

Physiological Dysregulation Predicted
Poorer Health and Lower Survival in a Survey of the Older Population

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ABSTRACT

Objective: We investigate whether a multi-system measure of physiological dysregulation based on 16 biological measures is associated with deterioration in physical and mental health over a three-year period.

Study Design and Setting: We use data from a national survey of persons 54 and older in Taiwan that collected standard clinical markers related to cardiovascular and metabolic function and “preclinical” measures pertaining to the immune, neuroendocrine and sympathetic nervous systems. The dysregulation score counts the number of biomarkers for which values are in the lowest or highest decile. Statistical models examine whether dysregulation predicts four health outcomes (survival, physical functioning, cognitive functioning and depressive symptoms), in the presence of extensive controls for baseline health.

Results: The estimates reveal significant associations between dysregulation and health for each outcome, although there is variability across outcomes. The associations are often attenuated in the presence of health controls, underscoring the importance of longitudinal analysis.

Conclusion: This study has extended previous research on the health consequences of physiological dysregulation by considering a broader range of outcomes and biomarkers in a non-Western population-based sample. Our analysis suggests that such dysregulation provides early warning signs of a broad range of co-morbidities.

Key words: physiological dysregulation; allostatic load; biological markers; mortality; health; Taiwan.

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INTRODUCTION

Recent analyses have suggested that physiological dysregulation, measured across multiple systems, is predictive of diminished physical and mental functioning in non-clinical populations. Here, we extend this prior work by using data from a national survey in Taiwan to explore the association between an improved measure of multi-system physiological dysregulation [1] and a broad range of health outcomes – survival, physical functioning, cognitive functioning, and depressive symptoms – ascertained three years after the assessment of the biological indicators. Our measure of dysregulation is based on markers of the cardiovascular, metabolic, immune, neuroendocrine, and sympathetic nervous systems and identifies elevated or blunted levels of these markers. Conditions defined by biological markers falling outside normal ranges, particularly long-term elevations in the levels of these markers, include hypertension, hypercholesterolemia, and diabetes [2].

The specific biological parameters comprise both standard clinical markers and nontraditional measures; we examine the linkages between both sets of markers and health. Clinical markers pertain to cardiovascular and metabolic function: obesity, blood pressure, lipids, and glucose metabolism. Additional biomarkers that are not customarily measured in medical exams comprise cortisol, dehydroepiandrosterone-sulfate (DHEA-S), epinephrine, norepinephrine, interleukin-6 (IL-6), insulin-like growth factor 1 (IGF-1), and dopamine. Biomarkers in this latter group, which we refer to as “preclinical” markers, are associated with both mental and physical well-being [3,4].

Previous research in this area has been limited by the use of cross-sectional data and select samples. For example, earlier analyses using the Taiwan data have examined biological and health measures obtained during a narrow time span, raising questions about whether causality

runs from the biological measures to health status or the reverse [1,3]. Other analyses using data from the MacArthur Studies of Successful Aging have identified linkages between multi-system physiological functioning and health status ascertained several years later [2,5-7], but they have been based on a non-representative sample of highly functioning older individuals. Compared with previous studies, our estimates are less likely to be plagued by biases related to sample selection and endogeneity because we use a national survey that collects extensive health information and biological measures at baseline and at the end of a three-year period.

METHODS

Data

We use data from the 2000 Social Environment and Biomarkers of Aging Study (SEBAS). SEBAS draws on a random sub-sample of respondents interviewed as part of the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan. This longitudinal survey began in 1989 with a national sample of 4049 persons aged 60 and older (response rate: 92%), and was expanded in 1996 to include a new cohort of 2462 persons aged 50 to 66 in 1996 (response rate: 81%). Both cohorts were re-interviewed in 1999 (response rate: 90% of survivors). At each survey, respondents were asked about their demographic characteristics, social and economic situation, physical and mental health, and health-related behaviors.

Among those interviewed in 1999, a random sub-sample was selected for the 2000 SEBAS. Respondents aged 71 and older (in 2000) and residents of urban areas were oversampled. A total of 1497 persons aged 54 and older completed in-home interviews (92% of survivors), and 1023 participated in the physical examination (68% of those interviewed). Exam participation was disproportionately low among the healthiest respondents as well as the least healthy. The net

impact of this pattern of non-participation is that persons who received the medical exam reported the same average health status (measured on a five-point scale) as those who did not. In addition, although respondents over age 70 were less likely than younger persons to participate, sex and measures of socioeconomic status were not significantly related to participation. These results suggest that, in the presence of controls for age, estimates derived from the medical exam portion of SEBAS are unlikely to be seriously biased [8].

Several weeks after the home interview, the SEBAS respondents who agreed to participate in the medical exam collected a 12-hour overnight urine sample (7pm to 7am), fasted overnight, and visited a nearby hospital for a physical examination the following morning. During the hospital visit, medical personnel drew a fasting blood sample and took blood pressure and anthropometric measurements. Written informed consent was obtained for participation in the interview and physical examination. Almost all exam participants provided suitable blood and urine specimens for analysis.

Blood and urine samples were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to the routine standardization and calibration tests performed by the laboratory, nine individuals (outside the target sample) contributed triplicate sets of specimens during the early stages of fieldwork. In each case, two sets were submitted to UCL and a third was sent to Quest Diagnostics in the US. The resulting data show high inter- and intra-lab reliability, with intraclass correlations of 0.80 or higher for duplicates sent to UCL and inter-lab correlations of 0.76 or higher between results from UCL and Quest Diagnostics. Details regarding the assays are provided in Seeman et al. [9] and Goldman et al. [10].

In 2003, the vital status of respondents in the previous waves of the Survey of Health and Living Status – including the sub-sample in SEBAS – was ascertained, and survivors were

re-interviewed with a questionnaire similar to those used in earlier interviews (response rate: 92% among survivors from the original cohorts and 97% for survivors who participated in the SEBAS medical examination). Any death reported by a relative, neighbor, or friend of the respondent was verified by using a citizen identification number linked to the Household Registration records maintained by the Ministry of Interior in Taiwan. Among the 1023 respondents that participated in the medical exams, 926 were interviewed in 2003, 11 were known to be alive but were not interviewed, 14 had unknown vital status and 72 were confirmed as dead.

Measures

Outcome Variables

We examine four outcomes capturing different dimensions of health (or survival) in 2003: depressive symptoms, cognitive impairment, mobility limitations and mortality. Depressive symptoms are measured by a 10-item short form of the full CES-D (Center for Epidemiologic Studies Depression scale), coded according to standard practice based on both the number and severity of symptoms (potential range from 0 to 30). Previous studies have demonstrated that a shortened form of the CES-D yields similar internal consistency, factor structure, and accuracy in detecting depressive symptoms as the full 20-item CES-D among elderly Chinese [11]. Cognitive impairment is based on items from the modified Short Portable Mental Status Questionnaire [12], the modified Rey Auditory Verbal Learning Test [13], and a modification of the Digits Backward test [14]. The measure is a count of the number of cognitive tasks completed incorrectly, including basic orientation questions, a series of four subtractions, and immediate memory recall (potential range from 0 to 24). The measure of mobility limitations counts the number of physical tasks, out of the following nine, that the respondent reports

difficult performing without aid: standing continuously for 15 minutes and for two hours, squatting, raising both hands over his or her head, grasping or turning objects with his or her fingers, lifting or carrying an object weighing 11-12 kg, running a short distance (20-30 meters), walking 200-300 meters, and climbing two or three flights of stairs. Mortality is a dichotomous variable denoting death over the three-year period (2000-2003) following the biomarker collection.

Physiological Dysregulation

The explanatory variable of interest is a measure of physiological dysregulation based on 16 biomarkers that have been shown to be individually associated with survival and a wide range of chronic conditions including diabetes, cardiovascular disease, obesity, poor cognitive function, depression, and cancer [3,5,15]. Nine of these are what we term the “clinical” markers; they are common elements of health assessments and were ascertained in this study as part of the physical examination or fasting blood samples: two measures of obesity (BMI and the waist-hip ratio), two measures of blood pressure (diastolic and systolic), three measures of lipid profiles (triglycerides, total serum cholesterol, and the ratio of total serum cholesterol to high-density lipoprotein (HDL) cholesterol), and two indicators of glucose metabolism (glycosylated hemoglobin and fasting glucose). BMI was calculated as weight divided by height squared (kg/m^2) and the waist/hip ratio was based on waist circumference measured at its narrowest point and hip circumference measured at the maximal buttocks. Blood pressure measurements were calculated as the average of two seated readings based on a mercury sphygmomanometer.

The remaining seven biological parameters comprise the “preclinical” measures. Four markers of neuroendocrine function – epinephrine, norepinephrine, dopamine, and cortisol – were obtained from the overnight urine specimen. The overnight specimen provides integrated

values of these neurotransmitters and hormones for a period when most participants were at home and resting; these markers are reported as micrograms per gram creatinine to adjust for body size. The remaining preclinical markers were obtained from the fasting blood specimen: dehydroepiandrosterone sulfate (DHEA-S), which is believed to act in part as an antagonist to the effects of cortisol, and two markers related to immune function – IL-6 (a pro-inflammatory cytokine) and IGF-1 (a polypeptide that aides in muscle growth and bone repair).

The most frequently used measure of physiological dysregulation in earlier research is a count based on a single tail of risk (i.e., *either high or low* quartile) for each of 10 biomarkers [2]. In this paper, we use a modified version of this score that (1) incorporates additional biomarkers believed to be associated with the stress response, including measures of immune function; (2) identifies risk in both the low and high tails where appropriate; and (3) uses deciles rather than quartiles to denote high and low values. These cutoff points, shown in Table 1, are intended to capture extreme values for these parameters, rather than clinical cut-points. The resulting two-tailed 16-item measure has been shown to predict several health outcomes better than the conventional one-tailed 10-item measure, and as well, if not better, than alternative measures of physiological dysregulation [1].

[INSERT TABLE 1 ABOUT HERE]

The measure is constructed as a count of the number of biomarkers for which the respondent's value falls below the 10th percentile or above the 90th percentile. There are some exceptions to this specification. First, because DHEAS and the ratio of total to HDL cholesterol have always been treated as one-tailed in previous research, we dichotomize the values for DHEAS (<10%) and the ratio of total to HDL cholesterol (>90%) to identify elevated risk with only one end of the distribution. Second, for IL-6 and epinephrine, a large number of readings

were too small to be detected (32% for IL-6 and 20% for epinephrine) so that the lowest category represents “undetectable” rather than the bottom decile. Although the theoretical maximum of the index is 16, it ranges between zero and 10 in our sample, with the vast majority of respondents having between one and five biomarkers above or below our defined cut-points, and less than one percent having more than eight.

In addition to this 16-item score, we calculate two sub-scores, one based on the nine clinical markers and one based on the seven preclinical measures [6]. As with the overall 16-item measure, each of these sub-scores is a count of the number of respective biomarkers for which the participant’s values fall into the designated intervals of risk.

Control Variables

In addition to the measures of physiological dysregulation, we include age and sex as well as urban-rural residence (to account for the sampling design) in the models. Although it is plausible that the health effects of physiological dysregulation may vary by age or sex, we do not explore interaction terms in this analysis because of the relatively low statistical power associated with a three-year follow-up period (e.g., there were only 72 deaths in the sample of 1,023 SEBAS respondents). In order to mitigate potential problems of reverse causality, we introduce five control variables for health status in 2000. These variables comprise (1) mobility limitations, depressive symptoms and cognitive impairments, each of which is defined analogously to the outcome variable but is based on 2000 data; (2) a measure of current illness that is derived as a count of the number of chronic conditions (out of 12) reported by the respondent; and (3) a dummy variable identifying respondents who smoked daily in the six months prior to interview.

Analytical Approach

The statistical analysis is based on two (overlapping) samples of SEBAS respondents: one for mortality and a second for mobility limitations, depressive symptoms and cognitive impairment. For the mortality analysis, we exclude from the total sample of 1023 SEBAS participants 14 with unknown survival status, 7 with missing data on the biological markers, and an additional 67 missing at least one of the control variables, leaving 935 for the analysis sample. For the analysis of health outcomes, we are restricted to the 926 SEBAS participants who were interviewed in 2003. Among these, we exclude 54 respondents who were missing information on any of the three health outcomes, five who were missing biomarker information and an additional 47 who were missing information on the control variables, resulting in an analysis sample of 820 respondents.

Table 2 provides descriptive statistics of the outcome and explanatory variables for the two analysis samples. The estimates show that the average age of respondents in these analyses is about 67 to 68 years and that there is a preponderance of males – a consequence of the migration of the Nationalist army from mainland China after World War II. Respondents have about three biomarkers in the designated high risk ranges, on average, comprising about equal numbers of preclinical and clinical markers. Health worsens over the follow-up period: the average depressive symptom score increases very slightly from 5.2 to 5.3, the average score for cognitive impairment increases from 7.0 to 8.6, the mean number of mobility restrictions increases from 1.8 to 2.3, and 6.6 percent of the sample died over this time interval.

[INSERT TABLE 2 ABOUT HERE]

We use multivariate models to examine the associations between our measures of physiological dysregulation measured in 2000 and each of three health outcomes assessed in

2003 as well as mortality over the period 2000-2003. All models include a dysregulation score (either the one based on all 16 parameters or the two sub-scores) along with demographic variables (age, sex and urban/rural residence). Because exploratory analyses revealed that the addition of quadratic terms for the dysregulation score did not result in a significant improvement for any of the four models, the score is treated as linear. In order to examine the extent to which the effects of the biological parameters are diminished or eliminated in the presence of health controls, we estimate models with and without the five health control variables, although we focus on the results from models that include such controls. Because of the multistage sampling design, we use a robust estimator of variance and adjust for clustering by primary sampling unit to produce correct standard errors for all models [16].

For each outcome, we use a statistical model that is appropriate for the measurement of the outcome. For the depressive symptom score, we use a linear regression model. For the two count measures (cognitive impairment and mobility limitations), we use a Poisson model. Given the large number of respondents with zero mobility limitations (34%), we use a zero-inflated Poisson model (ZIP) for mobility limitations [17]; this model provides a much better fit than a standard Poisson model. For mortality, which is a dichotomous outcome, we use a logit model. In the case of the mortality models, a value of one denotes death in the follow-up period and for the remaining three outcomes, higher values indicate poorer health at the end of the follow-up period (i.e., a higher depressive symptom score, more cognition questions answered incorrectly, or more mobility limitations). Thus, for all models, we expect *positive* coefficients for the dysregulation scores.

RESULTS

Table 3 presents multivariate results for each of the four outcomes: depressive symptoms, cognitive impairment, mobility restrictions and the probability of dying. For each outcome, estimates in the first two columns are from models that include the 16-item index, whereas those in the 3rd and 4th columns are from models in which the overall index is replaced by the two sub-scores. The second model of each pair includes controls for health status at baseline.

[INSERT TABLE 3 ABOUT HERE]

Overall, the estimates reveal significant associations between dysregulation and health for each of the outcomes, although there is variability in the estimates across outcomes. Coefficients associated with the health control variables, particularly the lagged dependent variable (i.e., the health measure at baseline that corresponds to the outcome), are often significant, and, for several models, the coefficients pertaining to dysregulation are reduced substantially in the presence of these controls. The results in the first panel show that physiological dysregulation is significantly associated with depressive symptoms even when controlling for health at baseline, although the introduction of health controls reduces the coefficient by about half. Models 3 and 4 suggest that this association is driven largely by the clinical markers. The results in the second panel show that although the overall dysregulation score is not significantly associated with cognitive impairment, the clinical sub-score is, and this association persists in the presence of controls for health at baseline.

Although there is no evidence of important associations between the preclinical markers and the presence of depressive symptoms or cognitive impairment, the estimates in the third and fourth panels suggest that these markers may play important roles in physical health and especially survival. For the count of mobility limitations, the dysregulation scores are reduced substantially in the presence of health controls, and the preclinical score loses its significance. In

contrast, the associations between the probability of dying and each of the clinical and preclinical scores remain strong and significant in the presence of controls for health at baseline. The magnitude of the associations are substantial: for example, the coefficient in model (2) suggests that a one unit increase in the overall dysregulation score (i.e., one additional biomarker outside the designated operating ranges) is associated with a 39 percent increase ($e^{0.3298}-1$) in the odds of dying over a three-year period, with effects of similar magnitude for both clinical and preclinical markers.

The estimates in Table 4, which are predicted or simulated values of the four outcome variables, provide additional information with which to gauge the magnitude of the association between the dysregulation score and the outcomes. These predicted values were obtained by (1) setting the dysregulation score for all respondents to one of four pre-selected values (0, 3, 6, and 9) and retaining all other explanatory variables at their observed values; (2) using the coefficients from Model 2 (in Table 3) to predict a given outcome for each respondent; (3) averaging the resulting predictions over the sample; and (4) repeating the procedure for each of the specified values of the score and each of the outcomes. The results suggest that an increase in the dysregulation score from very low (0) to very high (9) values, leads to an increase of 1.8 in the depressive symptoms score and an increment of one in the counts of cognitive impairment and mobility restrictions (note that each of these scores has a different range). The effects on three-year survival appear to be substantially greater, rising from 2.1 percent predicted mortality for those with a zero score to 11.5 for those with a score of six and about double that (22.8 percent) for those with a score of nine.

[INSERT TABLE 4 ABOUT HERE]

DISCUSSION

There have been relatively few studies that examine the effects of multi-system physiological dysregulation on subsequent health; many of the existing ones suffer from non-generalizable sampling designs, limited biological information or lack of longitudinal information [5,7]. The present study avoids some of these drawbacks, but is undoubtedly incomplete. For example, although we examine more biomarkers than previous research, we are limited to a set of markers that are feasible to measure in a survey (i.e., that are relatively inexpensive and non-invasive) and are hypothesized to be related to stressful experience and health. Future research will surely identify other relevant markers for the prediction of health and survival, and biomedical advances may simplify their measurement.

A second concern pertains to the use of a dysregulation score that is based on arbitrary cut-points and a simple atheoretical formulation. This type of cumulative score potentially masks the effects of individual biomarkers on health. For example, our work (not shown) suggests that individual preclinical markers (e.g., DHEAS, cortisol and IL-6) are significantly associated with several health outcomes, despite our finding that the preclinical subscore is not. Nevertheless, cross-sectional analyses based on SEBAS have shown that associations between the overall score and health outcomes are generally robust to the use of different types of measures (e.g., counts vs. grade-of-membership scores) as well as to the implementation of alternative cutoff points to define extreme values of biomarkers (quartiles rather than deciles) [1].

Additional concerns pertain to the use of medications by a substantial portion of the sample, some of which (e.g., antihypertensive drugs) are designed to alter values of the biomarkers that are being evaluated here; the relatively short (three years) follow-up period for evaluating major changes in health; the use of biological measures obtained at a single point in

time; and our treatment of the dysregulation score as linear in the statistical models. Although we found that adding quadratic terms to our models did not significantly improve their fit, it is possible that, with additional follow-up exposure, we would identify non-linearities or threshold effects similar to those found in the MacArthur studies [6].

Our strategy for evaluating the importance of physiological dysregulation for subsequent health and survival poses a stringent test. In essence, we are asking whether extreme values of a set of 16 biomarkers are associated with deteriorations in health over a three-year period, controlling for numerous aspects of physical and mental well-being at the start of this follow-up period. The answer appears to be affirmative and suggests that measures of cardiovascular function and metabolic syndrome are particularly important for the health outcomes examined here – although neuroendocrine and immune markers may be at least as important as the clinical measures for survival.

The coefficients associated with the dysregulation measures are often attenuated in the presence of health controls, but this finding is not surprising. This attenuation is likely to result from one or both of the following processes: (1) a reverse effect of poor health on physiological dysregulation; and (2) effects of the biological parameters on health in the past (i.e., prior to the start of the three-year follow-up period). The results suggest that estimates of the association between physiological dysregulation and health based on cross-sectional data are likely to be too large and underscore the importance of using longitudinal data with controls for physical and mental health status at baseline.

Our results are consistent with previous research. Based on data from the MacArthur study, Seeman et al. [2,6] demonstrate that higher physiological dysregulation scores are associated with poorer cognitive and physical functioning at both 2.5 years and seven years of

follow-up, independent of sociodemographic characteristics and health status at baseline. As in the present analysis, the later MacArthur study finds that neuroendocrine factors are important for predicting mortality, but that the corresponding associations are less consistent for both physical and cognitive functioning. Our findings are also similar to recent studies based on SEBAS data that examine the effects of individual biomarkers on mortality in Taiwan. These analyses underscore the importance of the preclinical (both neuroendocrine and immune) markers for survival, suggesting that the preclinical markers appear to provide a more accurate prediction of three-year mortality than standard clinical indicators [15].

Readers familiar with the literature on physiological dysregulation will recognize that our measure is based on biomarkers that have been hypothesized to be associated with *allostatic load*, the physiological burden exacted on the body because of its need to adapt to repeated or chronic challenge [18]. According to the conceptual framework of allostatic load, the sequence of events in the physiological response to stressors is initiated through a set of “primary mediators” (i.e., hormonal factors related to sympathetic nervous system (SNS) activity, hypothalamic-pituitary-adrenal (HPA) axis activity and inflammation). Dysregulation of the primary mediators, in turn, is hypothesized to result in the development of “secondary outcomes” at the system level, including cardiovascular risk factors and metabolic syndrome, and eventually chronic disease and death [18,19]. The sets of primary mediators and secondary outcomes in the allostatic load framework correspond to the clusters of biomarkers that we refer to as “preclinical” and “clinical” markers in this paper.

Despite our focus on the same group of biomarkers, we emphasize that this analysis does not provide a test of the theory of allostatic load, and, thus, we have refrained from using its vocabulary. In particular, we have not examined the association between physiological function

and stressful experience or the social environment, nor does our demonstration that physiological dysregulation is predictive of downstream health provide a meaningful test of this theory. Some scholars have claimed that, if notions of allostatic load are correct, cumulative measures of physiological dysregulation are likely to be predictive of future health even if the individual biomarkers fail to reveal notable associations. Thus, findings from the MacArthur studies that demonstrate that various measures of dysregulation are significantly associated with subsequent health and survival – even though individual biomarkers are not – have been used to support the construct of allostatic load (see, for example [5,6]). We suggest that such results may occur simply as a consequence of measurement error in the biological measures and because the summation of small effects yields a larger one, thus providing little information to support or refute the construct of allostatic load. This distinction is even less clear-cut in the present analysis because numerous individual biomarkers collected in SEBAS are significantly associated with health outcomes [15].

This study has extended previous research on the health consequences of physiological dysregulation by considering a broader range of outcomes and biomarkers in a non-Western population-based sample. Despite the inclusion of rigorous controls for prior health, our analysis confirms earlier findings that multi-system physiological dysregulation is predictive of mental and physical health and survival and suggests that such dysregulation provides early warning signs of the broad range of comorbidities that are becoming increasingly common among the elderly [7].

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Table 1. Cutoff points (10th and 90th percentiles) for individual biomarkers

Variable	N	Percentile	
		10 th	90 th
Preclinical Markers			
Cortisol (µg/g creatinine)	1,019	8.8	48.0
DHEA-S (µg/dL)	1,021	20.9	152.4
Norepinephrine (µg/g creatinine)	1,019	11.2	34.7
Epinephrine (µg/g creatinine) ^a	1,019	—	5.6
IL-6 (pg/mL) ^a	1,022	—	3.4
IGF-1 (ng/mL)	1,021	53.1	168.0
Dopamine (µg/g creatinine)	1,019	87.4	226.7
Clinical Markers			
BMI: weight in kg / (height in m) ²	1,022	20.0	28.9
Waist/hip ratio	1,020	0.8	1.0
Systolic Blood Pressure (mmHg)	1,023	114.0	166.0
Diastolic Blood Pressure (mmHg)	1,023	70.0	97.0
Total cholesterol (mg/dL)	1,022	153.0	252.0
Ratio of total to HDL cholesterol	1,022	2.8	6.1
Triglycerides (mg/dL)	1,022	54.0	204.0
Fasting glucose (mg/dL)	1,022	84.0	138.0
Glycosylated hemoglobin (% of Hb)	1,021	4.8	7.1

^a Approximately 32% of values on IL-6 and 20% on epinephrine were too low to be detected. So, the lowest category represents “undetectable” rather than the bottom decile.

Table 2. Descriptive statistics for outcome and explanatory variables

Variable^a	Analysis Sample for Health Outcomes (N=820)				Analysis Sample for Mortality (N=935)			
	Mean or percent	S.D.	Min	Max	Mean or percent	S.D.	Min	Max
Outcomes in 2003								
CES-D scale (0-30)	5.3	5.6	0	29				
Cognitive impairment (0-24)	8.6	3.9	0	24				
Mobility restrictions (0-9)	2.3	2.5	0	9				
Deceased (%)					6.6	—	0	1
Explanatory variables in 2000								
Physiological dysregulation score (0-16)	3.3	1.8	0	9	3.4	1.8	0	10
Sub-score: preclinical markers (0-7)	1.6	1.2	0	6	1.6	1.2	0	6
Sub-score: clinical markers (0-9)	1.7	1.4	0	7	1.8	1.4	0	8
Age (years)	67.4	8.1	54	91	68.2	8.4	54	91
Male (%)	57.8	—	0	1	58.8	—	0	1
Urban residence (%)	57.1	—	0	1	55.7	—	0	1
CES-D scale (0-30)	5.2	5.2	0	28	5.4	5.3	0	28
Cognitive impairment (0-24)	7.0	3.2	0	21	7.4	3.5	0	23
Mobility restrictions (0-9)	1.8	2.2	0	9	2.0	2.3	0	9
Chronic illnesses/conditions (0-12)	1.3	1.3	0	7	1.3	1.3	0	7
Smoked daily in past six months (%)	21.2	—	0	1	22.2	—	0	1

^a The numbers in parentheses for health measures denote the potential range of each variable.

Table 3. Regression coefficients [and standard errors] for four health outcomes

Variable	Depressive Symptoms (CES-D scale)				Cognitive Impairment			
	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
Physiological dysregulation score	0.4116** [0.0925]	0.2005* [0.0766]			0.0139 [0.0093]	0.0124 [0.0079]		
Sub-score: preclinical markers			0.3101 [0.1516]	0.0346 [0.1258]			-0.0074 [0.0114]	-0.004 [0.0113]
Sub-score: clinical markers			0.4850** [0.1145]	0.3169** [0.1127]			0.0290** [0.0099]	0.0236** [0.0083]
Age	0.0957** [0.0250]	0.0313 [0.0280]	0.0964** [0.0251]	0.0327 [0.0282]	0.0218** [0.0021]	0.0133** [0.0019]	0.0220** [0.0020]	0.0134** [0.0019]
Male	-1.4150** [0.3921]	-0.6472 [0.3970]	-1.4282** [0.3948]	-0.6580 [0.4045]	-0.1523** [0.0285]	-0.0347* [0.0168]	-0.1558** [0.0284]	-0.0360* [0.0165]
Urban residence	-0.2029 [0.4096]	0.3664 [0.4330]	-0.1867 [0.4152]	0.3868 [0.4362]	-0.1576* [0.0624]	-0.0488 [0.0536]	-0.1539* [0.0619]	-0.0466 [0.0530]
Chronic illnesses/conditions		0.1492 [0.2420]		0.1553 [0.2395]		-0.0157 [0.0108]		-0.0155 [0.0113]
Mobility restrictions		0.4016** [0.0865]		0.3979** [0.0874]		0.0202** [0.0070]		0.0199** [0.0071]
CES-D scale		0.2916** [0.0463]		0.2959** [0.0466]		0.0038 [0.0030]		0.0042 [0.0030]
Cognitive impairment		0.0696 [0.0717]		0.0655 [0.0719]		0.0540** [0.0051]		0.0535** [0.0050]
Smoked daily in past six months		1.0473* [0.4527]		1.0086* [0.4629]		-0.0107 [0.0365]		-0.0147 [0.0364]
Constant	-1.5845 [1.6065]	-0.4806 [1.6442]	-1.5992 [1.6152]	-0.5059 [1.6533]	0.7987** [0.1408]	0.8195** [0.1181]	0.7950** [0.1369]	0.8180** [0.1174]
Number of observations	820	820	820	820	820	820	820	820
Pseudo-R ² or R ²	0.057	0.188	0.057	0.190	0.062	0.113	0.063	0.114

Pseudo-R² statistics are derived from a Poisson model (cognitive impairment), a zero-inflated Poisson model (ZIP; mobility restrictions) and a logit model (probability of dying). The ZIP model used in this analysis incorporates the assumption that the probability of zero limitations is inflated by the same amount for everyone in the sample. The R² statistic is derived from linear regression (CES-D). Standard errors are based on a robust estimator of variance that adjusts for clustering by primary sampling unit (PSU).

* significant at 5%; ** significant at 1%

Table 3 (continued)

Variable	Mobility Restrictions				Probability of Dying			
	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
Physiological dysregulation score	0.0714** [0.0176]	0.0450** [0.0154]			0.3448** [0.0762]	0.3298** [0.0841]		
Sub-score: preclinical markers			0.0503** [0.0183]	0.0262 [0.0201]			0.3179** [0.0987]	0.3279** [0.1082]
Sub-score: clinical markers			0.0856** [0.0237]	0.0563** [0.0211]			0.3608** [0.0934]	0.3308** [0.0996]
Age	0.0342** [0.0054]	0.0243** [0.0048]	0.0344** [0.0053]	0.0245** [0.0048]	0.1169** [0.0225]	0.1019** [0.0234]	0.1173** [0.0226]	0.1019** [0.0235]
Male	-0.4146** [0.0821]	-0.2692** [0.0772]	-0.4180** [0.0826]	-0.2708** [0.0789]	0.8112* [0.3194]	0.8658* [0.3945]	0.8021* [0.3130]	0.8655* [0.3936]
Urban residence	-0.2757** [0.0748]	-0.2043** [0.0729]	-0.2705** [0.0732]	-0.2004** [0.0708]	-0.6546** [0.2247]	-0.5194* [0.2442]	-0.6571** [0.2243]	-0.5194* [0.2443]
Chronic illnesses/conditions		0.0607** [0.0186]		0.0607** [0.0188]		0.0007 [0.1230]		0.0006 [0.1237]
Mobility restrictions		0.1073** [0.0137]		0.1072** [0.0136]		0.1156 [0.0639]		0.1156 [0.0638]
CES-D scale		0.0053 [0.0068]		0.0056 [0.0066]		-0.0121 [0.0288]		-0.0121 [0.0288]
Cognitive impairment		0.0090 [0.0087]		0.0084 [0.0088]		0.0677 [0.0358]		0.0677 [0.0358]
Smoked daily in past six months		0.1458 [0.0876]		0.1394 [0.0847]		0.7862* [0.3188]		0.7854* [0.3183]
Constant	-1.1308** [0.3899]	-1.0222** [0.3838]	-1.1327** [0.3860]	-1.0204** [0.3809]	-12.5783** [1.6626]	-12.5623** [1.7357]	-12.5819** [1.6688]	-12.5624** [1.7364]
Number of observations	820	820	820	820	935	935	935	935
Pseudo-R ² or R ²	0.057	0.104	0.058	0.105	0.171	0.198	0.171	0.198

Pseudo-R² statistics are derived from a Poisson model (cognitive impairment), a zero-inflated Poisson model (ZIP; mobility restrictions) and a logit model (probability of dying). The ZIP model used in this analysis incorporates the assumption that the probability of zero limitations is inflated by the same amount for everyone in the sample. The R² statistic is derived from linear regression (CES-D). Standard errors are based on a robust estimator of variance that adjusts for clustering by primary sampling unit (PSU).

* significant at 5%; ** significant at 1%

Table 4. Predicted health outcomes^a by selected values of the physiological dysregulation score

Dysregulation Score ^b	Health Outcomes			
	CES-D scale (0-30)	Cognitive Impairment (0-24)	Mobility Restrictions (0-9)	Percent Dying
0	4.6	8.3	1.8	2.1
3	5.2	8.6	2.1	5.1
6	5.8	8.9	2.4	11.5
9	6.4	9.3	2.8	22.8

^a Predicted health outcomes are based on Model 2 for each health outcome in Table 3; see the text for method of calculation.

^b Zero is the lowest possible value on the dysregulation score; three is close to the median value. The percentage distribution is as follows: 3.3% of the sample has a value of zero; 53.8% has a value of three or lower; 13.0% has a value of six or higher; and 0.7% has a value of nine or higher.