crimmins et al., 2003; Seeman et al., 2001; Seeman et al., 1997; Singer and Ryff, 1999). These additional conventions are also followed here.

The NAL score is the dependent variable in various regressions (i.e., linear, ordered logit) and is scored using different cut-off points (i.e., 10^{th}, 15^{th}, 25^{th}, 75^{th}, 85^{th}, 90^{th}). See Table 2 for descriptive statistics and cut-points for the neuroendocrine biomarkers. Since subjects can be assigned 1 point on four biomarkers if they have high risk values, NAL scores can range from 0–4. 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. The combined z-score is again the dependent variable in various regressions and can range from 0 to no pre-determined upper limit.

The independent variables

The coding of the independent variables is straightforward. One item to note, though, is that the six social stressors asked in the survey are combined to form two indices. One of the indices represents the number of times any one of the stressors is reported. The second index sums the duration stress across each of the six stressors.

Software, weights, and sex stratification

All analysis is carried out using STATA version 8.0 (StataCorp, 2003) and, except for tabulations of descriptive statistics and biomarker cut-points (as presented in Tables 1-2), I use weighted data for all analysis. Because of potentially important sex differences stemming from biological, psychological, and social factors that could in the end affect NAL levels, the analysis of stress reporting and the multivariate analysis are conducted separately by sex.

Results

Stressors and their lengths

Table 3 shows the percent of male and female respondents reporting the prevalence of various stressors and the duration of those stressors. Thirty-four percent of the women in the sample are widowed compared to twelve percent of the men, and among the widowed of both sexes women have been in the state longer. For every familial stressor, a greater percentage of women report being stressed and over half of all women (compared to 44% of men) report one or more of the familial stressors, with the difference relative to men statistically significant. Also to note in the table are the long time periods of stress (such as three or four decades) reported by some respondents.

Multivariate analysis

Tables 4 and 5 present the results of multivariate analysis with NAL, scored using different methods, as the dependent variable[2]. Despite the different techniques used, results within each sex are quite consistent. For men, increasing age is positively and strongly correlated with greater NAL across all models and lack of group participation also is associated with higher NAL (at either the .05 or .10 level of significance). As with men, for women, age is significant in all models. Importantly, for women only, report of current stressors is also significant in all models. To confirm that women's, but not men's, report of current stressors is positively correlated with NAL, regressions were run including both sexes, all independent variables used in Tables 4 and 5, and additional terms interacting those independent variables with one indicating the respondent's sex (a dummy variable indicating the respondent's sex is also included in the models). Results from the linear regressions strongly support a conclusion of a sex difference in the association between the number of reported stressors and NAL levels[3].

Nearly identical regressions were performed for each sex that includes only widowed respondents, in an attempt to mainly examine whether length of widowhood correlates with

[2] Results from bivariate analysis in a sample combining men and women (and using the different methodological approaches and statistical techniques) reveal that the following respondent characteristics are consistently correlated with higher NAL levels: female sex, older age, lower levels of education, and widowhood status. Greater number of reported current stressors and a long period of reported psycho-social stress are only inconsistently correlated with higher NAL levels. In comparison, in the multivariate analysis presented in Tables 4 and 5, lower levels of education, widowhood status, and duration of psycho-social stress are no longer significant. This finding is primarily due to the fact that Tables 4 and 5 control for sex by virtue of an analysis split by sex and that low levels of education, widowhood status, and longer psycho-social stress duration are correlated with being female (which is strongly and positively correlated to higher NAL levels).

[3] The coefficients for the key interaction term (female*number of reported stressors) and the standard errors (in parentheses followed by indications of p-values through the use of asterisks) are: .13 (.053)*, .12 (.052)*, .09 (.056), .29 (.082)**, .30 (.087)** for the linear regressions using 25%, 15%, and 10% cut-points and for the linear regressions using z-scores with no outliers and one outlier removed, respectively. (Note: * and ** represent statistical significance at the .05 and .01 levels, respectively). Among other possible explanations for the stronger association between the number of currently reported stressors and NAL in women is that they may be more willing than men to acknowledge the stress in their lives. Such a differential would result in greater measurement error among men, thereby reducing the estimated relationship between perceived stress and psychological response (Goldman et al., 2005).

higher NAL. In these additional regressions, the binary "widowed or currently married" variable in Tables 4 and 5 is replaced by the continuous "years widowed" and "years widowed squared" terms. For both sexes, widowhood length appears to have no impact on the various NAL measures. Regarding the other independent variables, almost all appear to have the same trend compared to the regressions already presented containing all men and all women.

To account for the possibility that, for example, poor health is causing both a lack of group participation and higher NAL (and not that a lack of group participation is causing higher NAL and in turn eventually poor health, as originally hypothesized), all regressions were rerun with the additional inclusion of a covariate for self-rated health. As expected, there was a slight attenuation in the strength of the relationship between NAL and group participation for men, but otherwise the main results for both sexes remained essentially unchanged.

Further analysis explored whether social connection is beneficial only in the case of concomitant stress (i.e., the "stress buffering" hypothesis). In one set of regressions, the social connectedness measures were interacted with the total psycho-social years stressed variable and additionally included in the models. In a second set of regressions, the social connectedness measures were interacted with only the number of reported stressors and additionally included in the models[4]. The results reveal even less support for the stress buffering hypothesis than for the hypothesis that social connection exerts beneficial effects independent of stressful conditions (as presented in Tables 4 and 5).

In further sensitivity testing, I reran analyses using sex-specific cut-points, rather than cut-points based on the entire sample (as so far presented and discussed). Despite using the different cut-points, the main results remained essentially the same. Additionally, because of the

[4] Due to problems of high multicollinearity in the interaction effects examining the stress buffering hypothesis, interaction effects for both total psycho-social years stressed and number of reported stressors could not be included in the models simultaneously.

lack of statistically significant results in some of the key independent variables and the possibility that these findings are due to problems of high multicollinearity, I tested for high multicollinearity in the independent variables by comparing pairwise correlation coefficients, computing variation inflation factors (VIFs), combining data for men and women (to increase sample size), and using other methods. The results of these tests revealed that high multicollinearity was not a problem in this analysis. Lastly, to test whether the duration stressed variable was not significant because of the concomitant inclusion of a control for age, regressions were run without the age variable in the models (with and without the number of reported stressors also excluded), and the duration stressed variable was still far from significant.

Discussion

This paper investigated an index of neuroendocrine markers, or neuroendocrine allostatic load (NAL), in relation to various life stressors. The general hypothesis was that stressful life histories would positively correlate with higher NAL. By and large, the findings here have not supported this hypothesis. In contrast, an unexpected and important finding was discovered: report of a currently stressful state was positively and strongly correlated with higher NAL (among women only). A broader discussion of these findings follows.

Age, life condition variables, and years stressed variables

Reassuringly, in this analysis, age was positively and strongly correlated (for both men and women) with higher NAL levels. Nevertheless, this trend is a necessary, but not sufficient, condition in support of the AL framework. That is, increasing age can only bring about increased exposure to stress (and thus we should expect AL to accumulate). After establishing that biomarker values head toward higher-risk ranges with increasing age, the (greater) challenge then becomes demonstrating that more stressful life histories accelerate these physiological changes.

Regarding the analysis attempting to link life conditions thought to be stressful with higher NAL levels, outside of evidence suggesting the importance of group participation among men, none of the other life condition variables suggested such a link. For example, for both sexes, low education, living alone, widowhood status, and years widowed among those without a spouse were not correlated with NAL. Even though the literature suggests that the indicators of social isolation used in this survey, by and large, are capturing more stressful states, one might still reasonably ask if the respondents actually experienced those conditions to be stressful. To address, to some degree, this potential limitation, questions were used that probed respondents' subjective interpretation of their psychological state. The resulting measure from this series of questions, total psycho-social years stressed, also was not correlated with levels of NAL. On the one hand, the total psycho-social years stressed variable is a retrospective measure, and thus suffers from respondent recall bias. Clearly, a respondent reflecting on his life history and reporting, say, 20 years of stress about his family's financial situation, is not the same as a longitudinal survey over a period of 20 years periodically asking him the same question. On the other hand, it seems hard to argue that a different social reality is not being captured when comparing those who report few stressors for short periods of time, to those reporting many stressors for long periods of time.

The finding here that NAL levels appear unaffected by the duration of life stressors could nonetheless have been further investigated (and perhaps strengthened) if the SEBAS survey included more questions probing potentially important stressors over the respondents' life course. For example, the survey could have asked subjects whether they experienced the early death of a parent, the death of a child, and long periods of financial problems earlier in life. Additionally, the study here could have been improved through a tighter correspondence between life condition and subjective stress measures. For instance, this investigation assumed that widowhood was a more stressful state than being married based on a prior understanding of the social world and readings of the relevant literature. Combining the widowhood variable with questions probing respondents' subjective stress related to the loss would have been more ideal.

Current stress matters

As mentioned in the research hypotheses section, it follows from AL theory that a currently experienced stress (holding a history of stress constant) should have a negligible impact on current levels of AL. Here, however, among women only, the number of current stressors reported was positively correlated with higher NAL. 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 stress would be.

It is important to keep in mind that a nuanced formulation of what the neuroendocrine components capture emphasizes that the markers measure two phenomena simultaneously. One component of NAL supposedly captures readjusted baseline levels that become dysregulated through the life course. The second component can capture effects of more immediate stressful events (often relatively minor ones, such as daily hassles and work-related stresses) of the day or days before biomarker collection (Baum & Grunberg, 1995; Brantley, Dietz, McKnight, Jones, & Tulley, 1988; Kuiper, van der Beek, & Meijman, 1998; Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004; McEwen & Seeman, 1999; Sluiter, Frings-Dresen, Meijman, & van der Beek, 2000; Sluiter, van der Beek, & Frings-Dresen, 1998). I suggest here that, according to the literature on AL theory, the first component should predominate and can be thought of as the "signal," whereas the second part can be considered "noise" and should be reduced to the extent possible. However conceived, the interplay between more proximate and distal influences on AL biomarker values has probably been underemphasized in the literature.

AL was originally presented as a general theory, and it has since been operationalized by various biomarkers and various methodological approaches. The neuroendocrine markers used here have generally been thought to be "core" to any reasonably complete AL construct. However, it may turn out to be the case that resting, baseline levels of these neuroendocrine markers are an inaccurate measure of AL. In addition to examining resting levels, the clinical literature has commonly examined levels before, during, and after exposure to a stressor (Gallo, Smith, & Kircher, 2000; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Uchino et al., 1996). A healthy bodily response to stress shows elevated levels after a stressor, and then a return to baseline shortly after the threat has passed. For the biomarkers cortisol, epinephrine, and norepinephrine, persons of different ages show similar increases in levels after exposure to a stressor. However, older and younger subjects differ in the time it takes to return to baseline levels after the threat has passed; that is, older subjects have a "sluggish" recovery relative to younger ones (Sapolsky, 2004; Seeman & Robbins, 1994). It may turn out to be the case that AL is caused by, or revealed in, this recovery differential, and not in baseline levels. At least two authors quite familiar with AL and its measurement in surveys have suggested, financial and other considerations permitting, the collection of such “reactivity” data as a way to improve AL’s measurement (McEwen & Seeman, 1999).

To conclude, the analysis here suggests that more research is needed into whether baseline levels of the neuroendocrine markers of the AL construct truly represent any accumulated, physiological cost to the body stemming from stress experienced over the life course. Surveys investigating the posited connection between life history and load should strive to contain a wide array of questions on presumably stressful life events and respondents' subjective evaluation of their life history. Further, investigators should be alert to the possibility that baseline levels of the neuroendocrine markers may be largely capturing transient states at the time of the study.

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Table 1 Descriptive statistics for demographic, social connectedness, psycho-social, and stressor length variables used in the analysis -- effective sample, Taiwan (N = 880)[a]

Variables	% or Mean (SD)	Range
Demographic		
Age (years)	68.3 (8.4)	54-90
Male sex	57%	--
Education (years)	5.3 (4.7)	0-17+
Urban residence (v. rural)	56%	--
Mainlander ethnicity (v. Taiwanese)	15%	--
Social connectedness		
Current marital status		
Married (v. widowed)	75%	--
Residence		
Lives with married son	44%	--
Lives alone	4%	--
Other[b]	52%	--
Group participation		
Participant in 0 groups (v. ≥ 1 group)	53%	--
Psycho-social		
Current familial stressors	.93 (1.3)	0-5
Stressor length		
Widowhood[c]	13.3 (11.0)	0-49
Total psycho-social years stressed	7.2 (16.2)	0-150

[a] The tabulations are based on unweighted survey data.
[b] The other survey categories for residence are spouse/companion, unmarried children, daughter-in-law, husband's parents, wife's parents, married daughter and son-in-law, grandchildren, and other relatives, and other non-relatives.
[c] N = 217.

Table 2 **Descriptive statistics and cut-points for the neuroendocrine biomarkers – sample population, Taiwan (ages 54 to 90, year 2000, both sexes combined)[a]**

				Percentile cut-offs					
	Mean	SD	N	10th	15th	25th	75th	85th	90th
System									
HPA axis									
Cortisol	27.1	33.5	1018	--	--	--	29.9	38.5	47.9
DHEAS	80.7	58.6	1021	20.9	28.6	40.8	--	--	--
SNS									
Epinephrine	2.6	2.6	1019	--	--	--	3.7	4.8	5.6
Norepinephrine	21.9	9.9	1019	--	--	--	27.1	31.5	34.7

[a] The tabulations are based on unweighted survey data. The literature most often represents high risk by greater values for cortisol, epinephrine, norepinephrine, and lower values for DHEAS, a convention which is followed in this paper.

Table 3 **Percent reporting various stressors and stressor duration in years, estimated Taiwanese population (ages 54 to 90, year 2000), by sex[a]**

	% Reporting stressor			Duration of stressor in years[b]				
	Men	Women	p-value	Men Mean[c]	(Range)	Women Mean[c]	(Range)	p-value
Life event (social)								
Widowhood	12	34***	<0.001	10.3	(0–40)	14.6	(0–49)	0.072
Psycho-social								
Family's work situation	22	27	0.088	1.1	(0–30)	1.7*	(0–50)	0.014
Family's financial situation	24	33*	0.012	1.5	(0–42)	2.4*	(0–50)	0.018
Family's health	20	25	0.251	1.9	(0–89)	2.1	(0–50)	0.330
Family's marital situation	20	29**	0.009	1.2	(0–28)	1.8**	(0–50)	0.005
Familial tension/conflict	6	7	0.554	0.5	(0–31)	0.8	(0–30)	0.127
Other familial stressor (volunteered)	0.003	0.01	0.125	0.09	(0–40)	0.04	(0–8)	0.536
≥ 1 psycho-social stressor	44	53*	0.028	--	--	--	--	--
Total psycho-social years stressed	--	--	--	6.2	(0–146)	8.8**	(0–150)	0.007

[a] *, **, and *** represent statistical significance at the .05, .01, and .001 levels, respectively. The tabulations are based on weighted survey data.
[b] For determining the statistical significance of sex in regards to stressor lengths, length of stressor was the dependent variable in a linear regression with only sex and age included as covariates.
[c] For tabulations of the widowhood mean, only those widowed are included since the analysis of stressor length confines itself to those who have lost a spouse. In contrast, calculations of the mean for the psycho-social stressors do include zero values (i.e., those who do not report the stressor).

Table 4 **Estimated regression results with neuroendocrine allostatic load (NAL), scored using different methods, as the dependent variable – Taiwanese men (ages 54 to 90, year 2000)[a]**

	Cut-point scoring						Summed z-score scoring	
	Linear regression Percent cut-off points			Ordered logistic regression Percent cut-off points			Linear regression No. outliers removed	
	10%	15%	25%	10%	15%	25%	1	0
Widowed	-.03	-.06	-.03	-.08	-.34	-.24	.09	.24
	(.070)	(.104)	(.137)	(.350)	(.358)	(.316)	(.208)	(.240)
Lives alone	-.09	-.18	-.16	-.58	-.66	-.27	-.16	-.21
	(.083)	(.093)	(.191)	(.660)	(.563)	(.550)	(.205)	(.226)
Does not live with married son	-.01	-.02	-.04	-.03	-.10	-.12	-.09	-.12
	(.050)	(.047)	(.059)	(.251)	(.154)	(.125)	(.125)	(.111)
Participates in no group activity	.07	.11	**.12**	.44	.36	.29	.14	**.16**
	(.039)	(.055)	**(.056)***	(.210)	(.194)	(.141)	(.075)	**(.074)***
Reported family stressors (0-6)	.01	-.01	-.02	.08	-.04	-.05	-.04	-.05
	(.027)	(.029)	(.034)	(.150)	(.112)	(.085)	(.051)	(.047)
Total psycho-social years stressed	-.00	.00	.00	-.01	.00	.00	-.00	-.00
	(.002)	(.001)	(.003)	(.011)	(.005)	(.007)	(.002)	(.002)
Education (years)	.01	.01	.00	.04	.02	.01	.01	-.00
	(.006)	(.007)	(.010)	(.026)	(.022)	(.027)	(.017)	(.017)
Age (years)	**.01**	**.02**	**.02**	**.04**	**.06**	**.05**	**.03**	**.027**
	(.004)*	**(.004)****	**(.004)*****	**(.018)***	**(.014)****	**(.011)*****	**(.010)***	**(.010)***
Mainlander	-.06	-.12	-.08	-.35	-.36	-.08	.01	-.02
	(.071)	(.076)	(.080)	(.348)	(.284)	(.205)	(.150)	(.160)
Urban residence	-.06	-.05	-.03	-.36	-.09	-.08	-.14	-.06
	(.050)	(.064)	(.076)	(.260)	(.220)	(.200)	(.104)	(.110)
Constant	-.42	**-.87**	**-.77**	--	--	--	-.78	-.92
	(.290)	**(.316)***	**(.305)***				(.708)	(.677)
R^2	0.045	0.074	0.056	--	--	--	0.052	0.065
N	505	505	505	505	505	505	504	505

[a] *, **, and *** represent statistical significance at the .05, .01, and .001 levels, respectively. The regression coefficients are unstandardized and standard errors are inside the parentheses. All regressions include all the independent variables shown (e.g., widowed, lives alone) as well as controls for medication use, diet, exercise, alcohol consumption, betel quid chewing, and smoking. The analysis is based on weighted survey data.

Table 5 **Estimated regression results with neuroendocrine allostatic load (NAL), scored using different methods, as the dependent variable – Taiwanese women (ages 54 to 90, year 2000)[a]**

	Cut-point scoring						**Summed z-score scoring**
	Linear regression Percent cut-off points			Ordered logistic regression Percent cut-off points			Linear Regression
	10%	15%	25%	10%	15%	25%	
Widowed	-.09 (.089)	-.14 (.103)	-.16 (.107)	-.14 (.263)	-.17 (.242)	-.24 (.191)	-.20 (.213)
Lives alone	-.15 (.173)	-.01 (.110)	**.52 (.172)****	-.15 (.433)	.12 (.222)	**.90 (.326)***	.27 (.265)
Does not live with married son	.05 (.075)	.04 (.066)	-.01 (.113)	.13 (.231)	.09 (.158)	.05 (.200)	.001 (.149)
Participates in no group activity	.02 (.057)	-.01 (.062)	-.01 (.086)	-.03 (.159)	-.02 (.141)	-.08 (.146)	-.12 (.145)
Reported family stressors (0-6)	**.10 (.041)***	**.11 (.049)***	**.12 (.044)***	**.26 (.107)***	**.19 (.092)***	**.20 (.081)***	**.26 (.082)****
Total psycho-social years stressed	.00 (.004)	-.00 (.005)	-.00 (.004)	.00 (.010)	-.00 (.010)	-.00 (.007)	-.01 (.006)
Education (years)	-.01 (.013)	.00 (.012)	.02 (.016)	.02 (.036)	.02 (.027)	.04 (.029)	.00 (.032)
Age (years)	**.02 (.006)****	**.02 (.008)****	**.02 (.008)***	**.06 (.016)****	**.05 (.017)****	**.04 (.015)***	**.04 (.017)***
Mainlander	.09 (.287)	.15 (.304)	.15 (.278)	-.00 (.615)	.26 (.589)	.22 (.548)	.33 (.427)
Urban residence	.09 (.106)	.11 (.117)	.11 (.157)	.17 (.298)	.17 (.257)	.20 (.290)	.20 (.278)
Constant	**-1.03 (.356)****	-1.03 (.508)	.02 (.546)	--	--	--	-1.00 (1.18)
R^2	0.090	0.105	0.079	--	--	--	0.084
N	375	375	375	375	375	375	375

[a] *, **, and *** represent statistical significance at the .05, .01, and .001 levels, respectively. The regression coefficients are unstandardized and standard errors are inside the parentheses. All regressions include all the independent variables shown (e.g., widowed, lives alone) as well as controls for medication use, diet, exercise, alcohol consumption, betel quid chewing, and smoking. The analysis is based on weighted survey data.