

Predicting Mortality from Standard and Nontraditional Biomarkers

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## ABSTRACT

**Background:** Few studies focus on “preclinical” warning signs associated with mortality. In this paper, we investigate associations between all-cause mortality and two clusters of biological risk factors: 1) standard clinical measures related to cardiovascular disease and metabolic function; and 2) nontraditional measures pertaining to hypothalamic-pituitary-adrenal axis activity, sympathetic nervous system activity and inflammatory response.

**Methods:** Data come from the 2000 Social Environment and Biomarkers of Aging Study, a national sample of Taiwanese ages 54 and older: 1497 persons were interviewed in their homes and 1023 participated in a hospital examination. The analysis is based on 927 respondents with complete information. Logistic regression models describe the association between biomarkers and the three-year probability of dying.

**Results:** Although both groups of biomarkers are significantly associated with mortality, a model with nontraditional biomarkers has better explanatory and discriminatory power than one with clinical measures. The association between the nontraditional measures and mortality remains strong after adjustment for the clinical markers, suggesting that the physiological effects of the nontraditional biomarkers are broader than those captured by the cardiovascular and metabolic system measures included here.

**Conclusions:** Nontraditional markers are likely to provide early warning signs of deteriorating health and function beyond what can be learned from conventional markers. Our findings are consistent with recent studies that 1) demonstrate the importance of neuroendocrine and immune system markers for survival, and 2) indicate that standard clinical variables are less predictive of mortality in older than in younger populations.

## INTRODUCTION

Vast literatures investigate the associations between clinical risk factors and specific diseases, and again, between those diseases and subsequent mortality risk. Fewer studies directly examine associations between clinical risk factors and mortality (1, 2) and even fewer focus on “preclinical” warning signs associated with mortality, although research in this area has been increasing (3-10).

In this paper, we focus on the link between biological risk factors and mortality for an older population. We examine *all-cause* mortality because prediction of specific diseases is especially problematic at these older ages as a consequence of multiple co-morbidities (11). Rather than concentrating on individual biological risk factors, we focus on two clusters. The first comprises standard clinical risk factors related to cardiovascular and metabolic function: obesity, blood pressure, lipids, and glucose metabolism. The second cluster– which we denote by “nontraditional” measures – comprises 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 are not normally measured in medical exams; most do not have well-established clinical cut-offs.

The two clusters are motivated by a theoretical framework (12, 13) that hypothesizes that chronic exposure to stressors results in prolonged dysregulation of “primary mediators” (represented by the nontraditional cluster), leading to abnormal values for “secondary outcomes” (represented by the standard clinical cluster) and ultimately, disease and death. We compare the performance of the two clusters in predicting mortality over a three-year follow-up period.

## METHODS

### *Data Collection*

The data come from the 2000 Social Environment and Biomarkers of Aging Study (SEBAS), which is based on a random sub-sample of respondents 54 and older who were interviewed as part of the nationally representative Survey of Health and Living Status in Taiwan (14). SEBAS included an in-home interview and a hospital visit. Informed consent was obtained for participation in both components.

On a scheduled day several weeks after the in-home interview, participants collected a 12-hour overnight urine sample, fasted overnight, and visited a nearby hospital the following morning where medical personnel drew a blood specimen and took blood pressure and anthropometric measurements. Compliance was extremely high (95.7%).

Among the 1713 respondents selected for SEBAS, 1497 provided interviews (92% of survivors) and 1023 participated in the physical examination (68% of those interviewed). Disproportionately high non-participation rates were found among the healthiest respondents and the least healthy. Overall, persons who received the medical exam reported the same average health status (on a five-point scale) as those who did not. 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 based on the biomarkers are unlikely to be seriously biased (14).

Survival status was ascertained in 2003 by linking to the Household Registration file of the Taiwanese Ministry of Interior. Among the 1,023 exam participants, there were 72 verified deaths by 2003 and 14 respondents with unknown vital status in 2003. After excluding persons with missing vital status (14), missing data on explanatory variables (65), and proxy interviews (17), the analysis sample comprised 927 respondents: 866 survivors and 61 deaths.

### *Explanatory Variables*

The 13 biomarkers examined in this study were included in SEBAS because of their hypothesized association with stressful experience and chronic disease. They comprise six standard clinical indicators of cardiovascular risk and metabolic activity and seven nontraditional biomarkers related to hypothalamic-pituitary-adrenal (HPA) axis activity, sympathetic nervous system (SNS) activity, and inflammatory response.

Blood and urine specimens were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to routine standardization and calibration tests performed by the laboratory, during the early stages of fieldwork nine individuals outside of the sample contributed triplicate sets of specimens: two sets were submitted to UCL and a third was sent to Quest Diagnostics in the U.S. The resulting data indicate high inter- and intra-lab reliability (intraclass correlations  $\geq 0.80$  for UCL; inter-lab correlations  $\geq 0.76$  for UCL vs. Quest Diagnostics).

Systolic and diastolic blood pressures (in mmHg) were calculated as the average of two seated blood pressure readings taken with a mercury sphygmomanometer at least 20 minutes after the respondent arrived at the hospital. Measures of IGF-1, IL-6, DHEA-S, total cholesterol, high density lipoprotein (HDL) cholesterol, glucose, and glycosylated hemoglobin (HbA1c) were obtained from the fasting blood sample. Epinephrine, norepinephrine, cortisol, and dopamine measurements were based on the 12-hour overnight urine sample to provide integrated values of basal operating levels during a time that most participants were resting; they are measured in micrograms per gram ( $\mu\text{g/g}$ ) creatinine to adjust for body size. The assays used to measure the biomarkers derived from the blood and urine samples are described elsewhere (15).

We include age (in 2000), sex, and urban/rural residence as demographic control variables. Because of potential reverse causality (i.e., the possibility that prior health may influence

biomarkers), we incorporate extensive controls for health in 2000. These comprise (1) measures of chronic conditions, mobility limitations, global self-rated health, depressive symptoms, and cognitive function; (2) a five-point measure of the respondent's typical level of pain; and (3) a dummy variable indicating whether the respondent smoked in the past six months.

The measure of current illness counts the number (0-12) of chronic conditions reported by the respondent; the measure of mobility limitations counts the number (0-9) of physical tasks that the respondent reported difficulty performing without aid (14). Global self-rated health is described by a three-category reformulation of the conventional five-point ordinal scale (excellent/good; average; not-so-good/poor). Depressive symptoms are measured by a 10-item short-form of the Center for Epidemiologic Studies Depression scale (CES-D), coded according to standard practice (potential range 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 (16). Cognitive function is a count of cognitive tasks completed correctly, including basic orientation questions, a series of four subtractions, and immediate memory recall (potential range 0 to 24).

### *Analytic Strategy*

We estimate a series of four logistic regression models to describe the associations between the biomarkers and the probability of dying over a three year-period (2000-2003). Because the clustered sampling design may lead to underestimates of standard errors, we incorporate random effects for the primary sampling units. A baseline model includes the demographic and health control variables. The standard clinical markers are added in Model 1; the nontraditional biomarkers replace the clinical measures in Model 2. Model 3 includes both sets of biomarkers. All biomarkers are specified as continuous variables. Because outliers can have a substantial

impact on the parameter estimates, we recoded 25 biomarker values in the study sample that were larger than five standard deviations from the mean to equal this cut point.

We explored the inclusion of linear and quadratic terms in the models, because both low and high values of some measures (e.g., BMI, cortisol, diastolic blood pressure, and epinephrine) have been shown to be associated with adverse health outcomes (17). We included a quadratic term if two conditions were satisfied: (1) the quadratic term was significant ( $p < .05$ ) in a model that included only that biomarker along with age and sex; and (2) the quadratic term remained marginally significant ( $p < .10$ ) in a model that included all control variables, all biomarkers, and the quadratic terms satisfying the first condition. We excluded the quadratic term for systolic blood pressure because of its high correlation (0.7) with diastolic blood pressure, and because the literature suggests that the relationship between systolic blood pressure and mortality is monotonic (18). Because of the limited sample size, we do not include interaction terms in these models – for example, to capture potentially different effects of the biomarkers on mortality by sex or age.

In addition to identifying significant coefficients, we provide statistical comparisons of Model 1 (the standard clinical model) and Model 2 (the nontraditional biomarker model). We use likelihood-ratio tests for nested models to ascertain the joint significance of the set of standard or nontraditional markers. In addition, we calculate the Receiver Operating Characteristic (ROC) curve to evaluate the accuracy of the models in discriminating between decedents and survivors (19). For a given model, the ROC curve compares the probability that the regression equation correctly predicts death for those who died (sensitivity) with the probability of an incorrect prediction among survivors (1-specificity), across the entire range of possible cut points. We use the area under the ROC curve (AUC) to summarize the performance of a model (higher values

indicate better accuracy) and compare AUC values between models based on a chi-square test (20). All analyses are performed using Stata 8.2 (21).

## RESULTS

Average values and standard deviations of the biomarkers are shown in Table 1. Estimates from the logistic models are shown in Table 2. The baseline model (incorporating only the demographic and health controls) is not shown, but statistics derived from this model are presented in a footnote to the table.

Models 1 and 2 reveal that, despite the small number of deaths, numerous biomarkers are significantly ( $p < 0.05$ ) related to survival: BMI, diastolic blood pressure, and HbA1c for the clinical factors; and epinephrine and IL-6 for the nontraditional measures. The association with mortality is positive for HbA1c and IL-6, whereas for BMI, epinephrine and diastolic blood pressure, both high and low values are associated with higher death rates than intermediate values. The odds ratios change slightly when both sets of factors are included in Model 3; HbA1c is no longer significant at the 0.05 level.

Likelihood ratio tests suggest that both sets of biomarkers are significantly related to survival. Comparisons of Models 1 and 2 with the baseline model indicate that inclusion of either set of biomarkers significantly improves the model ( $p = 0.04$  for the standard clinical markers and  $p < 0.001$  for the nontraditional markers). Similarly, in comparison with the full model (Model 3), removal of either set of markers results in a significantly poorer fit ( $p = 0.04$  for the clinical measures and  $p < 0.001$  for the nontraditional ones).

Two comparative assessments provide evidence that the nontraditional biomarker model is superior to the standard clinical one. First, the nontraditional biomarker model has a substantially larger pseudo  $R^2$  value (0.26 vs. 0.21) despite having the same number of

parameters, suggesting better explanatory power (19). Second, the ROC curves depicted in Figure 1 illustrate the better discriminatory power of the nontraditional biomarker model. Chi-square tests indicate that the nontraditional biomarker model has a significantly higher AUC than the baseline model (0.852 vs. 0.790,  $p < .01$ ), whereas the difference between the standard clinical and baseline models is not significant (0.808 vs. 0.790,  $p = 0.23$ ). Although it is plausible that the superior performance of non-traditional measures results from correlation between the clinical markers and self-reported health measures, the results remain essentially unchanged when we exclude controls for health in 2000.

## DISCUSSION

In this population-based study of older Taiwanese, both standard clinical markers of cardiovascular and metabolic function and nontraditional biomarkers of HPA-axis, SNS and immune activity are significantly associated with all-cause mortality. An unanticipated finding is that the nontraditional biomarkers are better predictors of mortality than conventional risk factors. The notion that “primary mediators” affect disease largely through their effects on “secondary outcomes” is not supported by our results: the associations between nontraditional biomarkers and mortality change little after adjustment for conventional biomarkers. These findings strongly suggest that the physiological effects of the nontraditional biomarkers are broader than those captured by the cardiovascular and metabolic system measures included in this analysis.

Although there are few, if any, population-based studies in East Asian populations to corroborate our results, several recent community-based studies in the U.S. underscore the potential importance of markers of immune activity and inflammation for the functioning and survival of older persons. The Framingham Heart Study revealed that high levels of circulating

IL-6 and low levels of IGF-1 were associated with increased mortality after adjustment for important clinical conditions (9); similar results were obtained for a cohort of older women in the Women's Health and Aging Study (4). The Iowa 65+ Rural Health Study indicated that higher IL-6 levels were associated with substantially greater risk of death (5).

Estimates from Western populations also suggest that HPA-axis and SNS activity are related to survival. Although most studies document linkages between cortisol levels and the presence of chronic conditions and illnesses, cortisol levels have been shown to be predictive of mortality among adults who suffered an acute myocardial infarction (22) or a stroke (6, 23). DHEA-S, which is believed to counterbalance the effects of cortisol, is associated with mortality risks among men (7, 10). Older persons with high baseline urinary excretion of epinephrine or norepinephrine in the MacArthur Studies of Successful Aging had higher risks of dying (8).

The greater importance of nontraditional as compared with standard risk factors for older-age mortality is consistent with findings that conventional clinical measures are less predictive of morbidity and mortality among the elderly than among younger persons. For example, higher levels of cholesterol and blood pressure are generally related to higher adult mortality, but at older ages the relationship has been U-shaped or sometimes reversed (24-26). Research also suggests that the relationship of BMI with mortality weakens at older ages (27).

A limitation of the present study is the small number of deaths. The low statistical power makes it impossible to rule out associations between specific biomarkers and survival or to assess the relative importance of different individual markers. In addition, because of both genetic and environmental variation, there are questions regarding the generalizability of our results to Western populations. For example, previous studies have documented that: 1) the distributions of the biomarkers included in this analysis, especially the clinical measures, differ

between Taiwan and the U.S. (28), and 2) the effects of clinical biomarkers on mortality are likely to vary across populations (29).

Nonetheless, the findings of this study are sufficiently robust to suggest that, taken as a group, the nontraditional biomarkers are important predictors of future survival. They are likely to provide useful early warning signs of deteriorating health and function above and beyond what can be learned from standard clinical measures. At the same time, the results are not sufficient to warrant the inclusion of these nontraditional measures in a standard diagnostic toolkit. We have little information regarding what constitutes normal or abnormal levels of these markers, a limited understanding of the extent to which changes over time reflect normal processes of aging or are causally linked to health and survival, and few notions about how to modify levels of these markers (or, indeed, whether modification would ultimately enhance survival). But, with additional research, we are virtually certain to witness an expansion of the list of clinically-assessed measures that are predictive of future survival.

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## REFERENCES

1. Poulter N. Global risk of cardiovascular disease. *Heart* 2003;89:II2-II5.
2. Solomon CG, Manson JE. Obesity and mortality: a review of the epidemiologic data. *Am J Clin Nutr* 1997;66:S1044-S50.
3. Bruunsgaard H, Ladelund S, Pedersen AN, Schroll M, Jorgensen T, Pedersen BK. Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. *Clin Exp Immunol* 2003;132(1):24-31.
4. Cappola AR, Xue QL, Ferrucci L, Guralnik JM, Volpato S, Fried LP. Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. *J Clin Endocrinol Metab* 2003;88(5):2019-25.
5. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999;106(5):506-12.
6. Marklund N, Peltonen M, Nilsson TK, Olsson T. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. In: *J Intern Med*; 2004:15-21.
7. Mazat L, Lafont S, Berr C, et al. Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98(14):8145-50.
8. Reuben DB, Talvi SLA, Rowe JW, Seeman TE. High urinary catecholamine excretion predicts mortality and functional decline in high-functioning, community-dwelling older persons: MacArthur Studies of Successful Aging. *J Gerontol* 2000;55(10):M618-M24.
9. Roubenoff R, Parise H, Payette HA, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: The Framingham Heart Study. *Am J Med* 2003;115(6):429-35.
10. Trivedi DP, Khaw KT. Dehydroepiandrosterone sulfate and mortality in elderly men and women. *J Clin Endocrinol Metab* 2001;86(9):4171-7.
11. Austad SN. Concepts and theories of aging. In: Masoro EJ, Austad SN, eds. *Handbook of the biology of aging*. 5th ed. New York: Academic Press; 2001:3-22.
12. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. In: Adler N, Marmot M, McEwen B,

- Stewart J, eds. *Socioeconomic status and health in industrial nations: social, psychological and biological pathways*: Ann N Y Acad Sci; 1999:30-47.
13. McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. *Arch Intern Med* 1993;153(18):2093-101.
  14. Goldman N, Lin IF, Weinstein M, Lin YH. Evaluating the quality of self-reports of hypertension and diabetes. *J Clin Epidemiol* 2003;56(2):148-54.
  15. Goldman N, Gleib D, Seplaki C, Liu I-W, Weinstein M. Perceived stress and physiological dysregulation. *Stress* 2005;8(2):95-105.
  16. Boey KW. Cross-validation of a short form of the CES-D in Chinese elderly. *Int J Geriatr Psychiatry* 1999;14(8):608-17.
  17. Seplaki CL, Goldman N, Weinstein M, Lin YH. How are biomarkers related to physical and mental well-being? *J Gerontol* 2004;59(3):201-17.
  18. Pastor-Barriuso R, Banegas JR, Damian J, Appel LJ, Guallar E. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. *Ann Intern Med* 2003;139(9):731-9.
  19. Hosmer D, Lemeshow S. *Applied logistic regression*. Second ed. New York, NY: John Wiley & Sons Inc.; 2000.
  20. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating curves: a nonparametric approach. *Biometrics* 1988;44:837-45.
  21. StataCorp. *Stata statistical software: release 8.0*. College Station, TX: Stata Corporation; 2003.
  22. Bain RJI, Fox JP, Jagger J, Davies MK, Littler WA, Murray RG. Serum cortisol-levels predict infarct size and patient mortality. *Int J Cardiol* 1992;37(2):145-50.
  23. Christensen H, Boysen G, Johannesen HH. Serum-cortisol reflects severity and mortality in acute stroke. *J Neuro Sci* 2004;217(2):175-80.
  24. Blazer DG, Landerman LR, Hays JC, Grady TA, Havlik R, Corti MC. Blood pressure and mortality risk in older people: comparison between African Americans and whites. *J Am Geriatr Soc* 2001;49(4):375-81.
  25. Satish S, Freeman DH, Ray L, Goodwin JS. The relationship between blood pressure and mortality in the eldest old. *J Am Geriatr Soc* 2001;49(4):367-74.

- 26.Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001;358(9279):351-5.
- 27.Visscher TLS, Seidell JC, Menotti A, et al. Underweight and overweight in relation to mortality among men aged 40-59 and 50-69 years - the seven countries study. *Am J Epidemiol* 2000;151(7):660-6.
- 28.Goldman N, Weinstein M, Cornman JC, Singer B, Seeman T, Chang MC. Sex differentials in biological risk factors for chronic disease: estimates from population-based surveys. *Journal of Women's Health* 2004;13:393-403.
- 29.Cai J, Pajak A, Li Y, et al. Total cholesterol and mortality in China, Poland, Russia, and the U.S. *Ann Epidemiol* 2004;14(6):399-408.

**Table 1. Mean values of biological measures for analysis sample, SEBAS (2000)**

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<b>Biomarkers</b>	<b>Mean (standard deviation)</b>
<b>Standard Clinical Measures</b>	
BMI: weight in kg / (height in m) <sup>2</sup>	24.4 (3.6)
Systolic BP (mmHg)	138.6 (20.6)
Diastolic BP (mmHg)	82.3 (11.1)
Ratio of total cholesterol to HDL	4.4 (1.4)
Total cholesterol (mg/dL)	201.2 (39.7)
Glycosylated hemoglobin - HbA1c (% of HB)	5.7 (1.3)
<b>Nontraditional Measures</b>	
Cortisol (µg/g creatinine)	26.8 (29.5)
DHEA-S (µg/dL)	80.9 (58.3)
Norepinephrine (µg/g creatinine)	21.9 (9.9)
Epinephrine (µg/g creatinine)	2.6 (2.6)
IL-6 (pg/mL)	1.5 (4.2)
IGF-1 (ng/mL)	105.0 (47.5)
Dopamine (µg/g creatinine)	175.8 (368.3)
<b>Number of Respondents</b>	<b>927</b>

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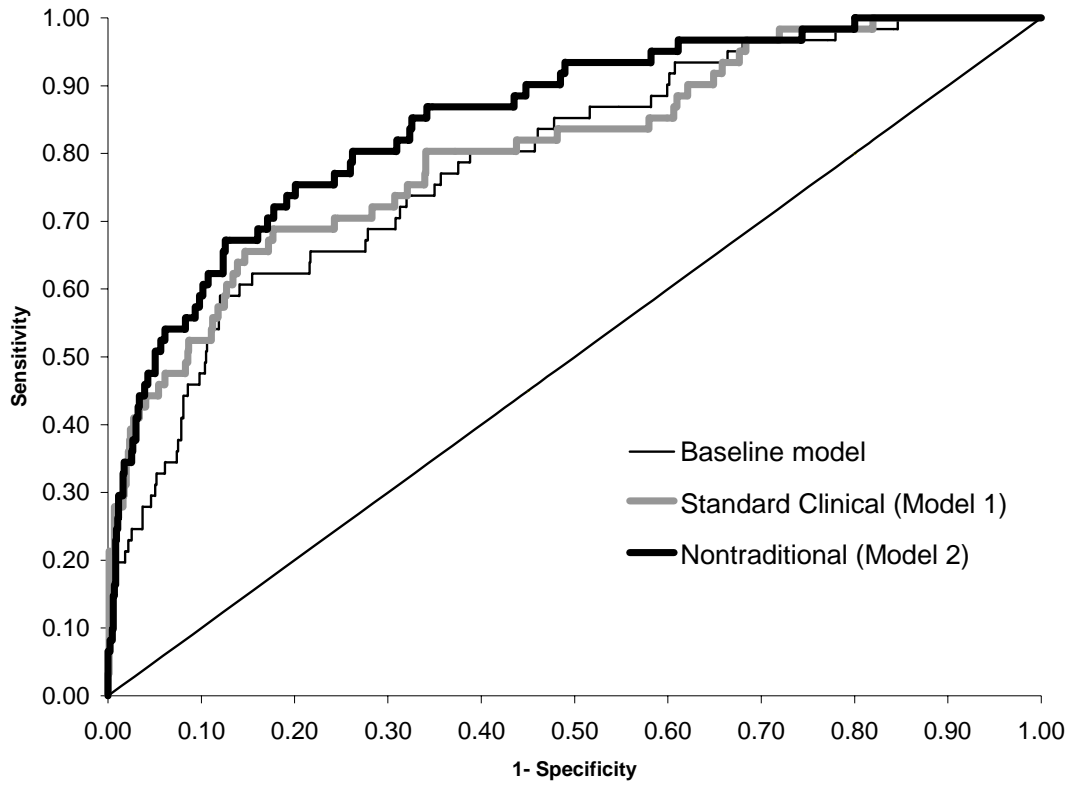
**Table 2 - Estimated odds ratios and 95% confidence intervals (CI) for logistic models of three year probability of dying in Taiwan**

Measures	Model 1	Model 2	Model 3
<b>Standard Clinical Measures</b>			
BMI	0.548* (0.321 - 0.936)		0.532* (0.297 - 0.954)
BMI <sup>2</sup>	1.011* (1.001 - 1.022)		1.012* (1.000 - 1.023)
Systolic BP (mmHg)	0.997 (0.978 - 1.015)		1.000 (0.980 - 1.021)
Diastolic BP (mmHg)	0.821* (0.681 - 0.991)		0.807* (0.669 - 0.974)
Diastolic BP <sup>2</sup>	1.001* (1.000 - 1.002)		1.001* (1.000 - 1.002)
Total cholesterol / HDL	1.156 (0.909 - 1.469)		1.226 (0.949 - 1.583)
Total cholesterol (mg/dL)	0.994 (0.985 - 1.003)		0.992 (0.983 - 1.002)
Glycosylated hemoglobin - HbA1c (% of HB)	1.262* (1.025 - 1.553)		1.233 (0.989 - 1.537)
<b>Nontraditional Measures</b>			
Cortisol (µg/g creatinine)		1.006 (0.999 - 1.013)	1.006 (0.999 - 1.014)
DHEA-S (µg/dL)		0.996 (0.989 - 1.003)	0.996 (0.988 - 1.003)
Norepinephrine (µg/g creatinine)		1.017 (0.984 - 1.052)	1.019 (0.984 - 1.055)
Epinephrine (µg/g creatinine)		0.821 (0.639 - 1.054)	0.817 (0.631 - 1.057)
Epinephrine <sup>2</sup>		1.030** (1.011 - 1.050)	1.029** (1.009 - 1.049)
IL-6 (pg/mL)		1.084** (1.038 - 1.133)	1.099** (1.050 - 1.151)
IGF-1 (ng/mL)		0.993 (0.985 - 1.001)	0.993 (0.985 - 1.002)
Dopamine (µg/g creatinine)		0.995 (0.988 - 1.001)	0.995 (0.989 - 1.002)
Log-likelihood	-178.91	-165.71	-157.58
Pseudo R <sup>2</sup>	0.205	0.263	0.299
Area under ROC curve	0.808	0.852	0.868

Notes: \*p < 0.05; \*\*p < 0.01

All models include a random effect for primary sampling unit and control for age, sex, rural/urban residence, self-rated health, number of chronic conditions, number of mobility restrictions, level of pain, depressive symptoms, cognitive function, and smoking status.

Baseline model (includes only control variables): Log-likelihood = -187.07, Pseudo R<sup>2</sup> = 0.168, and Area under ROC curve = 0.790



**Figure 1. ROC curve for models of three year probability of dying**