Determinants of Mortality at Older Ages: The Role of Biological Markers of Chronic Disease

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ABSTRACT

Since the first studies of mortality were published in the 17th century, social scientists and epidemiologists have had strong interests in understanding the determinants of mortality. Recently, the availability of micro-level data from demographic and health interview surveys and the concomitant use of multivariate models have generated more in-depth studies on this topic. Still, considerable uncertainty remains about the adequacy of self-reported measures of health in statistical models of mortality. In this paper, we aim to bridge this gap in the literature by examining the association between clinically assessed information on biomarkers and mortality for older adults. Using population-representative data from a national survey collected in Taiwan and binary logistic regression models, our paper assesses the differential impact of biological markers versus a wide range of self-reports of health on a three-year probability of dying. Our analysis confirms previous studies demonstrating the effects of markers for metabolic syndrome on mortality, particularly BMI, diastolic blood pressure, and levels of glucose in the blood. We also identify detrimental effects of neuroendocrine and immune-system markers, including high levels of IL-6, low levels of dopamine, and both high and low levels of epinephrine. Our results indicate that biomarkers provide independent explanatory power in the presence of self-reported health measures and are stronger predictors of the risk of dying than the health measures. The findings suggest that individuals may underestimate their probabilities of dying because they have no information about risk factors that act silently on the body and are not detected by clinical examination. The strong associations between biomarkers and mortality found here provide new avenues for projecting future mortality and elucidating differences in longevity across populations.

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INTRODUCTION

The study of mortality determinants has a long history in social science. Much of the early literature examined factors associated with mortality by estimating life tables for specific classifications of the population. These comparisons yielded meaningful information on the relation of mortality with age, sex, smoking habits and socioeconomic variables, but they were less useful in revealing the simultaneous influence of multiple factors or the impact of measures beyond the classic socio-demographic variables in the demographers' toolkit.

During the past few decades, the availability of micro-level data – especially from demographic and health interview surveys – and the concomitant use of multivariate models have generated more in-depth studies of the determinants of longevity (Elo & Preston, 1996; Hayward & Gorman, 2004). The resulting analyses have provided a better understanding of the complex mechanisms that mediate mortality risk. In particular, there is now a substantial literature investigating the importance of various self-reported dimensions of health for adult and old-age mortality (Hurd, McFadden, & Merrill, 2001; Nybo, Petersen, Gaist, Jeune, Andersen, McGue et al., 2003).

Nonetheless, self-reports are beset with a variety of problems, most notably the potential inaccuracy of the responses. These inaccuracies may result from respondents' being ill-informed about their own health, poor recall of health information from the past, or reluctance to reveal health problems to a stranger. Studies based on representative samples of both Western and Asian populations have found that the resulting measurement error compromises the validity of self-reports of heath for some subgroups, and health conditions (Goldman, Lin, Weinstein, & Lin, 2003; Vargas, Burt, Gillum, & Pamuk, 1997).

In light of these reporting problems, there is a compelling need to obtain objective measures of health status, such as biological or clinical markers. Although many studies have

obtained such measures, almost all have been based on clinical or community-level samples. The recent development of inexpensive diagnostic tests now makes it feasible to include clinical markers in national surveys (Boerma, Holt, & Black, 2001), thereby permitting researchers to integrate biology into social science research on aging.

In the analysis that follows, we aim to bridge this gap in the literature by examining the association of a broad array of biological measures with mortality at older ages based on a national survey in Taiwan. In doing so, we go beyond past research to assess the differential impact of biological markers versus a wide range of self-reports of physical and mental health on the risk of dying. Because Taiwan's life expectancy and cause-of-death structure are similar to those in Western industrialized populations, our findings are likely to be applicable to other parts of the world.

BACKGROUND

Determinants of Mortality in Social Science Research

Social scientists have identified a wide array of factors that influence mortality, including demographic, socioeconomic and health-related variables. Chronological age - an important proxy for both biological aging and life-cycle experiences - is positively related to mortality. Mortality also varies by sex: excess adult male mortality is a characteristic of most populations and has been attributed to biological, behavioral, and environmental factors (Waldron, 1995).

Studies have also identified differentials in mortality by marital status. The greater longevity of married, as compared with single and formerly married persons results both from marriage being selective of healthier individuals and from marriage promoting increased material wellbeing and social and psychological support (Waldron, Hughes, & Brooks, 1996). Previous research has demonstrated that persons who are more socially integrated – e.g., have more

extensive social networks, larger numbers of strong ties, and more frequent participation in social activities – have lower rates of illness and higher life expectancy than their more isolated counterparts (House, Landis, & Umberson, 1988). Mortality patterns often differ among racial and ethnic groups, but it is difficult to generalize across populations about the underlying sources of variation. In the U.S., differences between Whites and African-Americans have been explained in large part, but not entirely, by differences in socioeconomic conditions and health-related behaviors throughout the life course (Rogers, 1992).

There has been considerable research focused on understanding why socially and economically advantaged people generally enjoy longer lives. This advantage in longevity is thought to arise through numerous complex and interrelated pathways that link socioeconomic status and adult health: for example, higher education improves access to health information and deters unhealthy behaviors; income and wealth provide resources for obtaining better quality health care services; and higher occupational status may be associated with fewer psychosocial stressors and less detrimental environmental exposures in the workplace (Preston & Taubman, 1994). Socioeconomic differences in mortality appear to diminish with increasing age (Elo & Preston, 1996; Preston & Taubman, 1994), but this apparent weakening may partly reflect earlier mortality of persons with high risk of death. A relatively new area of research focuses on the effects of early life conditions on adult mortality. For example, parents' education and family arrangements have been shown to affect adult mortality (Hayward & Gorman, 2004; Preston, Hill, & Drevenstedt, 1998).

The increasing availability of survey data has also allowed researchers to examine the associations between self-reported measures of physical and mental health and the risk of dying. Several studies have shown that cognitive impairment, functional limitations, and conditions,

such as cancer and lung disease, are the strongest predictors of mortality in later-life (Hurd et al., 2001; Nybo et al., 2003). The five-point measure of self-rated health, which we refer to as SRH (e.g.,"Would you say your health in general is excellent, very good, good, fair, or poor?") is significantly associated with the risk of dying (Idler & Benyamini, 1997). SRH subsumes multiple domains of physical and mental well-being and increasing evidence shows that responses remain a strong and independent predictor of mortality after accounting for socio-demographic conditions, health behaviors and self-reports of physical health (Burstrom & Fredlund, 2001). Little is known, however, about the predictive strength of these reports in the presence of controls for biological markers of chronic disease.

Biological Markers of Chronic Disease

The analysis presented here focuses on the mortality impact of the set of biological markers collected in a nationally representative survey in Taiwan: Social Environment and Biomarkers of Aging Study (SEBAS). These biomarkers pertain to several interrelated physiological processes - cardiovascular, metabolic, immune, the hypothalamic-pituitary axis, and the sympathetic nervous system - and are comparable to those collected in recent U.S. surveys (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997; Singer & Ryff, 1999).

A large body of research has focused on markers of the cardiovascular and metabolic systems that are associated with relatively common chronic conditions. These indicators include body mass index (BMI), waist-hip ratio, blood pressure, cholesterol, and blood glucose. BMI, an indicator of obesity, is probably the most widely used biomarker in social science research. Longitudinal data have shown that both accelerated loss of lean body mass and excess fat are associated with acute and chronic diseases and subsequent mortality (Allison, Faith, Heo, & Kotler, 1997; Seidell & Visscher, 2000). Although the relationship of BMI with mortality

appears to weaken at older ages with the reduction of height and the redistribution of fat to the abdominal cavity, results are not conclusive (Calle, Thun, Petrelli, Rodriguez, & Heath, 1999; Seidell & Visscher, 2000). Waist circumference and the waist-hip ratio are alternative measures of obesity that focus on abdominal fat deposition and provide better predictions of cardiovascular mortality than BMI. The associations of each of these obesity measures with mortality in older samples vary across populations (Visscher, Seidell, Molarius, van der Kuip, Hofman, & Witteman, 2001; Woo, Ho, Yuen, Yu, & Lau, 1998), suggesting the potential importance of multiple indicators of obesity.

Blood pressure and total serum cholesterol are also well established markers for cardiovascular disease and mortality. Baseline measurements of systolic and diastolic blood pressure are significantly associated with the risk of stroke, myocardial infarction, heart failure and total mortality (Seshadri, Wolf, Beiser, Vasan, Wilson, Kase et al., 2001; van den Hoogen, Feskens, Nagelkerke, Menotti, Nissinen, & Kromhout, 2000). Both the level and composition of cholesterol in the blood are also related to longevity. Hypercholesterolemia increases the risk of atherosclerosis and deaths from coronary heart diseases among adults (Stamler, Stamler, & Neaton, 1993). In addition, higher concentrations of high-density lipoprotein cholesterol (HDL) are significantly associated with lower risk of coronary artery disease, stroke-related mortality and total mortality (Anderson, Castelli, & Levy, 1987; Chyou & Eaker, 2000).

Results among very old populations are less clearcut: U-shaped as well as negative associations have been documented (Satish, Freeman, Ray, & Goodwin, 2001; Schatz, Masaki, Yano, Chen, Rodriguez, & Curb, 2001). Possible explanations for a different pattern among the oldest-old include the selective survival of healthy adults and methodological challenges, such as the paucity of data on older people and lack of controls for other health conditions.

Regulation of glucose in the blood also plays an important role in survival. High levels of blood glucose have been independently associated with coronary heart disease, and premature disability and death (Saydah, Eberhardt, Loria, & Brancati, 2002). Although people with diagnosed diabetes have the highest risk of dying, recent studies have shown that mortality rates increase continuously as levels of glucose concentration rise (Khaw, Wareham, Bingham, Luben, Welch, & Day, 2004).

Biological markers of hypothalamic pituitary adrenal (HPA) axis activity are related to survival through a broad range of physiological mechanisms. Increased levels of cortisol are associated with immune, nervous and cardiovascular system functions. High levels of cortisol are predictive of mortality among adult patients with myocardial infarction (Bain, Fox, Jagger, Davies, Littler, & Murray, 1992), whereas both low and high cortisol levels are related to increased risk of dying among patients with acute ischemic stroke (Marklund, Peltonen, Nilsson, & Olsson, 2004). Low levels of dehydroepiandroesterone (DHEA) and its sulfate form (DHEAS), believed to act as antagonists to cortisol, have been related to several disorders, including increased cholesterol and blood sugar levels, and impairments of immune and cognitive function. Research based on Western populations demonstrates a negative relationship between DHEAS and the risk of dying, but only among men (Mazat, Lafont, Berr, Debuire, Tessler, Dartigues et al., 2001; Trivedi & Khaw, 2001).

Norepinephrine and epinephrine reflect sympathetic nervous system (SNS) activity, another central regulatory system in the body that is closely related to the HPA-axis function. SNS overactivity, manifested by increased plasma concentrations of norepinephrine and epinephrine, may result in cardiovascular disease and mortality (Katayama, Nakashima, Furudono, Honda, Suzuki, & Yano, 2004; Kaye, Lefkovits, Cox, Lambert, Jennings, Turner et

al., 1995). Research on dopamine, an intermediate substance in the synthesis of epinephrine and norepinephrine, suggests that declines in this hormone with age are related to the development of Parkinson's disease and deficits in cognitive function, both chronic conditions associated with decreased longevity (Backman & Farde, 2001; Rascol, Goetz, Koller, Poewe, & Sampaio, 2002).

Immune function, particularly inflammatory response, may have played a key role in the twentieth century mortality decline in the industrialized world (Finch & Crimmins, 2004). One important marker of immune system activity is interleukin-6 (IL-6), a multifunctional protein that stimulates the production of other acute-phase proteins in response to inflammatory processes (Guillen, Blanes, Gomezlechon, & Castell, 1995). IL-6 has been linked to numerous age-related diseases, including heart disease, diabetes, osteoporosis, and some cancers (Mendall, Patel, Asante, Ballam, Morris, Strachan et al., 1997; Salgado, Junius, Benoy, Van Dam, Vermeulen, Van Marck et al., 2003). Insulin-like growth factor-1 (IGF-1), which affects muscle growth and plays a important role in the regulation of immunity and inflammation (Heemskerk, Daemen, & Buurman, 1999), may also account for some of the variation in mortality risk among elderly populations (Katic & Kahn, 2005).

Mortality in Taiwan

Taiwan has experienced a remarkable decline in mortality in the last forty years: female life expectancy at birth rose to 78.4 years in 2000 from a level of 66.4 in 1960 and male life expectancy at birth rose from 62.3 to 72.7 years over this same period (Ministry of Interior, 2005). Forecasts of mortality suggest that life expectancy at birth in Taiwan will continue to rise, reaching about 80 years for both sexes combined in 2050 (Lee, Mason, & Miller, 2000).

Consistent with patterns in Western countries, improvements in adult mortality over the last two decades have been proportionately larger at older ages and especially pronounced

among Taiwanese men aged 85 and older (Leung, Tang, Chie, Lue, & Lee, 1999). Several factors may have contributed to this pattern, including major improvements in public health programs, medical developments and changes in socioeconomic and demographic conditions (Zimmer, Martin, & Lin, 2005).

Elderly Taiwanese have witnessed dramatic transformations in the socioeconomic environment. During the fifty years of Japanese occupation, which began in 1895, improvements in education and public health resulted in increases in the standard of living for most of the population (Fricke, Chang, & Yang, 1994). Yet, during that period, most of the population remained on farms and spent their childhood in a traditional agricultural society characterized by strong social norms, little opportunity for advanced education, and an unequal distribution of wealth. After World War II, Taiwan enjoyed a long-term economic expansion while achieving higher education levels and a more equitable distribution of educational opportunities. The adoption of an industrialization program fueled urbanization and economic growth, and allowed millions to have access to consumer durables and improved lifestyles (Hermalin, Liu, & Freeman, 1994).

Recent studies focusing on the elderly in Taiwan have identified possible pathways linking socioeconomic characteristics and the risk of dying. Liu, Hermalin & Chuang (1998) found a significant impact of education on mortality in Taiwan – one that operates largely through better health status, health behaviors and stronger social relationships. Zimmer, Martin & Lin (2005) using data based on the same study sample but on a longer period of observation, confirmed the association between education and old-age mortality and suggested that education may operate primarily by preventing the onset of functional limitations among the healthy.

Findings with regard to age, sex, marital status and self-reported measures of health have been fairly consistent with those for Western populations (Liu et al., 1998; Zimmer et al., 2005). In particular, poor self-assessed health, functional limitations, drinking and smoking habits, as well as conditions such as diabetes and lung problems, are significantly associated with the risk of dying for older Taiwanese (Zimmer et al., 2005). Nationalist civilians and military supporters who migrated from mainland China after World War II have a mortality advantage relative to native-born Taiwanese, a finding that may be attributable to the higher education levels, incomes and political status experienced by the Mainlanders (Beckett, Goldman, Weinstein, Lin, & Chuang, 2002).

Despite profound demographic and economic changes, Taiwan has maintained distinct social and cultural characteristics that are likely to have implications for mortality patterns (Beckett et al., 2002). These include the existence of extended households, particularly the coresidence of a married couple with the husband's parents (Weinstein, Sun, Chang, & Freeman, 1994), and the role of age, sex (male) and generation (elderly) as determinants of deference, access to power, and greater control over decision-making processes in the household (Fricke et al., 1994). Better social connections and emotional support are related to lower levels of mortality in Taiwan but, surprisingly, the associations appear to be weaker than those in Western populations (Beckett et al., 2002; Cornman, Goldman, Glei, Weinstein, & Chang, 2003).

DATA, VARIABLES AND METHODS

Data

The data for this study were obtained from the Social Environment and Biomarkers of Aging Study (SEBAS) conducted in 2000. SEBAS is based on a follow-up of the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan, a nationally representative longitudinal survey including the institutionalized population. The initial survey consisted of 4,049 eligible

respondents who were aged 60 years and older in 1989; they were reinterviewed in 1993. In 1996, the study added a new cohort of 2,462 near-elderly respondents aged 50 to 66. The two cohorts were interviewed again in 1999 and 2003. In 2000, a subsample of respondents for SEBAS was drawn randomly from the combined near-elderly and elderly cohorts who were alive in 1999. Persons aged 70 years and older and persons in urban areas were oversampled.

SEBAS consists of two parts: a face-to-face in-home interview and a medical exam. Among the 1,713 respondents selected for this study, 1,497 provided home interviews between July and December 2000 (92 percent of survivors). The interviews comprise information regarding demographic and socioeconomic characteristics, physical health, health-related behaviors, psychological well-being and health service utilization.

Among the 1,497 participants who completed interviews, 1,023 agreed to participate in the medical examinations (68% of those interviewed). Respondents collected a 12-hour urine specimen overnight and visited a nearby hospital the following morning for a physical examination. 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 the physical examination.

Although respondents over age 70 were less likely to participate in the medical examinations than younger persons, previous comparisons have shown that sex and other measures of socioeconomic status were not significantly related to participation. Restrictions regarding health conditions resulted in the exclusion of a disproportionate number of the least healthy respondents, but those who reported themselves in "excellent" health were also less likely to participate. Overall, persons who participated in the medical exam reported the same

average SRH as those who did not, suggesting that estimates derived from the biomarkers are unlikely to be seriously biased in the presence of controls for age (Goldman et al., 2003).

Survival status was ascertained for all SEBAS respondents in 2003. Vital status was verified by linking the survey data to the Household Registration file constructed by the Taiwanese Ministry of Interior. Of the 1,023 participants who completed medical exams in 2000, there were 72 verified deaths for the period 2000-2003. In addition, 937 respondents were known to have been alive as of the 2003 interview. Only 14 respondents (1.3 percent) had unknown vital status in 2003.

Our analysis is based on a sample of 929 respondents: 866 survivors and 63 deceased. Of the 1,009 individuals who completed a medical exam and for whom vital status is known, we excluded individuals for whom a proxy completed the interview (n=17), and cases with missing data on independent variables (n=63). Table 1 reveals that individuals for whom independent variables are missing are similar to the individuals included in the analysis with regard to most socio-demographic characteristics, except for being older and having lower participation in social activities ($p<0.05$). The two groups also have comparable values for most biomarkers and health measures, but the study sample has significantly higher total cholesterol, lower waist-hip ratio, a lower level of pain, and fewer mobility restrictions.

Variables

We examine three sets of determinants of mortality: demographic, social and economic characteristics; self-reported health measures; and biological markers.

Demographic, Social and Economic Characteristics. We include several socio-demographic characteristics that have been shown to affect adult mortality. Besides age and sex,

we include a dummy variable for Mainlanders, who comprise about 25 percent of men and 7 percent of women in the sample.

Educational attainment is based on answers to the 1989 (elderly sample) and 1996 (near elderly sample) waves and is measured in three-categories: no education or illiterate (omitted category), 1 to 6 years of education or literate, and 7 or more years of education. Although respondents were also asked to provide information on assets and main sources of income, we exclude these variables because they were not significantly associated with mortality in preliminary models, and because retaining them would have reduced the sample size for analysis (36 cases have missing information on income and 81 on assets). Marital status is measured as a dichotomous variable equal to one for respondents who had a spouse or partner in 2000. We do not separate widows from those who were divorced or had never married because of the small number of cases (8 percent) in the latter two categories. To assess the effect of childhood social conditions on mortality, we include a paternal occupation status index based on information on the major lifetime occupation of the respondent's father as recorded in the 1989 and 1996 waves. The index reflects the prestige of this occupation, ranging from 55 to 76, and is similar to an earlier measure of occupational status for the U.S (Tsai & Chiu, 1991).

We use two variables pertaining to social involvement to measure the effect of social networks on survival. The number of social ties with non-relatives (1999 interview) is constructed as a count of the number of close friends and neighbors that the respondent sees, speaks with, or contacts by phone at least once a week. The number of social activities (2000 interview) is measured as a count of eight activities in which the respondent reports current membership or participation: neighborhood associations, religious associations, professional or

civic groups, social service groups, political associations, village or lineage associations, elderly clubs, and elderly education.

Self-Reported Health Measures. All self-reported measures of health status are based on the 2000 interview, with the exception of level of pain or discomfort, which is derived from the 1999 wave.

We record current illness as a count of 12 chronic conditions that are leading causes of death in Taiwan or are related to other serious illnesses: high blood pressure, diabetes, heart disease, cancer or malignant tumor, lower respiratory tract disease, arthritis or rheumatism, gastric ulcer or stomach ailment, liver or gall bladder disease, cataracts, kidney disease, gout, and spinal or vertebral spurs. We also include a measure of the respondent's functional ability based on the number of mobility limitations in nine activities: standing continuously for 15 minutes and for two hours, squatting, raising both hands over the head, grasping or turning objects with the fingers, lifting or carrying an object weighing 11 to 12 kg, running a short distance (20-30 meters), walking 200 to 300 meters, and climbing two or three flights of stairs.

The respondent's cognitive function is assessed from a battery of 14 questions that are derived from several existing tests of cognition (Pfeiffer, 1975). The resulting score is a count of tasks that the respondent answered correctly, coded according to recommendations of Herzog & Wallace (1997). Depressive symptoms are measured by a 10-item short-form of the CES-D (Center for Epidemiologic Studies Depression) scale (Radloff, 1977). The shortened CES-D has been shown to perform well across different cultural settings and to provide estimates comparable to the twenty-item CES-D (Boey, 1999). The index is coded according to standard practice and ranges from 0 to 30, with higher scores indicating more depressive symptoms.

SRH is based on responses to a five-point ordinal scale: excellent, good, average, not so good, and poor. We use a three-category formulation of these responses, coded as excellent or good (omitted category), average, and not so good or poor. We also include a five-point measure that indicates the typical level of physical discomfort or pain experienced by the respondent, ranging from none to very serious (unbearable). Finally, we measure one health behavior, smoking status, which is coded as a dichotomous variable that takes the value of one for respondents who smoked daily in the six months before the interview.

Biological Markers. All 14 biomarkers examined in this study come from the physical examination and blood and urine collection undertaken in 2000. Blood and urine specimens were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to the routine standardization and calibration tests performed by the laboratory, duplicate samples for 10% of specimens were submitted to UCL and to Quest Diagnostics in the U.S. Data from these duplicates indicate high inter- and intra-lab reliability, with intraclass correlations of 0.80 or higher for UCL, and inter-lab correlations of 0.76 or higher between results from UCL vs. Quest Diagnostics.

We include two measures of obesity: BMI, calculated as weight divided by height squared (Kg/m^2), and waist-hip ratio, calculated as the ratio of waist to hip circumference. Two markers for hypertension – systolic and diastolic blood pressure – are derived from the average of two readings from a mercury sphygmomanometer with the respondent in a seated position. Additional markers of cardiovascular and metabolic function were obtained from the fasting blood samples. We include measures of total serum cholesterol and the ratio of total serum cholesterol to high-density lipoprotein (HDL) cholesterol. Glycosylated hemoglobin (HbA_{1c})

serves as an integrated measure of glucose metabolism over the past three months and is an indicator of a diabetic condition.

Four markers of neuroendocrine function are obtained form the 12-hour urine samples. Epinephrine, norepinephrine, cortisol, and dopamine measurements provide integrated values of these biomarkers for a period when most participants are at home and resting; they are measured in micrograms per gram (μg/g) creatinine to adjust for body size. We also include measures of IL-6, IGF-1, and DHEA-S, which were derived from the fasting blood specimens.

All biomarkers included in our models are specified as continuous variables. In light of the clinical literature that suggests that both low and high values are often associated with chronic disease and death, we explored the inclusion of both linear and quadratic terms. Following the results of an exploratory analysis, we included a quadratic term if two conditions were satisfied: (1) the quadratic term significantly ($p<.05$) improved the fit of the model that included only that biomarker along with age and sex; (2) the quadratic term was significant ($p<.05$) in the full model that controlled for all covariates. The quadratic terms for three biomarkers – BMI, diastolic blood pressure, and epinephrine – satisfied these criteria. Because outliers on the clinical measures can have a substantial impact on the parameter estimates, we recoded 60 values that were larger than five standard deviations from the mean to equal this cut point.

Analytical Approach

We use logistic regression to model the probability of dying over a three year-period (2000-2003). Because clustering of the sample by primary sampling units (PSUs) could lead to underestimates of the standard errors, we estimated models that incorporate random effects for the PSUs using Stata 8.2 (StataCorp, 2003). Multivariate models are based on unweighted data,

but include age and a dummy variable for urban residence in order to account for the sample design.

We specify a series of four logistic models to explore the associations between mortality and three sets of determinants. Model 1 examines the effects of demographic, social and economic characteristics on mortality. Model 2 adds self-reported health measures. Biological markers are added next in Model 3. Model 4 excludes the self-reported health measures from Model 3 (i.e., it contains the biomarkers but not the self-reported measures).

Our evaluation is based on a statistical comparison of models. We compare log-likelihood and pseudo R^2 values to assess the significance of adding health and biomarker variables to simpler models. Since models 2 and 4 are non-nested, we also estimate the Bayesian Information Criterion (BIC); (Raftery, 1996), to evaluate the relative fit of a model that includes biomarkers vis-à-vis one that includes self-reported measures of health.

To examine the magnitude of the association of selected variables with mortality, we compare predicted probabilities for self-reported measures of health and biological markers that reach the 10 percent significance level in the full model (Model 3). For each measure, these simulated probabilities were obtained by (1) assigning selected percentile values (1^{st}, 10^{th}, 50^{th}, 90^{th} and 99^{th}) of the given health or biomarker variable to all individuals; (2) retaining all other explanatory variables at their observed values; (3) using the coefficients of Model 3 to predict the probability of dying for each respondent; and (4) averaging the resulting predicted probabilities across individuals in the sample.

RESULTS

Estimated coefficients for the four models are provided in Table 2. Results for Model 1 confirm well-established associations: age and sex are significantly associated with the probability of

dying and education (7+ years) is marginally significant. Neither ethnicity nor marital status is significantly associated with mortality, a finding that contradicts several analyses for Taiwan (Beckett et al., 2002; Zimmer et al., 2005). Because these prior studies were based on a larger sample and longer follow-up than the present study, these discrepancies suggest that our statistical power may be limited by the small number of deaths.

A likelihood ratio test comparing Models 1 and 2 reveals that the inclusion of self-reported measures of health in Model 2 significantly ($p<0.05$) improves the basic socio-demographic model; the corresponding pseudo R^2 values increase from 0.16 to 0.20. The coefficients for age and sex remain virtually unchanged and statistically significant in Model 2, indicating that the effects of these variables persist after the inclusion of controls for health status. The effect of education (7+ years), however, is reduced by about 60 percent and becomes insignificant, suggesting that health-related behaviors and health status are mechanisms through which education affects adult mortality in Taiwan. Contrary to expectation, we do not find statistically significant associations for several self-reported health measures, including the counts of chronic conditions and mobility limitations. As with some of the socio-demographic covariates, studies based on the parent survey have identified significant associations between these health measures and mortality (Beckett et al., 2002; Liu et al., 1998; Zimmer et al., 2005), a finding that once again underscores the limited statistical power of our analysis. However, daily smoking is significantly associated with mortality ($p<0.05$) and SHR and cognitive function have marginally significant associations ($p<0.10$). Not surprisingly, our estimates show higher risks of dying for smokers, for persons with not so good/poor SRH, and for those with low cognitive function.

The addition of biological markers in Model 3 results in a further significant improvement of fit ($p<.01$ for the likelihood ratio test of Model 3 vs. Model 2); the corresponding values of pseudo R^2 rise substantially from 0.20 in Model 2 to 0.32 in Model 3. The coefficient for age changes little, indicating that most of the biological effect of age is not captured by the biomarkers. In contrast, the addition of the biomarkers substantially increases the coefficient of sex, suggesting that there are important associations between sex and the biomarkers. The association with daily smoking is insignificant in the presence of biological controls. However, the coefficients for cognitive function and SRH remain significant. Model 3 shows that numerous biomarkers are significantly related to survival: BMI, diastolic blood pressure, epinephrine, IL-6 and dopamine are each significantly ($p<0.05$) associated with the probability of dying over the 3 year-period; glycosylated hemoglobin is marginally significant ($p<0.10$). The coefficients in Model 3 indicate positive associations for glycosylated hemoglobin and IL-6, and negative associations for dopamine. Three biomarkers – BMI, epinephrine and diastolic blood pressure – are non-linearly related to mortality such that both high and low values are associated with larger death rates than intermediate values.

Given that some measures of health status (e.g., the presence of chronic conditions and illnesses such as heart disease, hypertension and diabetes) are likely to have strong associations with relevant biomarkers, it is not surprising that the magnitude of the coefficients associated with some biomarkers increases slightly when self-reported measures of health are excluded in Model 4. Two markers that are not significant in Model 3 – total cholesterol and the ratio of total to HDL cholesterol – are marginally significant ($p<0.10$) in Model 4, and both glycosylated hemoglobin and cortisol are significant ($p<0.05$). Although the value of pseudo R^2 decreases when the health measures are excluded (from 0.32 in Model 3 to 0.29 in Model 4), the value

remains high and a likelihood ratio test confirms that Model 4 is a significant improvement ($p<0.01$) over the socio-demographic model (Model 1).

The results presented above demonstrate that a comprehensive model of mortality should include *both* self-reports of health and physiological measures (i.e., the inclusion of either set of variables results in a significant improvement in fit over Model 1). Nevertheless, we introduce Model 4 into the analysis because a comparison of this model with Model 2 provides insights regarding the relative importance of self-reported health measures versus biomarkers as determinants of mortality. An informal comparison of the pseudo R^2 values (0.20 for the health model and 0.29 for the biomarker model) suggests that the biomarkers explain more variation in the data than do the health measures. However, they do so at the expense of many more parameters (17 denoting biomarkers versus 8 for the health measures). A comparison of these two non-nested models using the Bayesian Information Criterion (Raftery, 1996) – which takes into account the difference in the number of degrees of freedom between the models – suggests a strong preference for Model 4 (biological markers) over Model 2 (health measures).[1] In short, these results suggest that the inclusion of biomarkers leads to a marked improvement in models of mortality.

In order to assess the magnitude of these associations, in Table 3 we present predicted probabilities of dying over a three-year period for health and biomarkers variables that are significant at $p<0.10$ in Model 3. These simulated probabilities illustrate the non-linear relation of the association between mortality and BMI, diastolic blood pressure and epinephrine, supporting findings previously documented in the epidemiological literature (Calle et al., 1999; Christensen & Jensen, 1995; Satish et al., 2001).

The simulated values also suggest substantial effects of individual biomarkers on survival. For some biomarkers, we find large differences in predicted probabilities of dying between low percentile values and the highest percentile value (IL-6, epinephrine and glycosylated hemoglobin), differences which may arise in part from the effect of pre-morbid conditions on the biomarkers. But, there are also substantial differences across more modest ranges of some of these biomarkers (e.g., BMI and glycosylated hemoglobin). Not surprisingly, given that the health measures in this analysis integrate numerous dimensions of health (e.g., SRH) or are based on large numbers of individual questions (e.g., the index of cognitive function), the differences in mortality associated with some of these measures are larger than those for any single biomarker. However, in light of the possibility that individual biomarkers that are not statistically significantly associated with mortality in this analysis are likely to be so in a larger sample, and that many more biomarkers than those analyzed here are almost certainly related to longevity, the effects shown in Table 3 are notable.

DISCUSSION

This study has extended the large body of research on the determinants of adult mortality by simultaneously examining the importance of socio-demographic factors, self-reported health information, and a broad set of biomarkers. In contrast to earlier work involving biomarkers, much of which has been derived from clinical or community-based samples in Western populations, our analysis is based on a national survey in Taiwan.

Our results identify important associations between biomarkers and mortality among middle-age and elderly Taiwanese. These markers include both those that are part of routine medical exams and physiological parameters that are not commonly evaluated and for which there are no clinical thresholds. Specifically, our analysis confirms previous studies

demonstrating the effects of markers for metabolic syndrome on mortality, particularly BMI, diastolic blood pressure and levels of glucose in the blood. Our estimates also identify detrimental effects of neuroendocrine and immune-system markers, including high levels of IL-6, low levels of dopamine, and both high and low levels of epinephrine. In contrast to other epidemiological research, however, we have not found significant associations for other physiological parameters, such as the waist-hip ratio, systolic blood pressure and cortisol. It is possible that some of these effects fail to reach statistical significance because of insufficient statistical power in our study.

In models not presented here, we explored the robustness of our conclusions by using categorical rather than continuous specifications for the biomarker variables (i.e., we divided the observations for each biomarker into two or three discrete categories using different cutoff values to designate high and/or low values). These alternative formulations produced results similar to those described here for continuous variables.

Our findings demonstrate that biomarkers provide independent explanatory power in the presence of demographic, social and economic variables. The effects of biomarkers change only slightly with controls for self-reported health measures, even though some of the self-reported health measures partly capture the effects of biomarkers related to obesity, blood pressure, cholesterol, and glucose levels. Thus, our results suggest that individuals may underestimate their probabilities of dying because they have no information about risk factors that act silently on the body and are not detected by clinical examinations (Goldman et al., 2003). This interpretation is supported by an earlier study based on SEBAS that demonstrated that biomarkers are less powerful predictors of SRH than measures such as mobility limitations,

illnesses, and injuries (Goldman, Glei, & Chang, 2004). This finding stands in marked contrast to our results for mortality.

Our analyses also suggest that biological measures do not mediate the effects of social and economic conditions on mortality in Taiwan. Except for sex, we did not find any important changes in the effects of socio-demographic conditions when biological information was added into the analysis. These findings are consistent with recent findings from other analyses of SEBAS data (Dowd & Goldman, 2005; Seeman, Glei, Goldman, Weinstein, Singer, & Lin, 2004), but contradict results for the U.S. that suggest that biological mechanisms similar to those measured in the present analysis are potential pathways through which SES is likely to affect mortality (Seeman, Crimmins, Huang, Singer, Bucur, Gruenewald et al., 2004; Seeman, Singer, Ryff, Love, & Levy-Storms, 2002).

This contrast between Taiwan and the U.S. suggests that, although we find strong evidence to support the inclusion of biomarkers in studies of longevity, much remains to be learned about the nature of the physiological pathways that link the environment and mortality. Results are likely to differ across populations as a result of social and cultural variations, not only with regard to whether and how biomarkers account for socioeconomic differences in health, but quite likely with regard to what biomarkers are important in the prediction of mortality and whether biomarkers interact with other important covariates. The strong association between biomarkers and mortality found here, if confirmed by other population-based studies, may help social scientists and epidemiologists to elucidate differences in survival across populations and project future mortality.

Note

[1]The Bayesian Information Criterion (BIC) proposed by Raftery (1986) is a frequently used procedure for model selection, particularly for comparisons involving non-nested models. For a particular model M_k, BIC is defined as: $BIC_k = D(M_k) + df_k \ln N$, where D is the deviance for model M_k, df_k is the corresponding degrees of freedom, and N is the sample size. In a comparison of two models, the model with the smaller or more negative value of BIC is preferred; differences larger than 10 suggest strong support for the model with the smaller BIC. In the comparison between models 2 and 4, the difference in BIC values equals 17.5, with Model 4 having the smaller value.

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Table 1- Descriptive statistics for all measures

Variable	Mean(standard deviation) or % in category: Analysis sample (N=929)	Sample with missing information (N=80)	Test statistic [a]	p-value
Demographic characteristics				
Age	68.2 (8.5)	70.2 (8.5)	-2.03	0.04
Male (%)	58.4	50.0	1.47	0.14
Had spouse/partner in 2000(%)	71.6	70.0	0.30	0.76
Mainlander(%)	17.3	15.0	0.53	0.60
Socio and economic variables				
1-6 years of education or literate(%)	46.5	43.6		
7+ years of education(%)	26.6	23.4	1.63	0.44
Paternal SES occupational index (55.1-76.1)	57.7 (3.0)	57.4 (2.3)	1.08	0.28
# of social ties w/non-relatives	6.2 (7.3)	5.6 (6.8)	0.63	0.52
Number of social activities 2000	0.7 (1.0)	0.4 (0.7)	2.18	0.03
Biomarkers				
BMI: weight in kg / (height in m)^2	24.4 (3.6)	25.1 (3.9)	-1.76	0.08
Waist-hip ratio	0.9 (0.1)	0.9 (0.8)	-2.36	0.02
Systolic BP (mmHg)	138.6 (20.6)	138.3 (22.0)	0.14	0.89
Diastolic BP(mmHg)	82.3 (11.1)	81.5 (10.8)	0.60	0.55
Ratio of total cholesterol to HDL	4.4 (1.4)	4.4 (1.2)	-0.16	0.88
Total cholesterol (mg/dL)	201.7 (40.5)	192.1 (36.3)	2.06	0.04
Glycosylated hemoglobin(HbA_{1c})	5.8 (1.4)	5.9 (1.3)	-0.80	0.42
Cortisol(µg/g creatinine)	27.6 (32.9)	31.0 (43.4)	-0.85	0.40
DHEA-S (µg/dL)	81.3 (59.1)	78.2 (54.3)	0.46	0.65
Norepinephrine(µg/g creatinine)	22.1 (10.3)	21.8 (10.3)	0.18	0.86
Epinephrine (µg/g creatinine)	2.7 (2.7)	2.6 (2.9)	0.35	0.72
IL-6 (pg/mL)	1.6 (4.7)	1.7 (3.3)	-0.07	0.94
IGF-1 (ng/mL)	105.0 (48.0)	109.3 (57.6)	-0.74	0.46
Dopamine(µg/g creatinine)	193.7 (483.0)	224.1 (622.0)	-0.53	0.60
Self-reported health measures				
SRH:average (%)	47.7	51.3		
SRH:not so good / poor (%)	27.0	26.3	0.45	0.80
Number of chronic illnesses/ conditions (0-12)	1.3 (1.3)	1.6 (1.1)	-1.75	0.08
Number of mobility restrictions (0-9)	2.0 (2.3)	3.3 (2.9)	-4.39	0.00
Usual level of pain/discomfort	1.6 (0.8)	1.8 (1.0)	-2.70	0.01
CESD scale (0-30)	5.5 (5.3)	6.7 (6.4)	-1.62	0.11
Cognitive function (0-14)	7.2 (2.6)	7.0 (3.2)	0.69	0.49
Smoked daily in past six months (%)	22.1	21.5	0.11	0.91

[a] t-tests for means, z-tests for proportions and chi-square tests for variables with more than two categories (education and SRH)

Table 2 - Estimated coefficients from logistic models of 3-year mortality in Taiwan[a]

	Model 1	Model 2	Model 3	Model 4
Demographic Characteristics				
Age	0.1031**	0.0947**	0.0802**	0.0862**
	[0.0200]	[0.0226]	[0.0279]	[0.0243]
Male	1.0533**	0.9895*	1.4675**	1.5402**
	[0.3442]	[0.3920]	[0.5019]	[0.4490]
Had spouse/partner in 2000	-0.4758	-0.3869	-0.2542	-0.3744
	[0.3045]	[0.3143]	[0.3573]	[0.3459]
Mainlander	-0.2936	-0.2718	-0.1847	-0.1715
	[0.3784]	[0.3893]	[0.4426]	[0.4234]
Socio and economic variables				
1-6 years of education or literate	-0.5461	-0.4222	-0.2774	-0.4877
	[0.3330]	[0.3482]	[0.3916]	[0.3710]
7+ years of education	-0.7903+	-0.3431	-0.2240	-0.8033
	[0.4416]	[0.4761]	[0.5521]	[0.5129]
Paternal SES occupational index	-0.1250	-0.0938	-0.0859	-0.1084
	[0.1103]	[0.1153]	[0.1169]	[0.1095]
# of social ties w/non-relatives	-0.0443	-0.0343	-0.0429	-0.0528
	[0.0274]	[0.0261]	[0.0321]	[0.0331]
Number of social activities 2000	-0.0322	0.0114	-0.034	-0.0668
	[0.1570]	[0.1607]	[0.1770]	[0.1711]
Biomarkers				
BMI			-0.6406*	-0.7128*
			[0.3143]	[0.3026]
BMI ^{2}			0.0118+	0.0131*
			[0.0060]	[0.0058]
Waist-hip ratio			2.2064	2.4536
			[2.7490]	[2.5848]
Systolic BP			0.0002	0.0000
			[0.0107]	[0.0104]
Diastolic BP			-0.2140*	-0.1987*
			[0.0976]	[0.0958]
Diastolic BP ^{2}			0.0013*	0.0012*
			[0.0006]	[0.0006]
Ratio of total cholesterol to HDL			0.1881	0.2148+
			[0.1301]	[0.1228]
Total cholesterol			-0.0076	-0.0085+
			[0.0049]	[0.0047]
Glycosylated hemoglobin			0.2054+	0.2153*
			[0.1118]	[0.1056]
Cortisol			0.0064	0.0078*
			[0.0040]	[0.0038]
DHEA-S			-0.0041	-0.0043
			[0.0037]	[0.0037]
Norepinephrine			0.0086	0.0142
			[0.0172]	[0.0162]
Epinephrine			-0.1857	-0.1873
			[0.1333]	[0.1297]
Epinephrine ^{2}			0.0275**	0.0255**
			[0.0101]	[0.0098]
IL-6			0.1010**	0.0927**
			[0.0230]	[0.0215]
IGF-1			-0.0063	-0.0049
			[0.0044]	[0.0042]
Dopamine			-0.0013*	-0.0012*
			[0.0006]	[0.0005]

Table 2 (continued)

	Model 1	Model 2	Model 3	Model 4
Self-reported health measures				
SRH:average		0.8537+	0.7966	
		[0.4577]	[0.4965]	
SRH: not so good / poor		0.8326	0.9831+	
		[0.5184]	[0.5654]	
Number of chronic illnesses/ conditions		0.0853	-0.0691	
		[0.1190]	[0.1409]	
Number of mobility restrictions		0.0873	0.0562	
		[0.0719]	[0.0803]	
Usual level of pain/discomfort		0.0981	0.1830	
		[0.1785]	[0.1878]	
CESD scale		-0.0169	-0.0196	
		[0.0273]	[0.0311]	
Cognitive function		-0.1094+	-0.1572*	
		[0.0637]	[0.0732]	
Smoked daily in past six months		0.7618*	0.5817	
		[0.3499]	[0.3946]	
Constant	-2.1851	-4.2944	11.2967	12.6237
	[6.6229]	[7.0377]	[9.1457]	[8.5836]
Sample size	929	929	929	929
Log-likelihood	-194.33	-185.37	-155.65	-163.32
[b]Pseudo R^2	0.156	0.195	0.324	0.291

Standard errors in brackets

+ significant at 10%; * significant at 5%; ** significant at 1%

[a] All models include a random effect for primary sampling units.

[b] Measures the improvement in the value of the log-likelihood relative to the null model.

Table 3 - Predicted probabilities of dying (3-year period) by selected covariates

	Probability of dying[a]
BMI	
1st percentile (16.6)	0.129
10th percentile (19.9)	0.082
50th percentile (24.1)	0.058
90th percentile (28.8)	0.054
99th percentile (34.7)	0.085
Diastolic blood pressure	
1st percentile (60)	0.093
10th percentile (70)	0.069
50th percentile (81)	0.059
90th percentile (97)	0.071
99th percentile (110)	0.112
Glycosylated hemoglobin	
1st percentile (4.3)	0.054
10th percentile (4.8)	0.058
50th percentile (5.4)	0.063
90th percentile (7.2)	0.082
99th percentile (11.6)	0.144
Epinephrine	
1st percentile (0)	0.070
10th percentile (0)	0.070
50th percentile (2.1)	0.057
90th percentile (5.7)	0.062
99th percentile (13.6)	0.313
IL-6	
1st percentile (0)	0.055
10th percentile (0)	0.055
50th percentile (0.5)	0.058
90th percentile (3.4)	0.072
99th percentile (24.2)	0.258
Dopamine	
1st percentile (40.5)	0.078
10th percentile (87.9)	0.074
50th percentile (143.6)	0.071
90th percentile (226.7)	0.067
99th percentile (389.8)	0.058
Cognitive function	
1st percentile (1)	0.114
10th percentile (4)	0.085
50th percentile (7)	0.062
90th percentile (10)	0.045
99th percentile (14)	0.028
Self-reported health (SRH)	
Good/excellent (25.3%)	0.063
Average (47.7%)	0.091
Not so good/ poor (27.1%)	0.106

Percentile values are shown in parenthesis.

[a] Predicted probabilities are based on Model 3 in Table 2; see the text for method of calculation.