Do physicians measure the biomarkers that matter for survival?

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ABSTRACT

We use data from a nationally-representative sample of older adults in Taiwan to determine whether three clusters of biomarkers are significant predictors of mortality at the older ages: (1) standard cardiovascular and metabolic risk factors; (2) markers of disease progression; and (3) non-clinical (neuroendocrine and immune) markers. We also evaluate the extent to which these biomarkers account for the female advantage in survival. Preliminary results suggest that both the non-clinical markers and the markers of disease progression significantly improve six-year survival predictions in the presence of controls for standard cardiovascular and metabolic measures. In contrast to a simple indicator of smoking status, which explains about one-half of the excess male mortality at these ages, the biomarkers account for little of the sex difference in mortality. Nevertheless, measures of the predictive power of the statistical models underscore the importance of including biological measures along with sociodemographic and health measures in demographic models and of expanding epidemiological models to encompass a broader range of indicators of physiological function.

INTRODUCTION

John Graunt, often considered to be the father of both demography and epidemiology, is renowned for his systematic analysis of deaths in London's "bills of mortality" (Graunt, 1662). More than three centuries later, scholars are still engaged in mortality prediction, with demographers focusing on the influence of social, demographic, and behavioral factors and epidemiologists on risk factors for chronic disease. The recent proliferation of "biosocial surveys" – population-representative surveys that obtain extensive socio-demographic information through household interviews along with biological markers based on physical assessments and laboratory analyses (Weinstein, Vaupel, & Wachter, 2008) – provides researchers with an opportunity to enhance mortality prediction by taking advantage of this new information.

In this paper, we use data from a national sample of older adults in Taiwan to integrate a broad range of biological parameters, self-reports of physical and mental well-being, and social and demographic characteristics into statistical models of all-cause mortality. The survey is linked with death registration information for a six-year period following the interviews and medical examinations. Most population-based studies of all-cause mortality, such as those based on data in the Framingham study, the WHO Monica Study, or the seven countries study (Harris et al., 1988; Kronmal, Cain, Ye, & Omenn, 1993; Menotti et al., 2001; Norrish, North, Yee, & Jackson, 1995; Wilson, Abbott, & Castelli, 1988), focus on a set of risk factors for cardiovascular disease and metabolic syndrome (e.g., blood pressure and levels of cholesterol) that are typically collected in preventative health examinations. More recently, studies have included "new" measures associated with cardiovascular disease or inflammation (e.g., CRP, IL-6). However, most of these studies have also focused on cardiovascular events or cardiovascular mortality and many have included only a small number of biological measures (Cook, Buring, & Ridker, 2006; Jenny et al., 2007; Kistorp et al., 2005; K. W. Lee, Hill, Walley, & Frohlich, 2006; Lowe, 2006; Rackley, 2004; Stork et al., 2006; Wang et al., 2006). Despite the importance of cardiovascular disease as a leading cause of death in Taiwan and in other developed nations, a focus on a single group of causes is unlikely to provide a sufficiently general perspective of overall mortality.

Our goals are twofold. The first is to evaluate the potential links between mortality and a broad range of biological measures. We consider three clusters of biological variables: (1) standard cardiovascular or metabolic risk factors (which we refer to as "standard risk factors"), (2) markers of disease progression, and (3) markers of neuroendocrine and immune function. Because the second and third sets of markers have only rarely been included in survival models, we focus on the extent to which they enhance mortality prediction.

Our second objective is to use our findings to provide insight into the sex difference in mortality at middle and older ages. There is a vast literature documenting a female survival advantage in industrialized nations and a widening of this advantage through most of the twentieth century (Glei & Horiuchi, 2007; Lopez, 1983; Pampel, 2002; United Nations Secretariat, 1988). There also have been numerous efforts to use cause-of-death data and self-reports of diseases and health conditions to examine the sources of the sex difference (Case & Paxson, 2005; Lopez, 1983; Trovato & Lalu, 1998; Wong et al., 2006). In contrast, there have been very few attempts to use information on biological measures to ascertain whether higher death rates among men can be accounted for by male-female differences in the levels of these markers or in the

association between these markers and survival. Such information could be invaluable for identifying the biological pathways that underlie excess male mortality.

METHODS

Data

The data come from the 2000 Social Environment and Biomarkers of Aging Study (SEBAS). SEBAS comprises a nationally representative sample of persons aged 54 and older (in 2000) in Taiwan with an oversampling of persons 71 years and older and residents of urban areas (Goldman et al., 2003). The survey included an in-home interview and a hospital visit. Written informed consent was obtained for participation in both components.

On a scheduled day several weeks after the household interview, participants collected a 12-hour overnight urine sample (7pm to 7am), 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: 96% fasted overnight and provided a urine specimen deemed suitable for analysis.

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 as well as the least healthy, with persons who received the medical exam reporting the same average health status as those who did not. Results presented elsewhere (Goldman, Lin, Weinstein, & Lin, 2003) demonstrate that, in the presence of controls for age, estimates from the medical exam portion of SEBAS are unlikely to be seriously biased.

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, during the early stages of fieldwork nine individuals (outside the target sample) contributed triplicate sets of specimens. The results indicate intra-lab reliability of 0.86 or higher for duplicates sent to UCL and inter-lab correlations of 0.65 or higher (in most cases $\geq$ 0.92) between results from UCL and Quest Diagnostics (in the US).

Survival status was ascertained by linking to the Death Certificate file maintained by the Taiwan Department of Health and the Household Registration file maintained by the Department of the Interior. Among the 1,023 exam participants, there were 188 verified deaths by the end of 2006. After excluding one person with unknown vital status, those for whom a proxy completed the interview (n=17), and respondents with missing data on explanatory variables (n=58), the analysis sample comprises 946 respondents: 778 survivors and 168 deceased.

Biomarker Selection

The biological variables were obtained from physical measurements, the 12-hour overnight urine sample, and fasting blood specimens. The first of the three categories of biomarkers considered in this analysis comprises six well-established risk factors related to cardiovascular and metabolic function: hypertension, total cholesterol, HDL cholesterol, body mass index (BMI), waist circumference, and glycosylated hemoglobin. Many population-based studies have established a link between these risk factors and all-cause mortality (Keil et al., 1998; Norrish et al., 1995; Poulter, 2003; Solomon &

Manson, 1997; Turra et al., 2005), although the relationship tends to be weaker at older ages (Satish, Freeman, Ray, & Goodwin, 2001; Schatz et al., 2001).

The four markers in the second group indicate disease or disease progression. Creatinine clearance is a key indicator of kidney function (i.e., glomerular filtration rate, GFR); decreased GFR is associated with a wide range of complications including cardiovascular disease and mortality (Levey et al., 2003). Albumin represents a nonspecific but highly sensitive measure of disease progression (Volpato, Leveille, Corti, Harris, & Guralnik, 2001), and has been shown to predict mortality (Corti, Guralnik, Salive, & Sorkin, 1994; Djousse, Rothman, Cupples, Levy, & Ellison, 2002; Goldwasser & Feldman, 1997; Shaper, Wannamethee, & Whincup, 2004; Volpato et al., 2001). Leukocyte (white blood cell, WBC) count is an indicator of cellular response to inflammation (Margolis et al., 2005), which has been found associated with subsequent mortality (Jee, Park, Kim, Lee, & Samet, 2005; C. D. Lee et al., 2001; Leng et al., 2005; Margolis et al., 2005; Weijenberg, Feskens, & Kromhout, 1996). Neutrophils, the most abundant type of WBC in humans, are generally associated with acute inflammation; research suggests they may be more strongly associated with mortality than WBC counts (Duffy et al., 2006; Gillum, Mussolino, & Madans, 2005; Leng et al., 2005).

The third group of biomarkers includes four neuroendocrine measures – epinephrine, norepinephrine, cortisol, and DHEAS – and two immune markers – interleukin-6 (IL-6) and insulin-like growth factor 1 (IGF-1). These measures are not typically assessed in medical exams and most do not have well-established clinical cut-offs. Nevertheless, recent studies have shown that some of these markers are associated with mortality (Bruunsgaard et al., 2003; Cappola et al., 2003; Marklund, Peltonen, Nilsson, & Olsson, 2004; Mazat et al., 2001; Reuben, Talvi, Rowe, & Seeman, 2000; Roubenoff et al., 2003) and a study in Taiwan suggests that they may be stronger predictors of mortality than the standard risk factors (Goldman et al., 2006).

Biomarker and Control Variables

Variables based on the three groups of biomarkers are shown in Table 1. Classification of some of the standard risk factors is based on medical information. Specifically, categories for hypertension and total and HDL cholesterol are based on clinical guidelines (Chobanian et al., 2003; National Cholesterol Education Program (NCEP) Expert Panel, 2001). The classification for BMI conforms to the categories used by the Taiwan Department of Health (Department of Health, Taiwan, 2002). For waist circumference, we use the cutoffs recommended for Asian populations (Inuoe et al., 2000; World Health Organization, 1998). Glycosylated hemoglobin is parameterized as a continuous variable because reference ranges tend to vary across laboratories (Genuth et al., 2003). For all continuous biomarker measures, we recoded outliers that were larger than five standard deviations from the mean to equal that cut-point (see Table 1). Two additional variables are included in this group of biomarkers; these dichotomous measures capture use of anti-hypertensive and hypoglycemic medications.

The four markers of disease progression are obtained from the fasting blood sample. Creatinine clearance is estimated using the Cockcroft-Gault Formula, which is based on the level of serum creatinine taking into account age, sex, and body weight (Cockcroft & Gault, 1976). Serum albumin, WBC, and neutrophils are measured as continuous variables.

Because there are no established cutoff points for high risk values, the nonclinical measures are also treated as continuous variables. Epinephrine, norepinephrine, and cortisol measurements, which were obtained from the overnight urine specimen, are reported as micrograms per gram creatinine to adjust for body size. DHEAS, IL-6, and IGF-1 are based on the fasting blood sample.

Sociodemographic control variables comprise age, sex, ethnicity (Mainlander vs. Taiwanese), respondent's education, and urban residence. We also include six measures of baseline health status: (1) current illness – a count of the number of chronic conditions reported by the respondent (0-12); (2) functional limitations – a count of the number of physical tasks that the respondent reported difficulty performing without aid (0-9); (3) cognitive function – a count of cognitive tasks completed correctly (potential range 0 to 24); (4) depressive symptoms – a 10-item short-form of the Center for Epidemiologic Studies Depression scale (CES-D) (potential range 0 to 30); (5) global self-rated health (SRH) – a five-point ordinal variable (1=poor, 5=excellent);[1] and (6) smoking – a dummy variable indicating whether the respondent smoked in the past six months.

Analytical Strategy

We estimate a series of logistic regression models to describe the associations between the biomarkers and the probability of dying between 2000 and 2006. Because the clustered sampling design may lead to underestimates of standard errors, we incorporate random effects for the primary sampling units. The base model (Model 1) includes sociodemographic variables and measures of physical and mental health status in 2000. The subsequent three models each add one cluster of biomarkers to Model 1: Model 2 (cardiovascular/metabolic), Model 3 (disease progression), and Model 4 (non-clinical). Model 5 includes all three clusters of biomarkers. We tested quadratic terms for the continuous biomarkers and retained the two that were statistically significant ($p < .05$): WBC and epinephrine.

We calculate the receiver operating characteristic (ROC) curve to evaluate the accuracy of the models in discriminating between decedents and survivors. For a given

[1] Current illness is measured by a count of the following 12 self-reported conditions: 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. The measure of functional limitations counts how many of the following physical tasks 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. Cognitive function counts the number of cognitive tasks completed incorrectly, including basic orientation questions, a series of four subtractions, and immediate memory recall. Depressive symptoms are measured by a 10-item short form of the full CES-D scale, coded according to standard practice based on both the number and severity of symptoms. Global SRH is based on the following question: "Regarding your current state of health, do you feel it is excellent, good, average, not so good, or poor?"

model, the ROC curve compares the probability that the regression equation correctly predicts death for persons 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. All analyses are performed using Stata 9.2.

Finally, we examine the contribution of each biomarker in accounting for the sex difference in mortality. In light of a substantial literature that attributes a large fraction of excess male mortality in industrialized countries to smoking, we calculate the contribution attributable to smoking as a benchmark. Before determining the model to use for this exercise, we evaluated the extent to which the associations between the biomarkers and mortality for men differed from the corresponding associations for women by adding interaction terms between each biomarker and sex to Models 2-4. Because the results indicated that the interaction term was significant ($p<0.05$) for only one biomarker (WBC), consistent with what we would expect to occur by chance, we did not include interaction terms in the model.

We determine the odds ratio of dying for males (relative to females) from a base model (OR_{base}) that includes all of the sociodemographic and health status variables shown in Model 1 except for smoking. Since males have higher mortality than females in Taiwan, this odds ratio exceeds one and provides a measure of the degree of excess male mortality, in the presence of the control variables included in the model. Subsequently, we add to the model a single biomarker, such as hypertension or BMI, which may comprise more than one variable for biomarkers that are categorical, have a quadratic term, or include an associated variable denoting medication use. The resulting odds ratio for males associated with a given biomarker ($\mathrm{OR}_{\mathrm{w/marker(s)}}$) is used to calculate the percent change in excess male mortality attributed to that biomarker:

$$\%\mathrm{Change} = \left(\frac{\mathrm{OR}_{\mathrm{w/marker}} - \mathrm{OR}_{base}}{\mathrm{OR}_{base} - 1} \right) * 100 .$$

A negative result implies that inclusion of the selected biomarker accounts for some of the excess male mortality, whereas a positive estimate indicates that inclusion of this biomarker exaggerates the sex difference. Corresponding calculations are performed for the smoking variable as well as for the three *clusters* of biomarkers.

RESULTS

Table 2 presents estimated odds ratios for the five logistic models. Among the standard risk factors, only low BMI (underweight) is significantly associated with mortality ($p<0.05$). Three markers of disease progression (creatinine clearance, albumin and neutrophils) and two non-clinical measures (epinephrine and IL-6) are significantly associated with mortality over the follow-up period.

The ROC curves for Models 1-4 are presented in Figure 1. Chi-square tests based on the AUC values, shown at the bottom of Table 2, indicate that inclusion of each of the three sets of markers significantly improves discriminatory power compared with the base model ($p<0.05$ for Models 2 and 4 and $p<0.01$ for Model 3). Additional comparisons (not shown) between the AUC value for Model 2, which includes the standard risk factors, and those for models that add the disease progression or non-

clinical markers to Model 2, reveal that both sets of markers significantly increase the predictive power of Model 2 ($p<0.01$ for disease progression measures and $p<0.05$ for non-clinical measures). Among the three models that include a single set of biomarkers, the largest AUC value is associated with the disease progression model (Model 3).

The odds ratios for smoking are large and relatively constant across the models: recent or current smokers have between 2.6 and 2.8 times the odds of dying in the six-year period compared with non-smokers. The odds ratio for age in the base model suggests that each additional year of age is associated with an increase of 12% in the odds of dying within 6 years. Comparisons across the models reveal that only the disease progression variables (Model 3) account for a substantial fraction of the increased risk of dying with advancing age (a reduction of the OR from 1.12 in Model 1 to 1.07 in Model 3). The findings for excess male mortality are surprisingly similar to those for age: the coefficients for males suggest that neither the standard risk factors nor the non-clinical markers can explain the gap in mortality (i.e., inclusion of these markers in Models 2 and 4 respectively leads to an increase not a decrease in the odds ratio for males). In contrast, inclusion of indicators of disease progression results in a modest narrowing of the level of excess male mortality (from 1.61 in Model 1 to 1.49 in Model 3).

In Table 3, we consider the contribution of individual markers as well as smoking in explaining the sex differential in mortality, based on a model that excludes the smoking variable from Model 2. A simple indicator of whether the respondent smoked during the past six months accounts for more than half of excess male mortality. In contrast, most of the standard risk factors, except for HDL cholesterol and BMI, and all of the non-clinical markers are associated with a *widening* of the sex difference. This exaggeration of excess male mortality is particularly notable for the non-clinical markers (e.g., accounting for all six markers in this cluster leads to more than a 60% increase in the gap). Two markers of disease progression – albumin and neutrophils – are associated with a notable narrowing of the sex difference, about 12% for each marker, but still much more modest contributions than for smoking.

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Table 1. Descriptive statistics for variables in regression models, weighted analyses

	Mean (SD) or Percent
Sociodemographic variables	
Age in 2000 (54-91)	66.3 (8.0)
Male	57.6%
Mainlander	13.2%
Education (0-17 years)	5.2 (4.6)
Urban resident	43.3%
Baseline health status	
Smoked at all in the past six months	24.1%
Number of current conditions (0-12)	1.3 (1.2)
Number of mobility limitations (0-9)	1.9 (2.3)
Cognitive Function (0-24)	16.7 (3.5)
Center for Epidemiologic Studies Depression scale (CES-D, 0-30)	5.4 (5.3)
Self-assessed health status (1-5, 5=excellent)	3.1 (1.0)
Cardiovascular/metabolic risk factors	
Hypertension	
Normal (SBP < 120 mmHg & DBP < 80 mmHg)	15.5%
Pre-hypertension (SBP 120-139 or DBP 80-89)	34.6%
Stage 1 (SBP 140-159 or DBP 90-99)	32.3%
Stage 2 (SBP 160+ or DBP 100+)	17.5%
Using anti-hypertensive medication	22.9%
Total cholesterol	
Desirable (<200 mg/dL)	51.1%
Borderline high (200-239)	33.7%
High (240+)	15.2%
HDL cholesterol	
Low (< 40 mg/dL)	26.9%
Normal (40-59)	51.5%
High (60+)	21.7%
Body Mass Index (BMI)	
Underweight (<18.5)	3.3%
Normal (18.5-23.9)	44.9%
Overweight (24-26.9)	30.0%
Obese (27+)	21.8%
Waist circumference (Females >80 cm; Males >90 cm)	49.1%
Glycosylated hemoglobin (HbA_{1c}, %)*	5.8 (1.4)
Using hypoglycemic agents	11.8%
Markers of Disease Progression	
Creatinine clearance (ml/min)†	62.4 (18.0)
Serum albumin (g/dL)	4.5 (0.3)
White blood cell count (WBC, 10 x e^3/uL)*	6.1 (1.6)
Neutrophils (%)	56.4 (9.4)
Non-clinical markers	
Urinary Epinephrine (µg/g creatinine)*‡	2.5 (2.5)
Urinary Norepinephrine (µg/g creatinine)*	21.7 (9.6)
Urinary Cortisol (µg/g creatinine)*	26.7 (30.0)
Serum Dehydroepiandrosterone sulfate (DHEAS, µg/dL)*‡	81.0 (58.4)
Interleukin-6 (IL-6, pg/mL)*‡	1.5 (4.3)
Insulin-like growth factor 1 (IGF-1, ng/mL)*	107.0 (48.5)
Number of cases	946

Note: For continuous variables, the potential range is shown in parentheses.
SBP=systolic blood pressure; DBP=diastolic blood pressure
* Outliers (i.e., values > 5 SD above the mean) were recoded to that cut-point (i.e., trimmed): HbA1c (n=4), WBC (n=1), urinary creatinine (n=4), epinephrine (n=1), norepinephrine (n=1), cortisol (n=3), DHEAS (n=3), IL-6 (n=6), IGF-1 (n=1).
† Creatinine clearance is estimated based on the Cockcroft-Gault formula; outliers (n=5) on serum creatinine are trimmed before calculating this measure.
‡ Approximately 33% of values on IL-6, 20% on epinephrine, and 1% on DHEAS were below assay sensitivity; these cases were assigned a value of 0.

Table 2. Odds ratios from logit models of the probability of dying between 2000 and 2006 *(N=946)*

	(1)	(2)	(3)	(4)	(5)
Age	1.117**	1.118**	1.072**	1.112**	1.059**
Male	1.607+	1.777*	1.490	2.162**	2.635**
Smoked at all in the past six months	2.646**	2.465**	2.611**	2.787**	2.768**
Cardiovascular/metabolic risk factors					
Hypertension					
Normal		--	--	--	--
Pre-hypertension		0.829	--	--	0.763
Stage 1		0.719	--	--	0.633
Stage 2		1.321	--	--	1.344
Using anti-hypertensive medication		0.884	--	--	0.858
Total cholesterol					
Desirable		--	--	--	--
Borderline high		0.813	--	--	0.840
High		1.452	--	--	1.435
HDL cholesterol					
Low		--	--	--	--
Normal		0.668+	--	--	0.700
High		0.711	--	--	0.563+
Body Mass Index (BMI)					
Underweight		2.440*	--	--	1.741
Normal		--	--	--	--
Overweight		0.833	--	--	1.143
Obese		0.660	--	--	1.240
High waist circumference		1.306	--	--	1.649+
HbA_{1c} (%)		1.182+	--	--	1.162
Using hypoglycemic agents		0.952	--	--	1.133
Markers of Disease Progression					
Creatinine clearance		--	0.973**	--	0.961**
Albumin		--	0.334**	--	0.361**
WBC count		--	0.659	--	0.672
WBC count squared		--	1.039+	--	1.033
Neutrophils		--	1.026*	--	1.025*
Non-clinical markers					
Epinephrine		--	--	0.857+	0.861
Epinephrine squared		--	--	1.022**	1.021**
Norepinephrine		--	--	1.006	1.022+
Cortisol		--	--	1.004	1.005
DHEAS		--	--	0.997	0.998
IL-6		--	--	1.073**	1.062*
IGF-1		--	--	1.000	0.999
Log-likelihood	-357.8	-346.8	-335.2	-342.6	-311.1
Area under the ROC curve (AUC)	0.79	0.81	0.83	0.81	0.85
AUC test (vs. model 1)	--	p <0.05	p<0.01	p<0.05	p<0.001

Note: Models include a random effect for the primary sampling units and adjust for Mainlander status, education, urban residence, current chronic conditions, mobility limitations, cognitive function, CES-D, and self-assessed health status.

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

Table 3. Contributions to the sex difference in mortality *(N=946)*

	OR for male	% Change from base model
Base model†	2.33**	
Smoked in the past six months	1.61+	-54.5%
Cardiovascular/metabolic risk factors		
Hypertension & use of anti-hypertensives	2.35**	+1.1%
Total cholesterol	2.34**	+0.3%
HDL cholesterol	2.26**	-5.8%
BMI	2.22**	-8.4%
Waist circumference	2.37**	+2.7%
HbA_{1c} & use of hypoglycemic agents	2.55**	+16.4%
All biomarkers in this cluster	2.56**	+16.7%
Markers of Disease Progression		
Creatinine clearance	2.38**	+3.7%
Albumin	2.17**	-12.0%
WBC & quadratic term	2.39**	+3.9%
Neutrophils	2.18**	-11.5%
All biomarkers in this cluster	2.15**	-14.0%
Non-clinical markers		
Epinephrine & quadratic term	2.84**	+38.3%
Norepinephrine	2.45**	+8.5%
Cortisol	2.38**	+3.4%
DHEAS	2.45**	+8.6%
IL-6	2.39**	+4.0%
IGF-1	2.34**	+0.8%
All biomarkers in this cluster	3.18**	+63.1%

† The base model excludes smoking from Model 1 (Table 2).
+ significant at 10%; * significant at 5%; ** significant at 1%
Note: Each row represents the contribution of the specified biomarker (added individually) or cluster of biomarkers (added simultaneously) compared with the base model.

Figure 1. ROC curves for models of the probability of dying between 2000 and 2006