Published in final edited form as:

Am J Med. 2011 June ; 124(6): 566.e1–566.e7. doi:10.1016/j.amjmed.2010.11.030.

Associations of Serum Alkaline Phosphatase with Metabolic Syndrome and Mortality

Vidya Raj Krishnamurthy, MD^{a,b}, Bradley C. Baird, MS^b, Guo Wei, MS^b, Tom Greene, PhD^{a,b}, Kalani Raphael, MD^{a,b}, and Srinivasan Beddhu, MD^{a,b}

^aVA Salt Lake City Health Care System, Utah

^bDepartment of Medicine, University of Utah School of Medicine, Salt Lake City

Abstract

BACKGROUND—Recent data suggest that elevated serum alkaline phosphatase levels are associated with increased mortality, but the mechanisms for this association are unknown. As metabolic syndrome is associated with higher serum alkaline phosphatase levels, we examined the joint association of mortality with metabolic syndrome and serum alkaline phosphatase levels in the US general population.

METHODS—Retrospective observational study of 15,234 adult participants in the National Health and Nutrition Examination Survey III. Multivariable Cox regression analyses were used to jointly relate mortality risk to serum alkaline phosphatase and indicators of metabolic syndrome.

RESULTS—Prevalence of metabolic syndrome was 14% to 41% among patients in lowest and higher quartiles, respectively, for baseline serum alkaline phosphatase. The mortality hazard ratio for each doubling of serum alkaline phosphatase was 1.52 (95% confidence interval [CI], 1.35–1.72) adjusting only for demographic factors, and 1.37 (95% CI, 1.21–1.56) adjusting for both demographic and metabolic syndrome factors in the full cohort, and was 1.83 (95% CI, 1.36–2.46) adjusting for demographic factors in the subgroup without any of the component conditions of metabolic syndrome.

CONCLUSIONS—In the US general population, higher levels of serum alkaline phosphatase is a predictor of mortality independent of the baseline prevalence of metabolic syndrome. Further studies are warranted to unravel the mechanisms of this association.

Keywords

All-cause mortality; Metabolic syndrome; Serum alkaline phosphatase

Elevation of serum alkaline phosphatase levels up to 1.5 times the upper limit of normal is considered acceptable in asymptomatic individuals.¹ Liver and bone are the 2 main sources

Requests for reprints should be addressed to Srinivasan Beddhu, MD, Department of Medicine, University of Utah School of Medicine, 85 North Medical Drive East, Room 201, Salt Lake City, UT 84112. srinivasan.beddhu@hsc.utah.edu.

Conflict of Interest: None of the authors have any actual or potential conflicts of interest associated with the work presented in the manuscript.

Authorship: All the above listed authors had access to the data and played a role in writing this manuscript.

of serum alkaline phosphatase.¹ Alkaline phosphatase also is present in other tissues, including intestine, kidney, placenta, and leukocytes.² The elevation of serum alkaline phosphatase can be physiological, as seen in adolescents and women in the third trimester of pregnancy.^{1,2} Pathological causes of increase in serum alkaline phosphatase levels include bone disease (hyperparathyroidism, hypovitaminosis D, and bony metastasis) and liver disease.

Recent studies have shown that higher levels of serum alkaline phosphatase are associated with increased mortality in the general population,³ survivors of myocardial infarction,³ chronic kidney disease (CKD) patients not on dialysis,⁴ CKD patients on maintenance hemodialysis,⁵⁻⁸ patients with metastatic neuroendocrine tumors,⁹ metastatic prostate cancer,¹⁰ and patients with advanced renal cell carcinoma.¹¹ It is speculated that in dialysis patients, the association of elevated serum alkaline phosphatase and mortality is due to abnormal bone and mineral metabolism and vascular calcification.^{8,12} In patients with metastatic cancer, the increased mortality risk associated with elevated serum alkaline phosphatase can be explained by increased osteoblastic activity from bone metastasis. However, the possible mechanisms for the associations of higher serum alkaline phosphatase with increased mortality are unclear in the general population.

A potential explanation for the increased mortality risk associated with elevated serum alkaline phosphatase in the general population is that higher levels of serum alkaline phosphatase also have been found to be associated with higher risk of developing metabolic syndrome.¹³ Therefore, we examined to what extent association of mortality risk with serum alkaline phosphatase persists after alternative strategies for statistical adjustment for metabolic syndrome in the US population using the National Health and Nutrition Examination Survey III (NHANES III) data.

METHODS

From 1988 to 1994, the National Center for Health Statistics conducted NHANES III, a cross-sectional survey of the US population. A complex, multistage sampling design was used to allow results to be extrapolated to the entire noninstitutionalized civilian US population as of the early 1990s.¹⁴ Data on age, sex, race, current or past cigarette smoking, and history of comorbid conditions such as myocardial infarction, stroke, and congestive heart failure, were collected in a structured home interview conducted by trained personnel. A detailed questionnaire on leisure-time physical activity also was administered during the home interview. The home interview was followed by an examination by a physician at a mobile examination center, which included blood pressure measurement and extensive anthropometric, physiological, and laboratory testing.

Serum specimens from collection sites were transported on dry ice to the central laboratories and stored at -70°C until analysis. Serum biochemistry panel including serum alkaline phosphatase was measured by a Hitachi 737 automated analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Ind). Serum 25-hydroxyvitamin D level was measured by a radioimmunoassay using the 25-OH D ^{125}I radioimmunoassay kit (INCSTAR Corp., Stillwater, Minn). Serum C-reactive protein (CRP) was measured by latex-enhanced

nephelometry using a Behring Nephelometer Analyzer System and reagents from Behring Diagnostics Inc., Somerville, NJ.

Serum creatinine was measured using a kinetic rate Jaffe method in NHANES III. These serum creatinine measurements were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH) as standard creatinine ($= -0.184 + 0.960 \times \text{NHANES III-measured serum creatinine in mg/dL}$)². Estimated glomerular filtration rate (eGFR) was calculated as $175 \times (\text{standardized serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the individual is woman) $\times 1.212$ (if the individual is African American) mL/min/1.73 m². Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m².

Based upon the National Cholesterol Education Program – Adult Treatment Panel III definition,¹⁵ metabolic syndrome was considered present if any 3 of the following 5 conditions were present: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), increased serum triglyceride level (≥ 150 mg/dL after a 12-hour fast), decreased serum high-density lipoprotein (HDL) cholesterol level (<40 mg/dL in men and <50 mg/dL in women), hypertension (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or use of antihypertensive medications or a self-reported history of hypertension), and insulin resistance (fasting glucose ≥ 110 mg/dL or use of antidiabetic agents or self-reported history of diabetes).

Follow-up Data

The National Center for Health Statistics created an NHANES III-linked Mortality File that contains mortality follow-up data from the date of NHANES III survey participation (1988-1994) through December 31, 2006. This information was based upon the results from a probabilistic match between NHANES III and National Death Index death certificate records, the details of which are provided elsewhere.¹⁶

Data Analysis

Several aspects of the NHANES design must be taken into account in data analysis, including the sampling weights and the complex survey design. We used the “svy” suite of commands in Stata 10 (StataCorp LP, College Station, Tex) and followed the analytical guidelines for NHANES data proposed by the Centers for Disease Control and Prevention.¹⁶ It should be noted that the svy suite of commands in Stata uses the complex survey design of NHANES to calculate the expected means and proportions of the entire US noninstitutionalized civilian CKD population and hence, means and proportions are presented with the estimated value and 95% confidence intervals.

The associations of serum alkaline phosphatase quartiles with metabolic syndrome at baseline were examined in a multivariable logistic regression model adjusted for demographics, comorbid conditions (history of myocardial infarction, stroke, congestive heart failure, smoking, alcohol use, and hepatitis B and C seropositivity), leisure-time physical inactivity, eGFR and liver function tests (serum aspartate aminotransferase, serum alanine aminotransferase and serum total bilirubin levels), serum CRP, and vitamin D levels.

The associations of serum alkaline phosphatase with time to death in the entire cohort were examined in several Cox regression models. As alkaline phosphatase had a skewed distribution, it was log-transformed. The results of these models are interpreted as the hazards associated with each doubling of serum alkaline phosphatase. First, the unadjusted associations of serum alkaline phosphatase with mortality were examined. In the second step, demographics (age, sex, and race) were added to examine the degree of attenuation of the above associations when adjusted for the demographics. In the third model, insulin resistance (defined as diabetes or fasting blood glucose ≥ 110 mg/dL), systolic blood pressure, diastolic blood pressure, fasting serum triglycerides, serum HDL cholesterol, and waist circumference were added to examine the additional attenuation induced by including the metabolic syndrome-related variables in the model.

Finally, as sensitivity analysis, this model was adjusted for multiple factors, some of which might be in the causal pathway of the associations of elevated serum alkaline phosphatase with mortality. These variables included myocardial infarction, congestive heart failure, stroke, hepatitis B and hepatitis C, malignancy, smoking, alcohol use, leisure-time physical inactivity, eGFR, serum aspartate aminotransferase, serum alanine aminotransferase, serum total bilirubin, serum calcium, serum phosphorus, serum vitamin D, and serum CRP. The association of mortality with serum alkaline phosphatase within subgroups with fixed levels of parameters defining metabolic syndrome was further investigated by performing Cox regression analyses separately in the following sub-populations: those with none of the component conditions of metabolic syndrome (as defined by the National Cholesterol Education Program Adult Treatment Panel III, as described above), those with one condition alone, those with 2 conditions alone, and those with metabolic syndrome (3 or more component conditions). These models were adjusted for age, sex, race, insulin resistance, systolic blood pressure, diastolic blood pressure, fasting serum triglycerides, serum HDL cholesterol, and waist circumference. The possibility of effect modification was evaluated by separately comparing the Cox-regression coefficients relating mortality to alkaline-phosphorus between the subgroups with 1, 2, or 3-5 metabolic syndrome components and the subgroup with 0 metabolic syndrome components.

Diagnostic analyses were performed to assess the validity of assumptions of the Cox regression models. In particular, the assumption of proportional hazards was examined by comparing the logarithm of the hazard ratio for each predictor variable in the first 3 years of follow-up to the logarithm of the hazard ratio of the predictor variables after year 3. The model did not show proportional hazards assumption violations with respect to alkaline phosphatase levels.

The factors age, sex, stroke, hepatitis C, and serum CRP exhibited a significant deviation from proportional hazards ($P < .05$). Hence, the Cox regressions were stratified by each of these factors (using tertiles for the continuous variables age and serum CRP) to allow separate baseline hazard functions within each strata. Furthermore, within each age stratum, age was adjusted as a continuous variable.

RESULTS

The study population consisted of the 15,243 adults in the NHANES III database with serum alkaline phosphatase levels. The mean age was 44 ± 0.5 years; 48% were men, 85% of the study population was Caucasians, and 11% were African Americans.

The clinical characteristics of the study population by serum alkaline phosphatase quartiles are summarized in **Table 1**. There was a higher prevalence of myocardial infarction, stroke, congestive heart failure, and diabetes in the participants in the highest quartile versus the lowest quartile of serum alkaline phosphatase. There was a significant association between leisure-time physical inactivity and higher levels of serum alkaline phosphatase. Higher serum alkaline phosphatase levels were associated with higher levels of serum CRP. Furthermore, higher serum alkaline phosphatase levels were associated with low serum 25 (OH) vitamin D levels.

The associations of serum alkaline phosphatase quartiles with the parameters of metabolic syndrome are described in **Table 2**. In a multivariable logistic regression model after adjustment for factors listed in **Figure 1**, there were significantly higher odds of metabolic syndrome in participants with the highest quartile of serum alkaline phosphatase, compared with the lowest quartile.

There were 3590 deaths over an average 13.9-year follow-up. The associations of serum alkaline phosphatase as a continuous variable (expressed as doubling of serum alkaline phosphatase) with all-cause mortality are shown in **Table 3**. After adjustment for demographics, each doubling of serum alkaline phosphatase was associated with 52% (hazard ratio [HR] 1.52; 95% confidence interval [CI], 1.35-1.72; $P < .001$) higher hazard for all-cause mortality. This association was somewhat attenuated when adjusted for metabolic syndrome parameters (HR 1.37; 95% CI, 1.21-1.56; $P < .001$). More extensive adjustment for comorbidities, lifestyle factors, eGFR, liver function tests and hepatitis serology, serum calcium, phosphorus, serum vitamin D, and serum CRP led to further but not complete attenuation of the HR, with each doubling of alkaline phosphatase associated with a 20% increased risk of death (HR 1.20; 95% CI, 1.06-1.36; $P = .006$).

The unadjusted associations of serum alkaline phosphatase quartiles with mortality in those with and without metabolic syndrome are shown in **Figures 2 and 3**. **Figure 4** summarizes the associations of each doubling of serum alkaline phosphatase with mortality in sub-populations defined by the numbers of metabolic syndrome components. These data suggest that the associations of serum alkaline phosphatase with mortality were strongest in those with the lowest number of metabolic syndrome components. Indeed, the regression coefficient for each doubling of serum alkaline phosphates with mortality in participants with no metabolic syndrome components was significantly ($P = .005$) different from the regression coefficient for each doubling of serum alkaline phosphates with mortality in those with 3-5 components of the metabolic syndrome.

DISCUSSION

The prevalence of metabolic syndrome has been reported to be 24% in the US adult population.¹⁷ Factors that are associated with increased risk of metabolic syndrome are obesity, insulin resistance, sedentary lifestyle, and consumption of soft drinks.¹⁸ Higher serum alkaline phosphatase levels have been reported to be associated with incident¹³ as well as prevalent metabolic syndrome.¹⁹ Nonalcoholic fatty liver disease is a chronic liver condition and can be associated with isolated elevations of serum alkaline phosphatase.²⁰ Nonalcoholic fatty liver disease might be the link between higher serum alkaline phosphatase levels and metabolic syndrome as components of metabolic syndrome correlate with nonalcoholic fatty liver disease in the general population.^{17,21,22}

In this study, we examined the hypothesis that the known associations of serum alkaline phosphatase with mortality can be largely explained by the associations of both of these factors with metabolic syndrome. Contrary to our expectations, the results of the current study indicate that despite the associations of higher serum alkaline phosphatase levels with higher baseline prevalence of metabolic syndrome (**Figure 1**) in the US population, the associations of serum alkaline phosphatase with mortality persist after various strategies for statistical adjustment for metabolic syndrome. Indeed, the strongest association of serum alkaline phosphatase with mortality was observed in those with none of the conditions of metabolic syndrome (**Figure 4**), with an 83% increase in hazard of death (HR 1.83; 95% CI, 1.36-2.46) for each doubling of alkaline phosphatase. On the other hand, in those with 3 or more conditions of metabolic syndrome (**Figure 4**), there was a nonsignificant 10% increase in hazard of death (HR 1.10; 95% CI, 0.92-1.31).

There are other potential explanations for the associations of serum alkaline phosphatase with increased mortality. First, increased serum alkaline phosphatase might reflect osteoporosis, the prevalence of which increases with age. Therefore, age might be a major confounder of the association of serum alkaline phosphatase. Adjustment for demographics reduced the HR of death associated with each doubling of serum alkaline phosphatase from 2.55 to 1.52 (**Table 3**). However, the adjusted HR of 1.52 still represents a substantial risk that is not accounted for by age, race, and sex.

Inflammation might be another potential explanation for the associations of elevated serum alkaline phosphatase with mortality. In a previous study of 1740 middle-aged adults, compared with a normal alkaline phosphatase control group, elevated serum alkaline phosphatase (defined as the upper quartile) was associated with higher levels of serum CRP (2.58 vs. 1.66 mg/L, $P < .001$).²³ However, in this study the association of mortality with serum alkaline phosphatase remained significant after statistical adjustment for CRP (**Table 3**). Similarly, hypovitaminosis D has been previously reported to be associated with both higher alkaline phosphatase levels²⁴ and increased mortality, but adjustment for serum vitamin D levels did not eliminate the associations of serum alkaline phosphatase with mortality in the present study (**Table 3**).

Additionally, another potential explanation is vascular calcification. There is some evidence that alkaline phosphatase promotes vascular calcification by hydrolyzing pyrophosphate in

the arterial media.^{25,26} An independent association of elevated serum alkaline phosphatase with progressive arterial calcification was noted in a longitudinal study of stage IV and V CKD patients.²⁷ We are unable to examine whether vascular calcification explains the associations of serum alkaline phosphatase with mortality as there are no data on vascular calcification in the NHANES data.

The persistence of the serum alkaline phosphatase-mortality relationship after adjustment for metabolic syndrome and other covariates indicates that serum alkaline phosphatase can be viewed as an independent predictor of mortality in the US population. The persistence of the serum alkaline phosphatase-mortality relationship in the adjusted analyses and in patients without any of the components of metabolic syndrome also suggests that it is unlikely that the serum alkaline phosphatase-mortality relationship could be an artifact of joint effects of metabolic syndrome or the other covariates on serum alkaline phosphatase and mortality. In those without any components of metabolic syndrome there is increased hazard of mortality with elevated serum alkaline phosphatase and in patients with more components of metabolic syndrome, the effect is attenuated. This may be due to effect modification. Nonetheless, there could be residual confounding due to unmeasured confounders.

The implications of our results for the alternative hypothesis that metabolic syndrome might mediate effects of alkaline phosphatase on mortality are less clear. This is because assessments of the mediating role of a factor that is hypothesized to fall on the causal pathway between an exposure and outcome are subject to 2 different types of confounding.²⁸ The first type of confounding results from factors that jointly influence both the exposure (alkaline phosphatase in our case) and the outcome (mortality); the second type results from factors that jointly influence the hypothesized intermediate variable (metabolic syndrome) and the outcome (mortality).

The strengths of our study include a careful data collection in NHANES III in the noninstitutionalized general population and a large sample size. The study also has certain limitations; first, it is an observational, retrospective analysis of an existing database that limits causal inferences, as noted above. Second, residual confounding due to unmeasured confounders of the associations of serum alkaline phosphatase with mortality cannot be ruled out. This is a major limitation of this type of analysis. For instance, we adjusted for serum transaminase levels, but still we might not have adjusted for nonalcoholic fatty liver disease, as liver transaminase levels may be normal in that condition. Third, data on isoforms of alkaline phosphatase were not available and hence, we cannot draw inferences on whether the bone or liver source of alkaline phosphatase is associated with increased mortality.

In conclusion, the results of this study suggest that higher serum alkaline phosphatase levels are strongly associated with increased prevalence of metabolic syndrome and subsequent increase in all-cause mortality in the US general population. However, metabolic syndrome does not appear to explain the increased mortality risk associated with higher serum levels of alkaline phosphatase. Further studies are warranted to determine the molecular mechanism of the causal pathways involved in the associations of elevated serum alkaline phosphatase levels with all-cause mortality.

Acknowledgments

Funding: This investigation is supported by the following: National Kidney Foundation Research Fellowship grant awarded to VRK; RO1-DK077298 and RO1 - DK078112 awarded to SB; The University of Utah Study Design and Biostatistics Center, with funding in part from the Public Health Services research grant numbers UL1-RR025764 and C06-RR11234 from the National Center for Research Resources.

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CLINICAL SIGNIFICANCE

- Higher serum alkaline phosphatase levels are associated with smoking, physical inactivity, and metabolic syndrome in the general US population.
- The association of higher levels of serum alkaline phosphatase with all-cause mortality in the general population is independent of the presence of metabolic syndrome and its components.

Figure 1.
Association of serum alkaline phosphatase quartiles with metabolic syndrome.

Figure 2.
Kaplan-Meier plot of the associations of serum alkaline phosphatase quartiles with mortality in those with metabolic syndrome.

Figure 3.
Kaplan-Meier plot of the associations of serum alkaline phosphatase quartiles with mortality in those without metabolic syndrome.

Figure 4. Associations of each doubling of serum alkaline phosphatase with mortality in those with 0, 1, 2, and 3 or more components of metabolic syndrome.

Table 1**Baseline Characteristics by Serum Alkaline Phosphatase Quartiles**

	Serum Alkaline Phosphatase Quartiles				P-Value
	<69 (U/L)	69-83 (U/L)	84-101 (U/L)	102-952 (U/L)	
Serum alkaline phosphatase (U/L)	57 ± 0.30	76 ± 0.10	92 ± 0.20	126 ± 1.0	
Age (years)	40 ± 0.4	44 ± 0.6	46 ± 0.6	48 ± 0.6	<.001
Men (%)	39 (37-41)	50 (47-52)	56 (53-58)	53 (51-56)	<.001
African American (%)	10 (9-11)	10 (9-12)	10 (9-12)	13 (11-14)	.199
Clinical characteristics					
Myocardial infarction (%)	1.8 (1.5-2.3)	2.7 (2.1-3.5)	4.3 (3.3-5.7)	5.9 (4.9-7.2)	<.001
Stroke (%)	1.1 (1.0-1.5)	1.4 (1.2-1.9)	2.3 (1.8-3.0)	3.0 (2.7-4.5)	<.001
Congestive heart failure (%)	1.0 (0.7-1.4)	1.3 (0.9-1.7)	2.4 (1.8-3.2)	4.2 (3.4-5.7)	<.001
Malignancy (%)	3.0 (2.4-3.7)	3.4 (2.5-4.4)	4.0 (3.2-4.9)	4.7 (3.7-6.0)	.045
Diabetes mellitus (%)	3.8 (3.2-4.6)	5.5 (4.2-6.5)	7.7 (6.5-9.1)	14 (12.4-15.8)	<.001
Current smoker (%)	24 (22-26)	29 (26-32)	29 (27-32)	31 (28-33)	<.001
Alcohol use (%)	60 (57-63)	56 (52-59)	51 (47-54)	42 (39-46)	<.001
Leisure-time physical inactivity (%)	10 (9-12)	13 (11-16)	15 (13-17)	20 (17-22)	<.001
eGFR (mL/min/1.73 m ²)	94 ± 0.65	92 ± 0.67	92 ± 0.52	91 ± 0.75	.007
Serum calcium (mg/dL)	9.2 ± 0.02	9.3 ± 0.02	9.3 ± 0.02	9.3 ± 0.02	<.001
Serum phosphorus (mg/dL)	3.5 ± 0.01	3.4 ± 0.01	3.5 ± 0.02	3.5 ± 0.02	.069
Serum AST (U/L)	20 ± 0.2	21 ± 0.3	22 ± 0.3	23 ± 0.4	<.001
Serum ALT (U/L)	15 ± 0.3	17 ± 0.5	19 ± 0.6	21 ± 0.7	<.001
Serum total bilirubin (mg/dL)	0.63 ± 0.01	0.62 ± 0.01	0.62 ± 0.01	0.60 ± 0.01	.192
Serum LDH (U/L)	148 ± 1.61	157 ± 2.10	162 ± 2.13	168 ± 2.28	<.001
Serum hepatitis B surface antigen or core antibody positive (%)	5.3 (4.2-6.6)	5.7 (4.6-7.1)	6.2 (5.1-7.5)	7.2 (6.0-8.6)	.139
Serum hepatitis C antibody positive (%)	1.6 (1.0-2.6)	2.3 (1.6-3.3)	2.4 (1.6-3.5)	2.5 (1.7-3.7)	.321
Serum vitamin D (pg/ml)	31.4 ± 0.5	29.4 ± 0.4	28.9 ± 0.4	28.2 ± 0.4	<.001
Serum C-reactive protein (mg/dL)	3.1 ± 0.1	3.5 ± 0.1	4.2 ± 0.1	6.2 ± 0.2	<.001

Percentages shown as percent (95% confidence interval); continuous measures shown as mean ± SE.

ALT = alanine transaminase; AST = aspartate transaminase; eGFR = Estimated glomerular filtration rate; LDH = lactate dehydrogenase.

Table 2

Associations of Serum Alkaline Phosphatase Quartiles with Metabolic Syndrome Parameters

	Alkaline Phosphatase Quartiles				P-Value
	17-68 (U/L)	69-83 (U/L)	84-101 (U/L)	102-952 (U/L)	
Serum alkaline phosphatase (U/L)	57 ± 0.30	76 ± 0.10	92 ± 0.20	126 ± 1.0	
Waist (inches), men	36.7 ± 0.2	36.9 ± 0.2	37.3 ± 0.2	36.9 ± 0.3	.10
Waist (inches), women	32.1 ± 0.2	34.5 ± 0.2	36.1 ± 0.2	37.7 ± 0.2	<.001
Serum triglycerides (mg/dL)	118 ± 3.1	137 ± 2.8	155 ± 2.9	164 ± 3.3	<.001
Serum HDL cholesterol (mg/dL), men	48.3 ± 0.8	45.8 ± 0.4	44.4 ± 0.5	43.9 ± 0.5	<.001
Serum HDL cholesterol (mg/dL), women	58.6 ± 0.5	53.6 ± 0.4	52.8 ± 0.6	52.2 ± 0.7	<.001
Systolic BP (mm Hg)	117 ± 0.35	121 ± 0.58	125 ± 0.59	128 ± 0.48	<.001
Diastolic BP (mm Hg)	72 ± 0.22	74 ± 0.31	75 ± 0.25	75 ± 0.26	<.001
Fasting serum glucose (mg/dL)	94 ± 0.6	97 ± 0.5	100 ± 0.7	110 ± 1.2	<.001
Fasting serum insulin (μU/mL)	8.7 ± 0.2	9.7 ± 0.2	11.1 ± 0.3	12.3 ± 0.4	<.001

BP = blood pressure; HDL = high-density lipoprotein.

Continuous measures shown as mean ± SE.

Table 3

Cox Proportional Hazards Regression of All-cause Mortality for Each Doubling of Serum Alkaline Phosphatase

	Hazard Ratio	95% CI	P-Value
Model 1	2.55	2.31-2.82	<.001
Model 2	1.52	1.35-1.72	<.001
Model 3	1.37	1.21-1.56	<.001
Model 4	1.20	1.06-1.36	.006

CI = confidence interval.

Model 1 – Unadjusted.

Model 2 – Adjustment for age (within strata), race, and stratified by age and sex.

Model 3 – Model 2 with additional adjustment for continuous parameters of metabolic syndrome (waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood glucose, serum triglycerides, serum high-density lipoprotein).

Model 4 – Adjustment for stratified by age, stratified by sex, race, parameters of metabolic syndrome, myocardial infarction, congestive heart failure, stroke, hepatitis B and hepatitis C, malignancy, smoking, alcohol use, leisure-time physical inactivity, estimated glomerular filtration rate, serum aspartate transaminase, serum alanine transaminase, serum total bilirubin, serum calcium, serum phosphorus, serum vitamin D, and serum C-reactive protein.