Does Lower Subjective Standing Yield Riskier Biomarker Profiles?

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Abstract

Both objective and, more recently, subjective measures of standing have been linked to poor health outcomes. It is unclear, however, through which precise physiological mechanisms such standing may influence health. One possible mechanism is that lower status is stressful and that stress experienced over the life course engenders dysregulated biomarker profiles (that are a risk factor for poor health). Using a nationally representative survey conducted in Taiwan, the investigation here tests whether lower subjective standing (both in terms of SES in Taiwan and standing in the community) is associated with riskier neuroendocrine biomarker profiles. With the exception of the biomarker DHEAS, we find that there is no evidence that reports of low standing are associated with riskier biomarker profiles. The finding here is congruent with mounting evidence in the literature that suggests the difficulty in linking indicators of a stressful life history to an impaired neuroendocrine system.

Keywords

Subjective standing, stress, neuroendocrine biomarkers, neuroendocrine allostatic load (NAL), Taiwan, health

Introduction

Studies have shown that in both humans and animals, lower status is associated with worse health (Adler and Ostrove 1999; Sapolsky 2004; **cite**). For example, in one study of humans in the United States... (**cite**). The relationship between higher SES and better health outcomes has also been found in eastern contexts, such as in Taiwan, China,... (**cite**). In addition to research on humans, studies on nonhuman primates, for example, have shown that subordinate baboons... (**cite**). Other animals such as wolves, rats,... with subordinate status also have worse health than their higher status counterparts (**cite**).

It has been suggested that one mechanism by which those with lower status come to have worse health is through the differential experience of chronic stress (**cite**). Those with lower status might experience greater levels of chronic stress because, in part, their environment produces more stressors, and of a more severe nature, and fewer opportunities to engage in stress relieving activities, compared to those with higher status (**cite**). For instance, low SES individuals are more likely to live in neighborhoods characterized by more conflict and threat and fewer opportunities for exercise and recreation (**cite**). As well, higher stress might come about because of psychological factors independently related to feelings of lowliness or relative deprivation. That is, the feeling that one is of lower status, for whatever reason, may be in and of itself stressful, regardless of what "objective" indicators might suggest (Wilkinson 1999; **cite**).

Physiologically, chronic stress is thought to cause worse health through sustained activation of the sympathetic nervous system and the hypothalamus pituitary adrenal (HPA) axis, which, through cascading effects, impairs the function of other important biological systems

(**Timiras 2003**). It is hypothesized that the cost to the body in responding to stress builds up, in what has been termed allostatic load (AL). According to AL theory, the buildup of AL is revealed in the dysregulation of a number of bodily systems (i.e. the neuroendocrine, immune, cardiovascular, and metabolic systems) important to good health (**Timiras 2003**). AL is considered to be a precursor, or "early warning sign," of morbidity and mortality.

Of the various physiological systems thought to be impacted by AL, the neuroendocrine system has been one of the least studied in large-scale population studies. To date, most analyses of how neuroendocrine biomarkers behave under stressful conditions have been carried out in the context of small-scale and controlled laboratory experiments (**cite**). Nevertheless, despite the relatively recent inclusion of neuroendocrine biomarkers in population studies, mounting evidence from these studies suggest that certain levels of baseline neuroendocrine markers predict greater incidence of cardiovascular disease, more rapid decline in physical and cognitive function, and earlier mortality (**cite**). While the consequences of high AL are becoming clearer, what remains less clear is whether a stressful life history is associated with a riskier neuroendocrine biomarker profile, as is predicted by AL theory.

The paper here, then, seeks to extend the literature on the connection between stressful life history and baseline levels of the neuroendocrine markers by examining measures of subjective status in a nationally representative population survey conducted in Taiwan. The measure of status used here is "subjective" in that respondents rate themselves on a ladder representing their perceived status in Taiwan and in the community. Previous research using this subjective measure has shown that it is predictive of worse health, independent of objective measures of status such as respondents' own education, income, and the like (**cite**). Evidence also indicates that the subjective measure of status captures numerous salient features

of a respondent's life that relate to the level of their resources and, additionally, life stress experienced (Adler et al. 2000;**cite**).

For the purposes of this paper, then, we assume that the subjective measures of status used here are multidimensional measures reflecting much in the way of the respondents' lived experience over the life course and that lower status respondents likely experienced more life stress then their higher status counterparts. Specifically, we hypothesize that lower subjective status is correlated with riskier neuroendocrine biomarker profiles.

Data and Methods

Overview of the data set

We 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 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, 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 survivors 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). 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 we focus on cortisol, DHEAS, epinephrine, norepinephrine, and dopamine, a physiologically coherent class of markers representative of the neuroendocrine stress response (Sapolsky 2004; Cohen et al. 1995; Crimmins and Seeman 2001). The measure used here based on these markers is called NAL, for neuroendocrine allostatic load, and has been discussed in detail elsewhere (Gersten under review). Among NAL's greatest advantages is its interpretability that stems from grouping markers of a similar level of biological abstraction. NAL includes markers related to two neuroendocrine 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 (Sapolsky 2004; Cohen et al. 1995; Crimmins and Seeman 2001). 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 (Sapolsky 2004; Cohen et al. 1995; Crimmins and Seeman 2001).

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 sample, and during the same day blood was also drawn. The amount of DHEAS in the body was determined through the blood sample.

Independent variables

The three main independent variables of interest are all subjective status measures. The "subjective SES" measure asks respondents to place themselves on a ladder (a picture of which is shown) that corresponds to their SES relative to all others in Taiwan. The ladder has a total of 10

rungs, with the highest status corresponding to the 10th rung. Respondents are prompted to consider their level of education, prestige of their job, and their income level in determining their own SES. The "subjective community standing" measure also asks respondents to rate themselves on a ladder (which is identical to the one shown previously), but this time the respondents are instructed to rate themselves as regards their community standing. Community is not defined for the respondent, and the respondent is not given any prompts as to what might be important criteria for higher or lower community standing. The last main independent variable of interest is created from subtracting subjective SES from subjective community standing. The idea behind the creation of this variable is to try and capture the extent to which respondents have a positive self-image of themselves in the community relative to the wider, and arguably more abstract (and perhaps less pertinent), Taiwanese population.

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 2005), all models control for variables pertaining to diet, exercise, smoking, alcohol consumption, betel nut chewing, and medication use. Age and health status are also used as controls since both phenomena may have important relationships with the level of neuroendocrine biomarkers and status ratings. In the case of age, increasing age is associated with greater respect and authority in Taiwanese culture (**cite**) and increasing age may also be linked to worse biomarker profiles. In the case of health status, worse biomarker profiles may lead to poorer health (**cite**), and poorer health might lead to lower status rating (**cite**). Health status is proxied by self-rated health.

Methods

Biomarker index scoring

The most popular approach to operationalizing AL has been to create a score that gives one point for every biomarker for which 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 convention is followed here. 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, NAL scores can range from 0–4.

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 1 for descriptive statistics and cut-points for the neuroendocrine biomarkers. 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.

Software, weights, and sex stratification

All analysis is carried out using STATA version 8.0 (StataCorp 2003). The bivariate and multivariate analysis use weighted data. Because of potentially important sex differences stemming from biological, psychological, and social factors that could in the end affect biomarker levels, analysis of stress reporting, duration, and the multivariate analysis is conducted separately by sex.

Results

Table 1 depicts descriptive statistics (of the entire, unweighted sample) for variables that are used in this analysis. Of note is that because of mainly male emigration to Taiwan shortly after World War II (sparked by conflict on mainland China), there are more men than women in the sample. Also noteworthy is that respondents, on average, tend to rate themselves more highly (by about half a rung on the ladder) on their standing in the community when compared to their standing in all of Taiwan. As mentioned in the data and methods section, this analysis controls for various factors that might influence baseline neuroendocrine levels, independent of the degree of lifetime or current stress. As might be expected in a older population, over half the respondents take some sort of medication regularly.

Figure 1 presents the distributions of self-reported standing in Taiwan and in the community. Both distributions are right tailed, with comparatively few participants willing to rate themselves highly either relative to the Taiwanese population or their communities. This type of skewed distribution, which may partially reflect Taiwanese modesty, contrasts with

distributions stemming from Western populations which more resemble a normal curve (and sometimes even have a disproportionate amount of high values) (Adler et al. 2000; Singh-Manoux et al. 2005; Goldman et al. under review). Interestingly, participants in the SEBAS are more willing to rate themselves higher in reference to their community. For instance, nearly two times as many subjects were willing to give themselves a "7" rating in the community compared to that in Taiwan. Such a proportional increase also applies to other ratings at the higher end (i.e. 8, 9, 10) of the ladder.

Tables 2 and 3 present results in which different neuroendocrine biomarkers are dependent variables in linear regressions in which standing in the community, standing in Taiwan, and the difference in standing (community - Taiwan) are the key independent variables of interest. An important finding is that higher self-reported status (in both men and women) is correlated with higher (and thus less risky) DHEAS levels. In the case of men, for example, the relationship is most strong for that of subjective standing in Taiwan and logged DHEAS values, but is also supported by standing in Taiwan and unlogged DHEAS values, as well as by unlogged and logged DHEAS values and standing in the community. In data not shown, the cutpoint method of scoring for which values above a certain percentile (i.e. 75, 85, 90) are considered risky and those below it are considered not risky, are supportive of the shown data. Another feature of Tables 2 and 3 is that (contrary to predictions) for the other biomarkers a clear relationship between subjective status and biomarker levels is not apparent.

To do: Creation and discussion of Tables 4 and 5 in which a summary index of the biomarkers (i.e. neuroendocrine allostatic load) is the dependent variable and the key independent variables are subjective ratings of status, similar to that in Tables 2 and 3.

(Preliminary) Conclusion

- DHEAS is the only biomarker that shows a consistent relationship between subjective status and risky biomarker levels.

- Results differed little whether using the question referring to subjective status relative to Taiwan or relative to the community.

- An improvement on the subjective status question could involve reformulating the text accompanying the ladder so that no prompts are provided to the respondent about the criteria he should use in answering the question. Also, the order of the subjective status questions might change subjects' responses and this could be investigated. Lastly, there should be standardization regarding the number of rungs on the ladder (9 or 10), since the number of rungs likely yields different responses.

- To date, most studies (including this one) have found little evidence linking risky baseline neuroendocrine levels with stressful life events (e.g. social status, widowhood, living alone).

References

Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. Ann N Y Acad Sci. 1999;896:3-15.

Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data and healthy white women. Health Psychol. 2000 Nov;19(6):586-92.

Cohen S, Kessler RC, Gordon LU. Strategies for measuring stress of psychiatric and Li physical disorders. In: Measuring stress: a guide for health and social scientists. Cohen S, Kessler RC, Gordon LU, eds. 1995. New York: Oxford University Press, pp. 3-26.

Crimmins E, Seeman T. Integrating biology into demographic research. In: Cells and surveys: should biological measures be included in social science research? Finch CE, Vaupel JW, Kinsella K, eds. 2001. Washington, DC: National Academy Press, pp. 9-41.

Gersten O. Bridging the biological and social worlds: neuroendocrine biomarkers, social relations, and the costs of cumulative stress in Taiwan. 2005. Ph.D. dissertation: UC Berkeley.

Goldman N, Cornman J, Chang MC. Measuring subjective social status: a case study of older Taiwanese. Under review.

Goldman N, Weinstein M, Chang MC, Lin HS, Chuang YL, Lin YH, Lin SH, Liu IW, Liu HY. 2000 Social Environment and Biomarkers of Aging Study in Taiwan (SEBAS): Main documentation for SEBAS public use data. (Accessed in Aug 2003). ICPSR (http://www.icpsr.umich.edu).

Sapolsky RM. Why zebras don't get ulcers, 3rd edition. 2004. New York: Henry Holt & Co.

Singh-Manoux A, Marmot MG, Adler NE. Does subjective social status predict health and change and health status better than objective status? Psychosom Med. 2005 Nov-Dec;67(6):855-61.

StataCorp. Stata statistical software: release 8.0. 2003. College Station: Stata Corporation.

Timiras PS. The adrenals and pituitary. In: Physiological basis of aging and geriatrics, 3rd edition. Timiras PS, ed. 2003. Boca Raton: CRC Press, pp. 167-88.

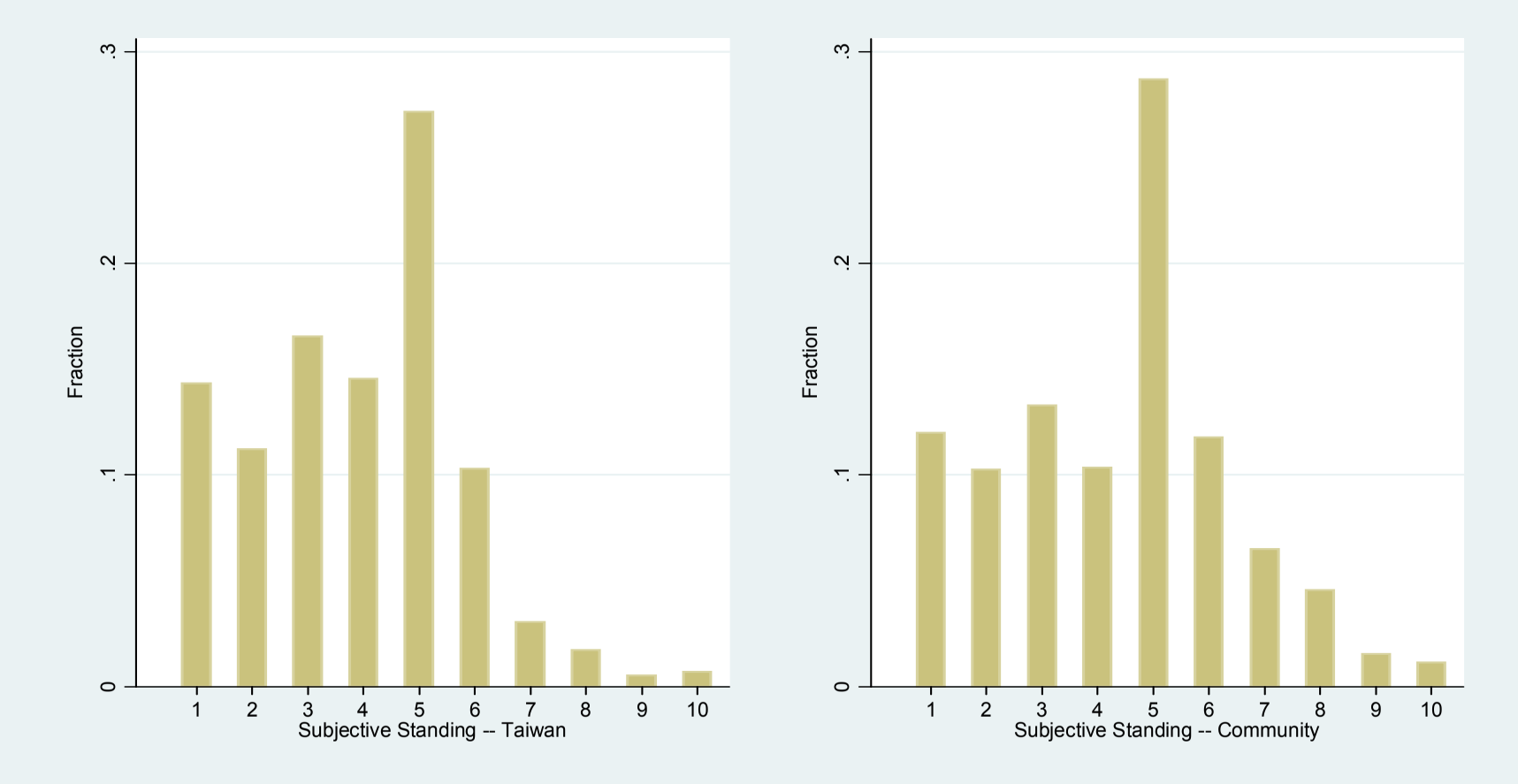
Wilkinson RG. Health, hierarchy, and social anxiety. 1: Ann N Y Acad Sci. 1999;896:48-63.

Table 1 Descriptive statistics for all of the dependent and independent variables used in the analysis -- sample population, Taiwan (ages 54 to 91, year 2000, both sexes combined)

Variables	% or Mean (SD)	Range	N
Dependent			
Neuroendocrine markers			
Cortisol (μg/g creatinine)	27.1 (33.5)	2.3-514.9	1018
DHEAS (μg/dl)*	80.7 (58.6)	0-496.6	1021
Epinephrine (μg/g creatinine)*	2.6 (2.6)	0-19.9	1019
Norepinephrine (μg/g creatinine)	21.9 (9.9)	1.6-74.7	1019
Dopamine (μg/g creatinine)	175.7 (441.7)	6-8989.6	1017
Independent			
Subjective standing			
SES	3.9 (1.9)	1-10	991
Community	4.3 (2.1)	1-10	986
Difference (Community - SES)	.47 (1.3)	-6-7	984
Controls			
Demographic			
Age	68.3 (8.5)	54-91	1023
Sex (Male)	58%	--	1023
Health			
Self-rated health	2.9 (.99)	1-5	1005
Takes medication	57%	--	1023
Chews betel nut daily	2%	--	1020
Smokes daily	22%	--	1022
Consumes alcohol daily	5%	--	1020
Exercises six times a week or daily	41%	--	1022
Diet of at least two fruits and three vegetables daily	53%	--	1021

Note: Tabulations based on unweighted data.
* Values below assay sensitivity were coded as 0.
Source: Author's tabulations based on the 2000 SEBAS (Goldman et al. 2003).

Figure 1 Distributions of self-reported standing in Taiwan and in the community*



Note: * Ten represents the highest status and one represents the lowest.

Table 2 **Estimated regression results with different neuroendocrine biomarkers as dependent variables and reports of subjective status as independent variables – Taiwanese men (ages 54 to 91, year 2000)**

	DHEAS[a] (Unlogged)	DHEAS[a] (Logged)	Cortisol[b] (Logged)	Epinephrine[b] (Logged)	Norepinephrine[b] (Unlogged)	Dopamine[b] (Unlogged)
Model 1						
Standing, Community	1.54 (0.152)	0.02 (0.132)	-0.01 (0.680)	0.01 (0.599)	0.19 (0.307)	-2.72 (0.670)
Model 2						
Standing, Taiwan	**2.50 (0.027)****	**0.04 (0.007)****	-0.00 (0.948)	0.02 (0.233)	0.39 (0.051)	-6.71 (0.138)
Model 3						
Standing, Difference (C – T)	-1.13 (0.619)	-0.03 (0.367)	-0.01 (0.549)	-0.02 (0.428)	-0.31 (0.188)	6.13 (0.697)

Note: *, **, and *** represent statistical significance at the .05, .01, and .001 levels, respectively. Precise levels of statistical significance are inside the parentheses. All regressions control for age, health status, medication use, diet, exercise, drinking, betel quid chewing, and smoking. Analysis based on weighted survey data.

[a] µg/dl.

[b] µg/g creatinine.

Source: Author's calculations based on the 2000 SEBAS (Goldman et al. 2003).

Table 3 **Estimated regression results with different neuroendocrine biomarkers as dependent variables and reports of subjective status as independent variables – Taiwanese women (ages 54 to 91, year 2000)**

	DHEAS[a] (Unlogged)	DHEAS[a] (Logged)	Cortisol[b] (Logged)	Epinephrine[b] (Logged)	Norepinephrine[b] (Unlogged)	Dopamine[b] (Unlogged)
Model 1						
Standing, Community	**2.38 (0.041)***	0.04 (0.178)	0.01 (0.724)	0.03 (0.163)	0.11 (0.654)	-2.40 (0.230)
Model 2						
Standing, Taiwan	1.80 (0.101)	0.03 (0.338)	-0.01 (0.610)	0.03 (0.083)	0.37 (0.250)	-1.95 (0.350)
Model 3						
Standing, Difference (C – T)	2.71 (0.293)	0.06 (0.276)	0.04 (0.236)	0.02 (0.650)	-0.39 (0.407)	-2.66 (0.361)

Note: *, **, and *** represent statistical significance at the .05, .01, and .001 levels, respectively. Precise levels of statistical significance are inside the parentheses. All regressions control for age, health status, medication use, diet, exercise, drinking, betel quid chewing, and smoking. Analysis based on weighted survey data.

[a] µg/dl.

[b] µg/g creatinine.

Source: Author's calculations based on the 2000 SEBAS (Goldman et al. 2003).

Appendix

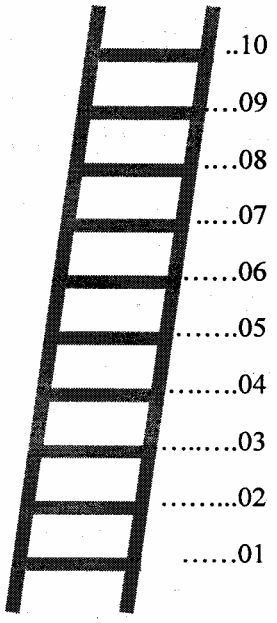
★D1 **[Show the figure on the right-hand side of this page to the respondent]**

Here is a ladder. There are also ten stairs in total from the bottom to the top.

Think of this ladder as representing where people stand in Taiwan. At the top of the ladder are the people who are the best off – those who have the most money, the most education and the most respected jobs. At the bottom are the people who are the worst-off – who have the least money, least education, and the least respected jobs or no jobs.

The higher up you are on this ladder, the closer you are to the people at the very top; the lower you are, the closer you are to the people at the very bottom.

If you consider your current situation and compare it with all other people in Taiwan, where would you place yourself on this ladder? Please indicate it to me.



[Please circle the rung that respondent indicates.]

☐66 Other response (Please specify)

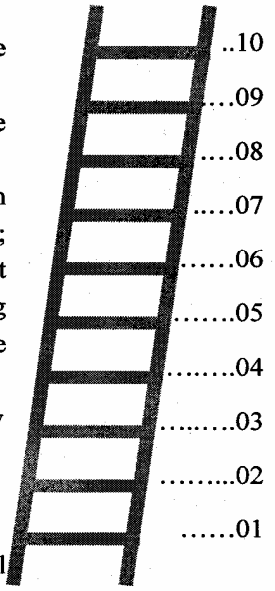
★D2 **[Show the figure on the right-hand side of this page to the respondent]**

Here is another ladder. In total, there are ten stairs from the bottom to the top.

Think of this ladder as representing where people stand in their communities. People define community in different ways; please define it in whatever way is most meaningful to you. At the top of the ladder are the people who have the highest standing in their community. At the bottom are the people who have the lowest standing in their community.

[Interview note: Please let respondents define community by themselves. If respondents really don't know or don't understand, please probe using the word neighborhood (where you live and the surrounding area).]

If you consider your current situation and compare it with all other people in your community, where would you place yourself on this ladder? Please indicate it to me.



[Please circle the rung that respondent indicates.]

☐66 Other response (Please specify)