Predicting Mortality with Biomarkers among Elderly Costa Ricans

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Short abstract (150 words)

Biomarkers have increasingly been added to population surveys in recent years, but few studies document how well they relate to mortality outcomes. We considered 22 baseline biomarkers as three-year prospective death predictors in a nationally representative longitudinal sample from the Costa Rican Longevity and Healthy Aging Study (CRELES). The sample includes about 2,500 Costa Ricans born before 1945, of whom about 400 died. The strongest mortality predictors are markers of body functioning (hands, legs, lungs, and kidneys). C-reactive protein and HbA1c are also strong predictors. Low levels of DHEAS predict increased mortality only among men. Strikingly, traditional indicators of cardiovascular risk, such as high blood pressure and total cholesterol, unexpectedly predict lower mortality. Obesity increases the risk of dying but only among younger individuals. Results suggest the need for deeper understanding of the meaning of such biomarkers, particularly outside of the developed country settings where they have been primarily studied.

Introduction

This paper aims at identifying relationships between biological markers and mortality in an elderly population (aged 60 +) of a middle-income country—Costa Rica. We intend to identify the effect pattern (positive/negative, linear/non-linear/u-shaped) of 22 biomarkers, measured at a baseline, upon prospective mortality (all-cause and cardiovascular) in the 2005-2008 period. We also study age and sex variation in these patterns, the amount of the aging and gender effects on mortality that is explained by these biomarkers, possible interactions and synergisms between biomarkers' effects, and the added value of biomarkers to predict further mortality above and beyond self reported health behaviors and health status at the baseline.

Although the paper does not intend to go as far as to establish causal relationships that would translate into clinical interventions, its results can be used to identify individuals and populations at high risk of dying, as well as to generate hypotheses about possible pathways toward higher or lower mortality levels. This paper's results are also useful for checking whether paradigms derived from studies in developed countries (e.g. the Framingham study) hold in a developing world that is following a different path in its

epidemiological and nutritional transitions as well as in the speed of population aging. Very little is known about adult health and mortality relationships outside the rich Northern part of the world, in part because until recently few datasets have contained the necessary biomarker data in representative populations. And given that most of the prior developing country mortality research concentrates in children and middle age adults, there is scope for concern about whether such paradigms will translate to the elderly in non-developed countries. Furthermore, this paper contributes to the handful of studies that have attempted to assess the extent to which mortality is predicted by non-traditional biomarkers that have increasingly been added to population-based health surveys as preclinical risk indicators, such as C-reactive protein and DHEAS. Seeman et al. (PNAS 2001) and Gruenewald et al. (PNAS 2006) have shown that both traditional clinical risk factors and newer biomarkers are predictive of mortality among an elderly sample in the U.S. MacArthur Study of Successful Aging. But Goldman et al. (Journal of Gerontology 2006, American Journal of Epidemiology 2009) have found that in an elderly sample from a middle-income country (Taiwan) the traditional clinical factors hypertension and cholesterol are not significantly related to 3-year and 6-year prospective mortality, while pre-clinical neuroendocrine and inflammatory factors are significantly related. This paper exploits a new dataset from a middle-income Latin American country (Costa Rica) to attempt to replicate and extend these prior studies.

Data and methods

Data for this analysis come from Costa Rican Longevity and Healthy Aging Study (CRELES), an on-going longitudinal study of a nationally representative sample of adults born before 1945 (aged 60 and over in 2005) residing in Costa Rica, with over-sampling of the oldest old. We used the nested sub-sample of more than 2,800 individuals for whom there is an in-depth, longitudinal survey that includes biomarkers, with a follow-up to establish survival through December 2008 (449 deaths were identified). The baseline information on biomarkers and other health conditions come from the first wave of interviews, conducted from November 2004 to September 2006.

The original sample was randomly selected from the 2000 census database after stratification by 5-year age groups. Sampling fractions ranged from 1.1% among those born in 1941-45 to 100% for those born before 1905. For the in depth longitudinal survey, CRELES took a systematic subsample of 60 “health areas” (out of 102 for the whole country). This subsample, which included originally more than 4,000 individuals covering 59% of Costa Rican territory, yielded the following non-response rates: 19% deceased between the 2000 census and the contact date (about 2005), 18% were not found in the field, 2% moved to other addresses, 2% rejected the interview, and 2% remained as pending interviews after several visits (likely rejections). Inability to find certain individuals in the field was primarily due to vagueness of the census address (and the lack of an accurate address system in Costa Rica), as well as from address changes during the approximately five year lag between the census and our visit. There are weighting factors to correct the over-sampling of the old as well as some differentials by age, SES and region of residence in the response rates. Among those interviewed, 95%

provided a blood sample, 92% collected urine overnight, 91% had all anthropometric measures, and 24% required a proxy to answer the questionnaire.

All the data and blood and urine specimens were collected at the participants' homes, usually in two visits. In the first visit, participants provided informed consent and answered a 90-minute long questionnaire (including some mobility tests and two blood-pressure measures) as well as a 10-minute questionnaire on frequency of food consumption for 27 tracer foods. In a second visit early the next day, fasting blood samples were collected by venipuncture: one EDTA tube (for 3-4 ml of whole blood) and two serum-separating tubes (SST), with a clot activator (for 10-12 ml of blood, to obtain 4-6 ml of serum). In this second visit, the field team also picked up a cooler containing 12-hour overnight urine and took the anthropometric measures. All field data were collected using Personal Digital Assistants (PDAs), also known as palm computers, with software applications developed by the Central American Population Center (CCP) for this study.

A field team of five interviewers, two phlebotomists and a supervisor collected the information and the blood and urine specimens using a continuous fieldwork design over a period of nearly two years. The field team received a two-week training course that included standardized anthropometric measures. Several Costa Rican laboratories analyzed the blood and urine specimens, depending on the type of biomarker. All laboratories were certified by a national reference center of clinical chemistry, an agency under the Ministry of Health. In addition to the internal reliability tests that these laboratories must conduct as part of their quality control procedures, we conducted reliability analyses in lots of 20 to 40 specimens that were re-analyzed for each biomarker in a different laboratory. We report elsewhere the results of these reliability analyses, as well as some adjustments introduced to standardize measures across laboratories (Méndez-Chacón et al. 2007)

The dependent variable--death

We identified 449 deaths by computer follow-up in the national death registry through December 2008, using the unique identification number (the *cédula*) that all Costa Ricans have. Prior research has indicated that the death registry is virtually 100% complete (Rosero-Bixby, 2008). We also identified the deceased in the field (this was the only way to identify deaths for the foreigners who comprised 4% of the sample) during the second and third waves of visits. To further validate the death registry integrity, we were able to successfully match in the registry 98% of citizens' deaths found in the field (it is possible that the non-found 2% will register at some point in the future). About 10% of the registered deaths were not detected in the field, appearing in the second and third waves as losses of follow-up (suggesting caution in relying exclusively on fieldwork to identify deaths). A record linkage of 95% of deaths with the Vital Statistics data base (provided by the National Statistics Institue, INEC), allowed us to identify the basic cause of death, 10th International Classification of Diseases. We considered cardiovascular deaths (CVD) those coded I001 to I999.

The data were organized as a survival-time data set, with origin in the birthdate (more precisely, the date of the 60th birthday). This is not self-reported information but it comes from an official document (birth registry, *cédula* or passport), avoiding the problem of age exaggeration that is so pervasive among the oldest old and that biases down mortality estimates. The date of the first interview is the entry point into observation. The exit date is death, December 31 2008 for those non-deceased, and the date of last contact for non-deceased foreigners. The non-deceased are treated as censored observations in the survival-time models. In the analysis of CVD mortality, deaths by other causes are considered censored observations on the death date.

The biomarkers (explanatory variables)

We considered biomarkers those health indicators that can be objectively measured by well-established laboratory essays on body specimens (blood and urine in this study) or by anthropometrics and other physical instruments such dynamometers, sphygmomanometers, chronometers, or peak-flow meters. Biomarkers are thus objectively measured features of the body, in contrast to health conditions assessed subjectively by questions and answers.

We analyzed 22 biomarkers grouped in seven groups as follows (within each group, some biomarkers are redundant but others we hypothesize complement each other—to be tested in the data):

Group 1. Metabolic indicators

- Glycosylated hemoglobin (HbA1c) (chronic indicator of glucose bond to red blood cells, indicating diabetes)
- Fasting Glucose (level of sugar at the moment fasting blood was drawn)

Group 2. CV biomarkers

- Diastolic Blood Pressure (average of two measures, digital sphygmomanometer)
- Systolic Blood Pressure (average of two measures, digital sphygmomanometer)

Group 3. Metabolic - lipids

- Triglycerides in fasting serum
- Total Cholesterol in fasting serum
- HDL (good) Cholesterol in fasting serum
- Total/HDL cholesterol ratio (the two previous markers)
- LDL (bad) Cholesterol (determined from total chol. and triglycerides)

Group 4. Stress hormones

- Urinary cortisol (overnight activity in the hypothalamic-pituitary axis (HPA) in response to stressors)
- Dehydroepiandosterone sulfate DHEA-S (antagonist to HPA activity)
- Epinephrine in overnight urine (neuroendocrine functioning)
- Norepinephrine in overnight urine (neuroendocrine functioning)

Group 5. Inflamation, immune system

- C-Reactive Protein (CRP)

Group 6. Specific body functioning

- Creatinine Clearance (kidney and cardiovascular function)
- Handgrip Strength (arm muscular functioning)
- Walking distance in 10 seconds (leg muscular functioning)
- Pulmonary Peak Flow (lungs functioning)

Group 7. Nutrition, body shape

- Waist circumference (central obesity)
- Knee height (height)
- Body Mass Index (BMI, weight relative to height)
- Waist/hip ratio (body shape)

Control variables

In addition to age and sex, whose effects on death risk this paper controls in all analyses, we consider as controls in some analyses the following 14 indicators of health behavior and health status at the baseline:

- Smoking
- Alcohol intake
- Calorie daily intake
- Carbohydrate daily intake
- Total fat intake
- Taking blood pressure medicine
- Taking cholesterol-lowering medicine
- Taking diabetes medicine
- Visited by a primary health worker last year
- Self reported health scale
- Self reported health relative to others at same age
- Multiple chronic diseases (number diagnosed out of 11)
- Functioning scale (number out of 14 ADLs and IADLs performed with no help)
- Cognitive capability (Folstein mini mental test, scale 0 to 15)

Statistical analysis

We normalized all biomarkers into variables with mean zero and standard deviation (SD) of one. In this way, all their effects on mortality are in the same scale: as the effect of increasing the biomarker in one SD.

We used parametric proportional hazard models assuming a Gompertz distribution, that this and other data sets have shown fits well adult mortality. The proportional

assumption was removed by including interactions with age and sex variables. The Gompertz's assumption of linearity in the logarithms was examined and modified accordingly by including a quadratic term of the biomarker in the models. We also allow for differential effects by sex by including a sex-interaction variable. After preliminary analyses, we keep in models only those interaction and quadratic terms that had a significant effect ($p < 0.05$).

Results

The mean age of the individuals in the sample is 76.4 years (70.5 after correction for sampling weights). Because of over-sampling of the oldest old we have more than 600 (21%) observations for individuals aged 85 and more, which is an unusually large sample size for those old ages. The non-weighted and weighted proportion of women in the sample is 54% and 53%, respectively. Table 1 shows descriptive statistics (corrected for sampling weights) for each of the 22 biomarkers. Outliers were excluded from these statistics and in all analyses. For most biomarkers we have a sample size above 2,500. For those from a urine specimen the numbers are smaller; for epinephrine and norepinephrine about one-third of observations were eliminated because the stored urine sample had degraded and results were not reliable (assays on the other two-thirds had been conducted in fresh specimens).

A quick comparison with published results from the SEBAS study in Taiwan (Turra et al. 2005) and the MacArthur study in the USA (Grunewald et al. 2006) suggests that, according to existing paradigms of what levels in these markers are good or bad for health, elderly Costa Ricans would be worse off in most of them. The only exceptions, compared to the USA, are glucose and obesity indicators and norepinephrine, whereas there are no differences with Taiwan in glucose indicators and cortisol.

Before using mortality data in this sample, a mortality validity check is necessary. Figure 1 shows the age-specific death rates derived from the CRELES sample, including their confidence intervals, and compares them with the national rates from the official life table for the period 2000-05 (Source: Rosero-Bixby & Collado 2008). The CRELES rates appear congruent with the series for the entire Costa Rican population, suggesting no biases in the CRELES sample or in the identification of deaths among participants. The figure also shows that both CRELES and national death rates increase almost linearly with age in the logarithms. Given this shape, modeling the series of rates with a Gompertz function seems appropriate as shown in the figure. The constant term of the function shown in the figure estimates the death rate at age 60 given that we use as the time variable a transformation of age with zero being the 60^{th} birthday. The "gamma" coefficient estimates the rate at which mortality increases with each year of age. We call it the rate of aging or senescence of the population. Costa Ricans show a rate of senescence of 8.4% (7.6-9.3 CI) per year. Including sex in the model results in aging rates of 7.5% for men and 9.3% for women; i.e., the aging process is slower for men in this population, although men start from substantially higher levels of mortality at age 60: 0.0127 compared to 0.0066 in women.

[Figure 1]

In a first stage of the analysis the crude effect of each biomarker on mortality is estimated controlling only for age and sex. An average effect is first estimated by including in the model just the normalized values of the biomarker in addition to age, sex and their interaction. Then in a second model we explore non-linearities by the inclusion of a quadratic term of the marker as well as interactions of the marker with age and sex. Then we keep in the model only significant effects at $p>0.05$. Table 2 and the series of figures 2a to 2e show these one by one effects of biomarkers on mortality. Given that interaction and quadratic terms are hard to interpret, we summarized them with the figures and, in table 2, by showing the effect in four groups resulting from combining sex and two ages (65 and 85). The table also shows in the first column the crude, overall effect of the marker (which sometimes is misleading) before adding interactions and non-linearities.

The most striking results are the apparently protective effect against death from higher levels of blood pressure and "bad" lipids (triglycerides, total and LDL cholesterol). These effects are statistically significant and are not restricted to extremely low values of the marker, but they show up around their mean values. For example, an increase of one SD in the systolic blood pressure around the mean would reduce the risk of dying by 21% and one SD increase in triglycerides would reduce the risk of dying by 23%. These results curiously contradict standard evidence from elsewhere that high levels of blood pressure and "bad" lipids increase the risk of CVDs and other diseases as well as the general risk of dying.

Table 2 also shows that the markers with larger effects on mortality are those included in the group of "specific body functions". Reduced mean values of handgrip strength or peak flow in one SD predict three-fold increases in the risk of dying for people in their sixties (the effect is smaller at older ages). A similar increase in creatinine clearance doubles the death rate.

Two other markers with large effects on mortality are HbA1c and CRP, which increase the risk of dying by more than 80% with an extra SD. These effects are again weaker at older ages.

For cortisol and DHEA-S, or HPA activity, these data show effects on mortality of some importance concentrated in the male population. One SD increased DHEA-S is associated with a decrease by one third of mortality, whereas the effect of cortisol is in the opposite direction: one extra SD increases the risk of dying by 18%. These effects are in the male population only.

The group of nutrition and size markers also show interesting effects on the risk of dying that are strongly conditioned by age. For individuals in their sixties there is a strong effect of central obesity (one extra SD increases death rate by 30%) and protective effect of height, measured by knee height (mortality diminishes by 28% with an extra SD). At older ages, these effects tend to vanish and higher BMI emerges as a protective factor

against death, which is reduced by 17% with one extra SD of BMI, perhaps reflecting wasting among the sick elderly.

Among the curvilinear relationships identified by the model, most reflect the fact that after certain levels (usually one SD above the mean) of the marker the data show little or no effect on the risk of dying (Figures 2a to 2e). In a few cases a U-shaped relationship is identified with an optimal point in which mortality is minimal. That is the case for diastolic BP with an optimal at 0.57 SD or 90.5 mm/Hg. It is also the case for DHEA-S: increasing this hormone above one SD (95 ug/dl) has little protective effect for men and seems to be harmful for women.

The next steps in the analyses are to identify "joint" effects of the biomarkers, after excluding those that are redundant (add little explanatory power beyond others in the same group) as well as "net effects." Then we will identify the predictive power of biomarkers above and beyond baseline health status, as well as their explanatory power (as pathways or intermediate variables) in the aging process and the sex gap.

Preliminary results suggest that in this population the sex gap in mortality is not explained by these markers. On the contrary, the sex gap becomes larger after controlling the effects of biomarkers (a logical result given that usually women have worse biomarker levels and, paradoxically, higher survival rates). In turn, the senescence rate estimated by the Gompertz function is explained by the biomarkers: about one-third of the rate for women and four-fifths for men. These Costa Rican data thus suggest that traditional biomarkers (the ones included in the study) are better markers of the aging process among men. Among women, their explanatory power is limited.

Another important finding is that the two big traditional biomarkers of CVD risk – high levels of blood pressure and cholesterol (as well as to some extent waist circumference and BMI) –do not show negative effects in this population. On the contrary, they even seem to be protective factors. Said in another way, low levels of cholesterol and blood pressure seem to be a problem and not a desired status. This surprising result is in line with a few other recent studies showing similar patterns in elderly populations and in unconventional places such as Korea and Hawaii (Song, Sung & Kim 2000; Schatz et al. 2001). Further work is needed to reconcile these findings with the strong adverse mortality effects of elevated levels of these markers in other developed country studies.

References

Goldman, N., Glei DA, Lin YH, Weinstein M (2009) Improving mortality preduction using biosocial surveys. *American Journal of Epidemiology* 169(6):769-79.

Goldman N., Turra C., Glei D., Seplaki C., Lin Y. and Weinstein M. (2006). Predicting Mortality from Clinical and Nonclinical Biomarkers. *Journals of Gerontology, Series A: Medical Sciences and Biological Sciences*, 61:1070-4.

Gruenewald, T. L.; Seeman, T. E.; Ryff, C. D.; Karlamangla, A. S. & Singer, B. H. (2006) Combinations of biomarkers predictive of later life mortality. *PNAS 103*(38): 14158-14163.

Méndez-Chacón, E.; Rosero-Bixby, L.; Fernández-Rojas, X. & Barrantes-Jiménez, K. (2007) Comparación de los resultados de pruebas de laboratorio seleccionadas de un estudio poblacional de adultos mayores de Costa Rica. *Población y Salud en Mesoamérica (Revista electrónica), 5*(1).

Rosero-Bixby, L (2008). The Exceptionally High Life Expectancy of Costa Rican Nonagenarians. *Demography 45(3):* 673-691.

Rosero-Bixby, L. & Collado, A. (2008) Tablas de mortalidad, jubilación e invalidez, Costa Rica 2000-2005. En *Población y Salud en Mesoamérica*. Revista Electrónica, Vol. 5(1), artículo 5.

Schatz, I. J.; Masaki, K.; Yano, K.; Chen, R.; Rodriguez, B. L. & Curb, J. D. (2001) Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet 358*: 351–55

Seeman TE, McEwen BS, Rowe JW, Singer BH (2001) Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci USA* 98:4770–4775.

Song, Y. M.; Sung, J. & Kim, J. S. (2000). Which Cholesterol Level Is Related to the Lowest Mortality in Population with Low Mean Cholesterol Level: A 6.4-Year Follow-up Study of 482,472 Korean Men. *American Journal of Epidemiology 151* (8): 739-747

Turra, C.M.; Goldman, N.; Seplaki, C. L.; Glei, D. A.; Lin, Y. H. & Weinstein, M. (2005) Determinants of Mortality at Older Ages: The Role of Biological Markers of Chronic Disease. *Population and Development Review* 31(4): 675-698

Table 1. Descriptive Statistics of the 22 biomarkers in the study

Biomarker	Units	Mean	SD	Median	P25	P75	N
Metabolic hormones							
Glycosilated hemoglobin (HgA1c)	Percent	5.76	1.13	5.50	5.20	5.90	2616
Fasting glucose	mg/dl	110.64	45.39	98.24	88.48	116.56	2659
CV biomarkers							
Diastolic blood pressure	mmHg	83.66	12.10	83.00	75.50	91.50	2793
Systolic BP	mmHg	144.00	23.18	141.00	128.00	157.50	2793
Metabolic - lipids							
Triglycerides	mg/dl	162.84	85.27	143.94	105.94	194.94	2650
Total cholesterol	mg/dl	215.54	49.42	212.00	181.00	245.00	2657
HDL cholesterol	mg/dl	44.25	13.12	42.59	35.00	51.85	2654
Total/HDL cholesterol ratio	Ratio	5.18	1.60	5.03	4.06	6.08	2654
LDL Cholesterol	mg/dl	138.48	40.73	135.20	109.60	164.00	2495
Stress hormones							
Urinary cortisol	ug/g	26.22	24.99	19.75	12.99	30.78	2249
DHEA-S	ug/dl	54.06	41.72	42.30	23.50	73.20	2617
Epinephrine	ug/g	7.41	10.95	4.17	2.13	9.11	1520
Norepinephrine	ug/g	37.60	32.17	28.73	19.24	46.55	1570
Inflammation, immune system							
C-Reactive Protein (CRP)	ml/l	5.61	6.69	3.20	2.65	5.87	2588
Specific body functions							
Creatinine clearance	mg/min	74.74	30.16	71.40	54.33	92.35	2346
Handgrip strength	kg	26.89	9.08	25.50	20.00	33.50	2528
Distance in 10 seconds	meters	5.51	2.52	5.66	4.47	6.96	2703
Pulmonary Peak Flow	l/min	304.66	118.65	290.00	214.00	370.00	2572
Nutrition, body size							
Waist Circumference	cm	93.88	12.37	93.50	85.80	101.00	2627
Knee height	cm	49.41	3.35	49.30	47.10	51.70	2697
Body Mass Index (BMI)	kg/m2	26.87	5.25	26.00	24.00	30.00	2698
Waist/hip ratio	Ratio	0.948	0.077	0.951	0.900	0.994	2563

Outlier observations were dropped as follows: Triglycerides (6 observations), LDL-c (4), Cortisol (7), DHEA-s (4), Epinephrine (2), Noerepinephrine (2), CRP (4), Creatinine (3), Waist (5).

Table 2. Crude effects (relative hazard) of one SD around the mean biomarker on all-cause mortality

Biomarker	Aver-age	Females		Males		Square*	N	Deaths
		Age 65	Age 85	Age 65	Age 85			
Metabolic hormones								
Glycosylated hemog. (HgA1c)	1.15	1.82	1.38	1.82	1.38	-0.084	2603	440
Fasting glucose	1.10	1.10	1.10	1.10	1.10	…	2682	445
CV biomarkers								
Diastolic blood pressure	0.89	0.88	0.88	0.88	0.88	0.076	2810	459
Systolic BP	0.82	0.79	0.79	0.79	0.79	0.057	2810	459
Metabolic - lipids								
Triglycerides	0.85	0.77	0.77	0.77	0.77	0.058	2637	444
Total cholesterol	0.79	0.78	0.78	0.78	0.78	0.066	2644	444
HDL cholesterol	0.95	0.80	0.93	0.80	0.93	…	2641	444
Total/HDL cholesterol ratio	0.95	0.89	0.89	0.89	0.89	0.016	2641	444
LDL Cholesterol	0.81	0.80	0.80	0.80	0.80	0.056	2484	428
Stress hormones								
Urinary cortisol	1.10	1.04	1.04	1.18	1.18	…	2237	336
DHEA-S	0.87	0.88	0.88	0.66	0.66	0.093	2604	442
Epinephrine	0.99	…	…	…	…	…	1547	278
Norepinephrine	1.13	1.13	1.13	1.13	1.13	…	1595	285
Inflammation, immune system								
C-Reactive Protein (CRP)	1.22	1.81	1.61	1.81	1.61	-0.050	2611	436
Specific body functions								
Creatinine clearance	0.80	0.51	0.83	0.51	0.83	0.100	2370	343
Handgrip strength	0.49	0.32	0.53	0.32	0.53	…	2552	387
Distance in 10 seconds	0.59	0.42	0.60	0.42	0.60	…	2726	456
Pulmonary Peak Flow	0.57	0.34	0.61	0.34	0.61	…	2595	394
Nutrition, body size								
Waist Circumference	0.98	1.30	0.98	1.30	0.98	…	2650	419
Knee height	0.97	0.72	0.94	0.72	0.94	…	2720	452
Body Mass Index (BMI)	0.83	1.08	0.83	1.08	0.83	…	2721	452
Waist/hip ratio	0.99	1.19	1.00	1.19	1.00	…	2588	388

* Gompertz regression coefficient of the squared biomarker term.

Fig 1. Death rates by age, Costa Rica 2000-5 and CRELES sample 2005-8

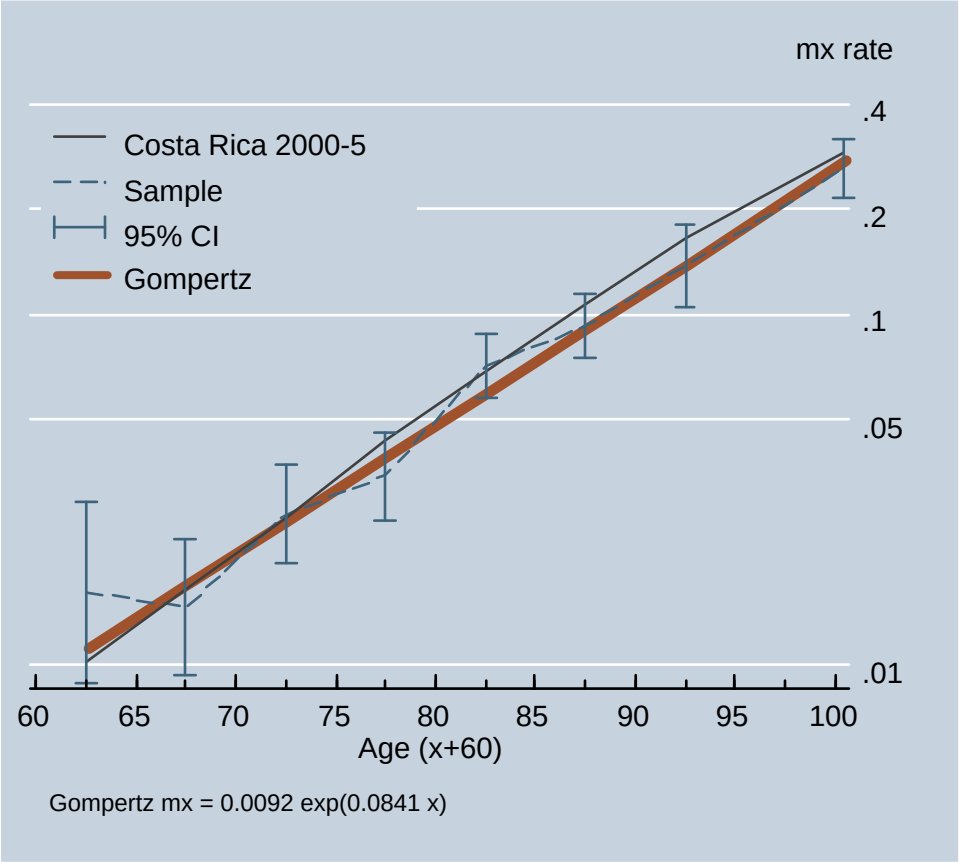

Fig 2-a. Crude effects of metabolic hormone biomarkers upon all-cause mortality

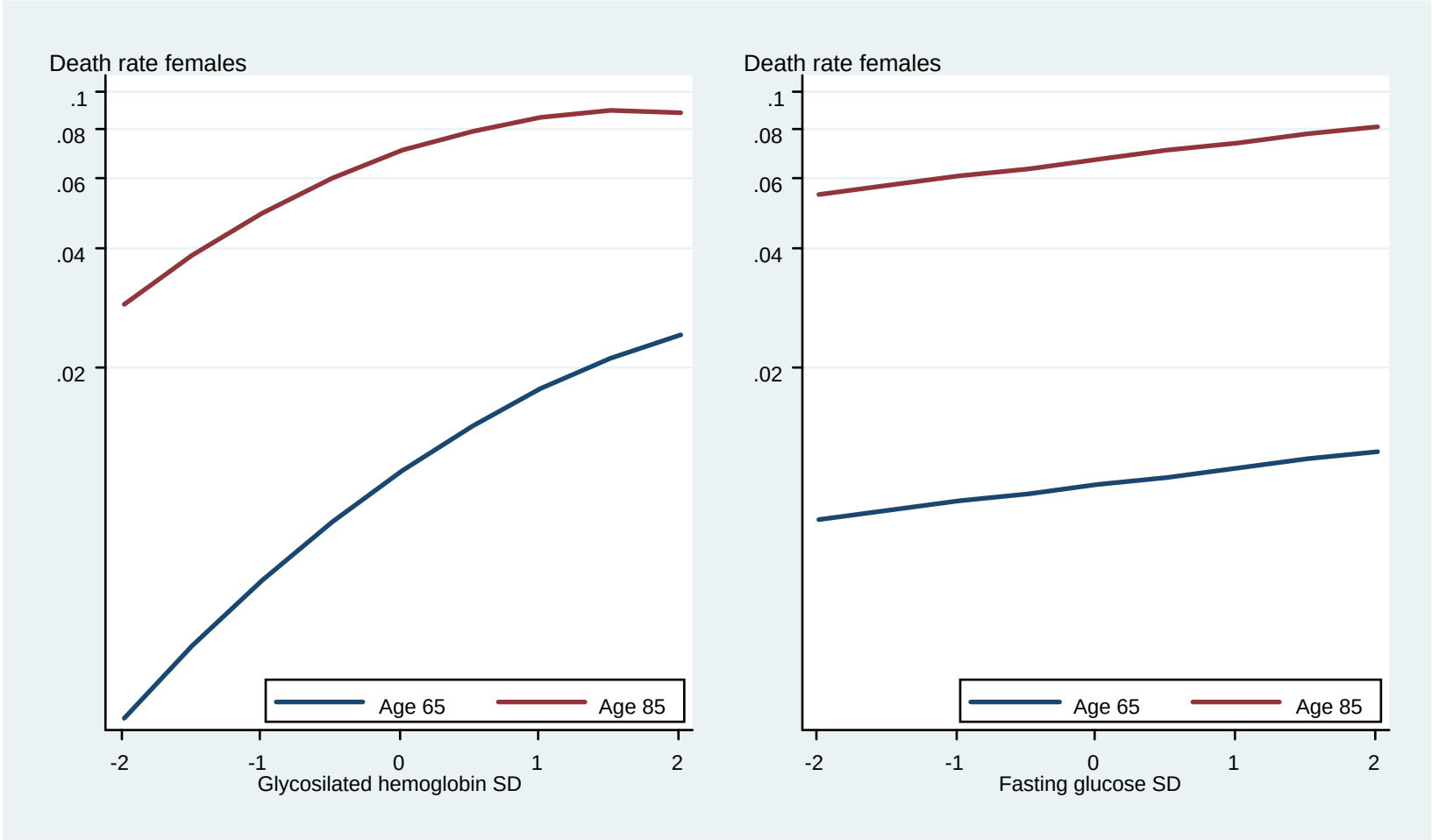

Fig 2-b. Crude effects of blood pressure biomarkers upon all-cause mortality

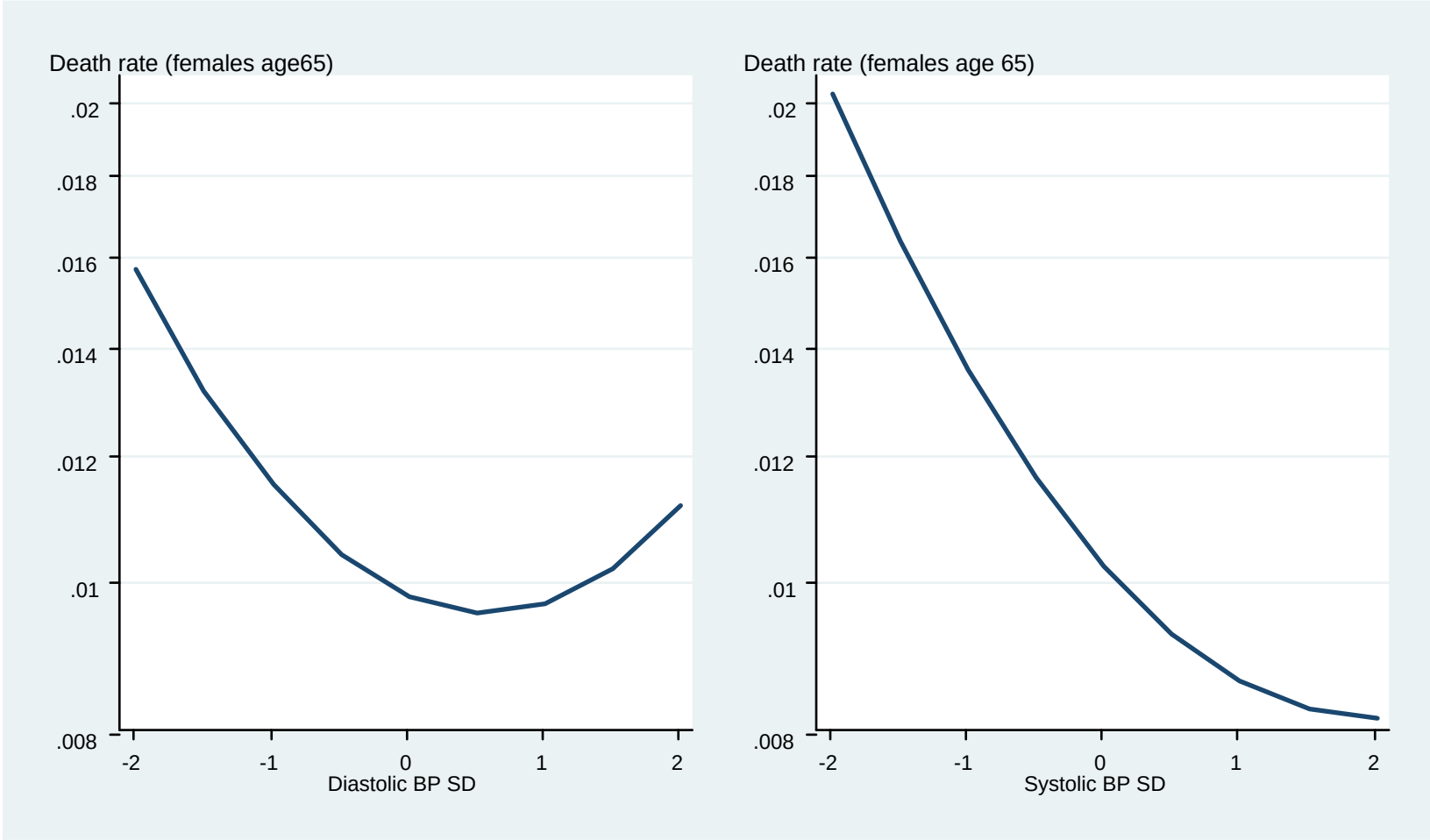

Fig 2-c. Crude effects of metabolic lipid biomarkers upon all-cause mortality

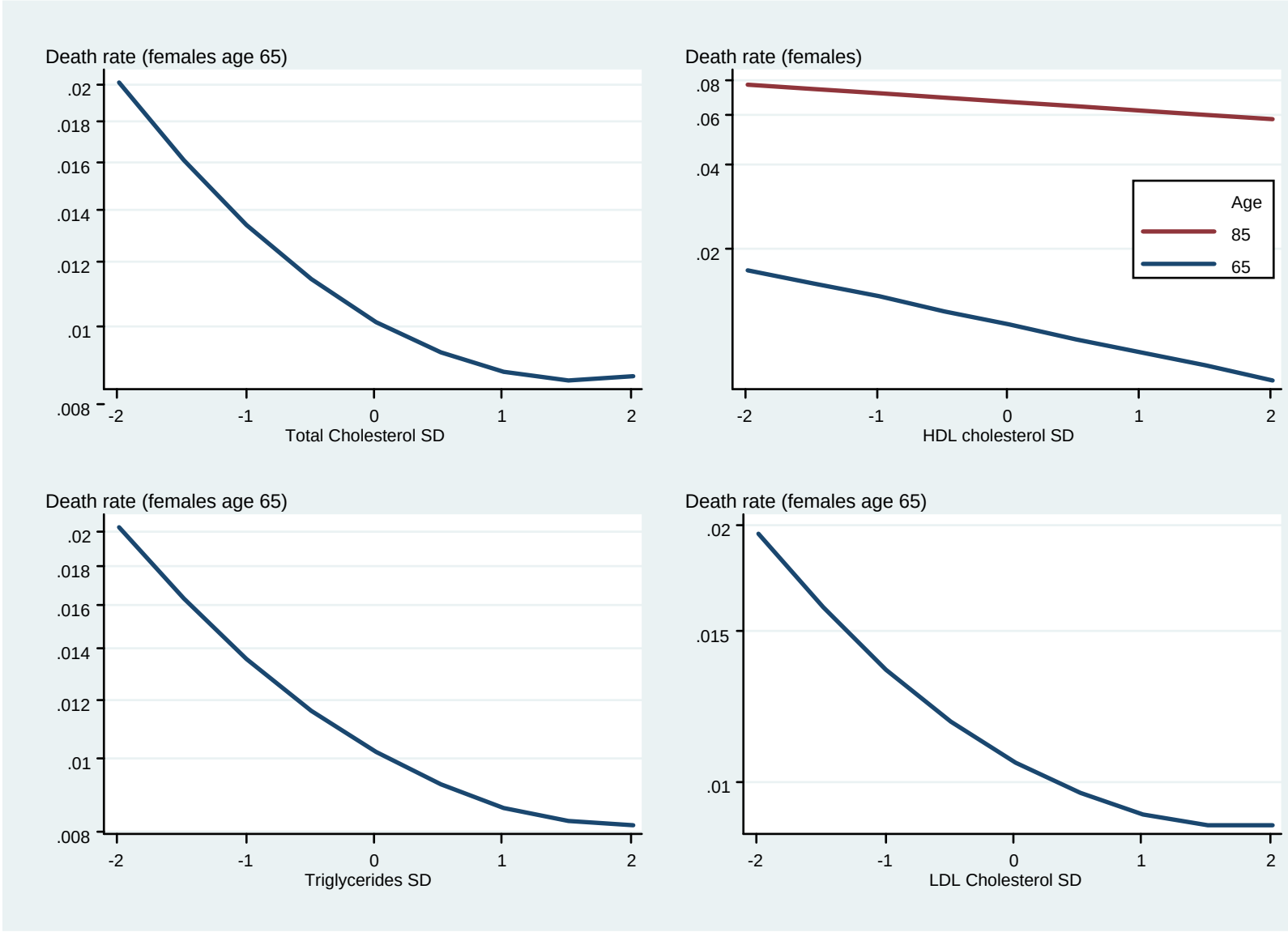

Fig 2-d. Crude effects of stress hormone biomarkers upon all-cause mortality

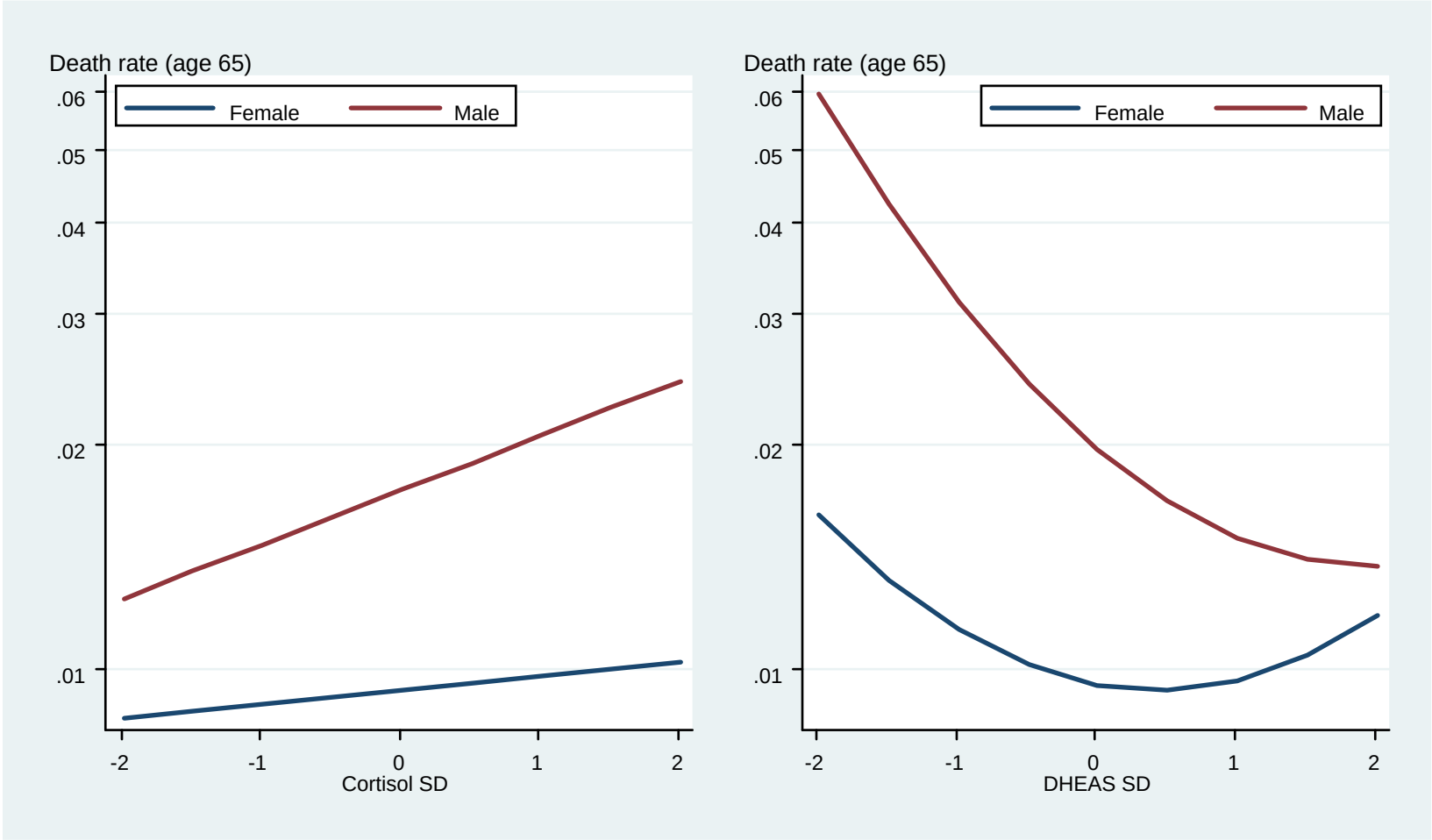

Fig 2-e. Crude effects of inflamation and organ functioning biomarkers upon all-cause mortality

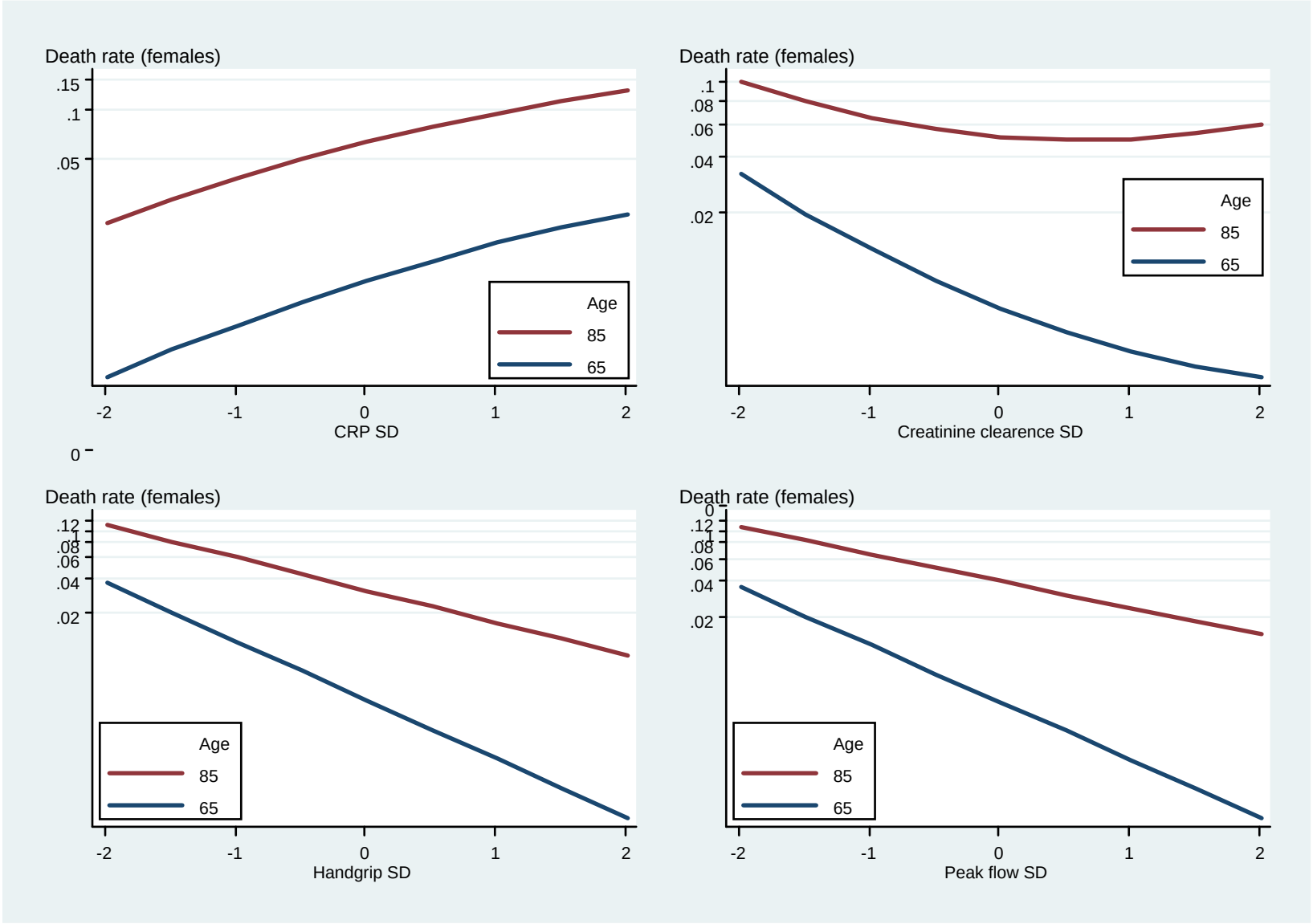

Fig 2-f. Crude effects of nutrition biomarkers upon all-cause mortality