Relations of Serum Phosphorus and Calcium Levels to the Incidence of Cardiovascular Disease in the Community

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Background: Higher levels of serum phosphorus and the calcium-phosphorus product are associated with increased mortality from cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) or prior CVD. However, it is unknown if serum phosphorus levels influence vascular risk in individuals without CKD or CVD.

Methods: We prospectively evaluated 3368 Framingham Offspring study participants (mean age, 44 years; 51% were women) free of CVD and CKD. We used multivariable Cox models to relate serum phosphorus and calcium levels to CVD incidence.

Results: On follow-up (mean duration, 16.1 years), there were 524 incident CVD events (159 in women). In multivariable analyses and adjusting for established risk factors and additionally for glomerular filtration rate and for hemoglobin, serum albumin, proteinuria, and C-reactive protein levels, a higher level of serum phosphorus was associated with an increased CVD risk in a continuous fashion (adjusted hazard ratio per increment of milligrams per deciliter, 1.31; 95% confidence interval, 1.05-1.63; P=.02; P value for trend across quartiles=.004). Individuals in the highest serum phosphorus quartile experienced a multivariable-adjusted 1.55-fold CVD risk (95% confidence interval, 1.16%-2.07%; P=.004) compared with those in the lowest quartile. These findings remained robust in time-dependent models that updated CVD risk factors every 4 years and in analyses restricted to individuals without proteinuria and an estimated glomerular filtration rate greater than 90 mL/min per 1.73 m². Serum calcium was not related to CVD risk.

Conclusion: Higher serum phosphorus levels are associated with an increased CVD risk in individuals free of CKD and CVD in the community. These observations emphasize the need for additional research to elucidate the potential link between phosphorus homeostasis and vascular risk.

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SERUM PHOSPHORUS LEVELS ARE tightly regulated within a narrow range in healthy individuals because inorganic phosphorus plays a fundamental physiological role in energy production, membrane transport, and signal transduction.¹ Recent experimental and clinical data both implicate higher serum phosphorus levels in the pathogenesis of vascular disease. In murine models, deletion of the fibroblast growth factor–23 gene (that regulates renal and intestinal phosphorus absorption) or the Klotho gene (that encodes a transmembrane protein in the renal distal convoluted tubule) are associated with a phenotype that is characterized by hyperphosphatemia, premature aging, arteriosclerosis, and vascular calcification. In addition, the phenotype in the Klotho null mice is reversed by a low-phosphorus diet.⁴ On a parallel note, several clinical studies have shown that higher serum phosphorus levels and the calcium-phosphorus product in patients with CKD are associated with increased carotid atherosclerosis and coronary calcification cross-sectionally⁵⁶ and with an elevated risk of all-cause mortality and cardiovascular disease (CVD) mortality longitudinally.⁷⁻¹¹ Recently, Tonelli et al¹² reported an association of higher serum phosphorus levels within the reference range with an increased risk of CVD events during a 5-year follow-up period in patients with a previous myocardial infarction who have dyslipidemia but normal kidney function. Of note, polymorphisms of the Klotho gene have been associated with an adverse risk factor profile,¹³ and with atherosclerotic coronary disease in some reports¹⁴ but not in others.¹⁵ The aforementioned investigations¹²⁻¹⁴ raise the possibility that serum phosphorus levels within the reference range may influence the risk of CVD in asymptomatic individuals free of prevalent CKD or CVD.

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in the general population. Accordingly, we investigated the clinical correlates of serum phosphorus levels and related levels of serum phosphorus and calcium to the incidence of CVD in a large, community-based sample of individuals who were free of CVD and CKD at baseline.

METHODS

STUDY SAMPLE

The design and selection criteria of the Framingham Offspring Study have been described previously.16 All participants undergo routine physical examinations at the Framingham Heart Study approximately every 4 years. For the study described herein, we evaluated participants who had levels of serum phosphorus and calcium measured routinely at the second examination cycle (1979-1982)(n=3676). We excluded participants with prevalent CVD (n=167), defined as any history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, or heart failure.23 The Modification of Diet in Renal Disease equation was used to calculate an estimated glomerular filtration rate (eGFR): 186.3 × (serum creatinine)−1.154 × age−0.203 × (0.742 for women).18 Individuals with an eGFR of less than 60 mL/min per 1.73 m² at baseline were considered to have impaired kidney function and were excluded (n=141). After exclusions, a total of 3368 individuals (53% of whom were women) were eligible for the present investigation. All participants provided written informed consent, and the study protocol was approved by the institutional review board of the Boston Medical Center, Boston, Mass.

MEASUREMENT OF RISK FACTORS

At each examination visit, medical histories were taken, and participants underwent a physical examination (including blood pressure measurements), anthropometry, and laboratory assessment of risk factors. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive medications.19 Smoking 1 or more cigarettes daily on a regular basis in the year prior to the examination visit was considered current smoking. Total intake of alcohol was assessed by averaging the self-reported weekly consumption of alcoholic drinks. Fasting levels of total cholesterol, high-density lipoprotein cholesterol, serum albumin, blood glucose, and hemoglobin were measured using standardized assays and serum creatinine levels by using the modified Jaffe method. To be consistent with other laboratories, serum creatinine values were calibrated to the Cleveland Clinic Laboratory standard using a correction factor of 0.23 mg/dL (20.33 μmol/L).20 Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dL (7 mmol/L) or higher or the use of insulin or any hypoglycemic agents. Proteinuria was measured by a urine dipstick test (Amsabix; Ames Co Inc, Elkhart, Ind) and coded as none, trace, 1+, or 2+ or more. For analytical purposes, we dichotomized proteinuria as “none” vs “trace or more.” High-sensitivity C-reactive protein (hsCRP) was measured with a nephelometer (model BN100; Dade Behring; Deerfield, Ill) with an average intra-assay coefficient of variation of 3.8%.

MEASUREMENTS OF SERUM PHOSPHORUS AND CALCIUM LEVELS

Serum phosphorus and calcium levels were measured using a standard colorimetric method (Roche Diagnostics, Alameda, Calif). Serum phosphorus had an intra-assay coefficient of variation of 5.6%, and serum calcium had an intra-assay coefficient of variation of 2.5%.

ASSESSMENT OF CVD OUTCOMES

All participants in the Framingham Heart Study are under continuous surveillance for CVD events and death. A committee of 3 experienced investigators (who were blinded to serum phosphorus and calcium levels) reviewed all suspected CVD events by examining hospitalization records, physician office visit notes, and pathology reports, if appropriate. A Framingham Heart Study neurologist evaluated participants with suspected cerebrovascular events, and a separate review committee that included a neurologist adjudicated these events. Criteria for CVD have been described previously.13 For the present study, incident CVD was defined as fatal or nonfatal myocardial infarction, angina pectoris (stable or unstable), cerebrovascular events (stroke or transient ischemic attacks), peripheral vascular disease, or congestive heart failure. This composite definition of CVD has been used consistently by Framingham investigators consistently over the years.17

STATISTICAL ANALYSES

To maximize our statistical power, we evaluated first-onset CVD (and not individual CVD outcomes separately). Primary analyses focused on serum phosphorus and calcium and the calcium-phosphorus product, each considered separately. Baseline characteristics of study participants were compared across quartiles of serum phosphorus using analysis of variance. Multivariable regression analysis was used to test for trends in clinical characteristics across phosphorus quartiles adjusted for age and sex. We evaluated the cross-sectional correlates of the continuous measure of serum phosphorus using sex-pooled multivariable linear regression analyses.

We calculated age- and sex-adjusted incidence of CVD on follow-up according to quartiles of serum phosphorus and calcium and the calcium-phosphorus product. Cox proportional hazard regression models were estimated to analyze the relations of serum phosphorus and calcium levels, and the calcium-phosphorus product to incident CVD events after confirming the assumption of proportionality of hazards for each variable.21 Serum phosphorus and calcium levels and the calcium-phosphorus product were analyzed as continuous variables and as quartiles. Because tests of interaction for sex with serum phosphorus and calcium levels and the calcium-phosphorus product were not statistically significant, all analyses were performed for pooled sexes to maximize statistical power.

Two sets of multivariable models were constructed to begin with: (1) initially adjusting for age and sex and (2) adjusting for other covariates (including established vascular risk factors), age, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), diabetes mellitus, systolic blood pressure, treatment for hypertension, smoking, alcohol consumption, total/high-density lipoprotein (HDL) cholesterol ratio, levels of hemoglobin and serum albumin, eGFR, proteinuria, and hsCRP (multivariable model 1). Proteinuria and eGFR were used as covariates to account for subclinical renal disease. We adjusted for hsCRP because of its association with CVD incidence.23 We also adjusted for the total/HDL cholesterol ratio instead of low-density lipoprotein cholesterol levels because Framingham data indicate that the total/HDL cholesterol ratio is a better predictor of coronary disease risk relative to low-density lipoprotein cholesterol.24 In models considering the quartiles, we compared hazard ratios in the second, third, and fourth quartiles with those in the first quartile (referent) and tested for a linear trend in risk across quartiles.
In our sample, there were 9 participants with serum phosphorus levels exceeding 4.5 mg/dL (1.49 mmol/L), the upper limits of the reference range level for serum phosphorus level as described in the literature. Because we were interested in the relations of serum phosphorus levels within the reference range to CVD risk, analyses were repeated excluding these individuals.

In primary analyses, we used serum calcium levels and adjusted for serum albumin values. We performed secondary analyses using serum calcium levels corrected for serum albumin values using the following formula:

\[ \text{corrected serum calcium (in milligrams per deciliter)} = \text{observed serum calcium} + [0.8 \times (4 – \text{serum albumin})]. \]

if the serum albumin level is less than 4 g/dL.

Although the primary objective of our study was not to estimate CVD risk prediction models, we assessed if the addition of serum phosphorus levels improved the discrimination (assessed by C statistic) and/or the calibration (assessed by Hosmer-Lemeshow $\chi^2$ statistic) of a multivariable model that incorporated standard risk factors.

All analyses were performed with SAS statistical software (version 9.1; SAS Inc, Cary, NC), and the S-plus program (Insightful Corp, Basel, Switzerland) was used to plot the regression splines. A 2-sided P value of $P<.05$ was considered statistically significant.

### ADDITIONAL ANALYSES

In our sample, there were 9 participants with serum phosphorus levels exceeding 4.5 mg/dL (1.49 mmol/L), the upper limits of the reference range level for serum phosphorus level as described in the literature. Because we were interested in the relations of serum phosphorus levels within the reference range to CVD risk, analyses were repeated excluding these individuals.

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### RESULTS

#### CROSS-SECTIONAL CORRELATES OF SERUM PHOSPHORUS LEVELS

Serum phosphorus and calcium levels and calcium-phosphorus product were normally distributed in both sexes. Quartile ranges and mean values of serum phosphorus and calcium were similar among both men and women. The baseline characteristics of participants are displayed in Table 1 accordingly to quartiles of serum phosphorus.
phosphorus levels. The prevalence of several established CVD risk factors (except smoking) decreased with increasing levels of phosphorus (Table 1). In a multivariable linear regression model, serum phosphorus values were positively associated with age, hsCRP, eGFR, serum albumin level, and total/HDL cholesterol ratio but were inversely related to BMI, systolic blood pressure, and hemoglobin level (<.02 for all). Multivariable-adjusted levels of serum phosphorus were lower in men compared with women (<.001).

Serum phosphorus levels were weakly and positively correlated with serum calcium levels (r = 0.12 in men and 0.16 in women; P < .001 for both). The calcium-phosphorus product was highly correlated with serum phosphorus (r = 0.96 in both sexes; P < .001) but only modestly so with serum calcium levels (r = 0.39 in men and 0.42 in women; P < .001 for both). Consequently, the distribution of individuals in the quartiles of the calcium-phosphorus product mirrored their distribution in serum phosphorus levels (data not shown).

**RELATIONS OF SERUM PHOSPHORUS LEVELS, CALCIUM-PHOSPHORUS PRODUCT, AND SERUM CALCIUM LEVELS TO CVD INCIDENCE**

During a follow-up period of 20 years (mean, 16.1 years), 524 participants experienced a first CVD event (159 in women); these included 138 myocardial infarctions, 173 angina pectoris events, 93 cerebrovascular events, 18 sudden cardiac deaths, 63 peripheral vascular disease, and 39 congestive heart failure events. The age- and sex-adjusted incidence of CVD rose across quartiles of serum phosphorus levels (Table 2) that were supported by regression splines (Figure). The graded association of serum phosphorus with CVD risk remained robust in multivariable models updating established CVD risk factors as time-varying covariates every 4 years (Table 3, multivariable model 2). These results remained robust in analyses restricted to individuals with an eGFR greater than 90 mL/min per 1.73 m² and without proteinuria (Table 3, multivariable model 3). We did not observe effect modification by age, sex, hypertension status, serum calcium level, or eGFR (interaction terms were not statistically significant).

The analyses of the calcium-phosphorus product to the risk of CVD yielded results similar to those for serum phosphorus levels. The calcium-phosphorus product also was positively related to CVD risk (hazard ratio = 1.12 increase per SD increment; 95% CI, 1.02-1.24; P = .02). There was also a significant trend of increasing CVD risk across quartiles of calcium-phosphorus product (P = .01). These relations were maintained in time-dependent Cox models.

Serum calcium levels were not related to increased CVD events in age-adjusted or in multivariable models (Table 3; a 1 mg/dL (0.25 mmol/L) increment was associated with a hazards ratio for CVD of 1.10; 95% CI, 0.81-1.49; P = .56).

**ADDITIONAL ANALYSES**

The association of serum phosphorus levels with increased CVD risk remained robust when analyses were repeated excluding the 9 participants with values exceeding 4.5 mg/dL (1.45 mmol/L). We repeated analyses using corrected serum calcium levels (adjusted for serum albumin levels), and observed results identical to models using uncorrected serum calcium levels.

The C statistic for the multivariable model incorporating standard CVD risk factors was 0.79 (95% CI, 0.77-0.81) with good calibration ($\chi^2 = 14.1$). On addition of serum phosphorus values (modeled as quartiles), the C statistic increased minimally to 0.80 (95% CI, 0.78-0.82), but the calibration improved modestly ($\chi^2 = 6.5$).

**COMMENT**

**PRINCIPAL FINDINGS**

Our principal findings are 3-fold. First, cross-sectionally, serum phosphorus levels demonstrated an interesting relation to CVD risk factors, being positively related to age and total/HDL cholesterol ratio but inversely related to BMI.

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**Table 2. Age- and Sex-Adjusted Cumulative Incidence Rates of CVD According to Quartiles of Serum Phosphorus and Serum Calcium Levels**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Events, No.</th>
<th>Patients at Risk, No.</th>
<th>Age- and Sex-Adjusted 20-Year Incidence of CVD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137</td>
<td>815</td>
<td>16.4 (13.2-19.6)</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>868</td>
<td>17.9 (14.6-21.2)</td>
</tr>
<tr>
<td>3</td>
<td>129</td>
<td>915</td>
<td>17.5 (14.2-20.8)</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>770</td>
<td>21.1 (17.1-25.0)</td>
</tr>
</tbody>
</table>

**Note:** SI conversion factor: To convert serum calcium to millimoles per liter, multiply by 0.25.

*Calculated from $r=0.39$ in men and 0.12 in women; $r=0.96$ in both sexes.*

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**Table 3. Age- and Sex-Adjusted Cumulative Incidence Rates of CVD According to Quartiles of Serum Phosphorus and Serum Calcium Levels**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Serum Phosphorus Level</th>
<th>Patients at Risk, No.</th>
<th>Age- and Sex-Adjusted 20-Year Incidence of CVD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>816</td>
<td>19.4 (15.7-23.0)</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>1023</td>
<td>16.4 (13.4-19.4)</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>698</td>
<td>17.2 (13.7-20.7)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>831</td>
<td>19.9 (16.4-23.5)</td>
</tr>
</tbody>
</table>

**Note:** SI conversion factor: To convert serum calcium to millimoles per liter, multiply by 0.25.

*Calculated from $r=0.39$ in men and 0.12 in women; $r=0.96$ in both sexes.*

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**Figure**

The graded association of serum phosphorus with CVD risk remained robust in multivariable models updating established CVD risk factors as time-varying covariates every 4 years (Table 3, multivariable model 2). These results remained robust in analyses restricted to individuals with an eGFR greater than 90 mL/min per 1.73 m² and without proteinuria (Table 3, multivariable model 3). We did not observe effect modification by age, sex, hypertension status, serum calcium level, or eGFR (interaction terms were not statistically significant).

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**ADDITIONAL ANALYSES**

The association of serum phosphorus levels with increased CVD risk remained robust when analyses were repeated excluding the 9 participants with values exceeding 4.5 mg/dL (1.45 mmol/L). We repeated analyses using corrected serum calcium levels (adjusted for serum albumin levels), and observed results identical to models using uncorrected serum calcium levels.

The C statistic for the multivariable model incorporating standard CVD risk factors was 0.79 (95% CI, 0.77-0.81) with good calibration ($\chi^2 = 14.1$). On addition of serum phosphorus values (modeled as quartiles), the C statistic increased minimally to 0.80 (95% CI, 0.78-0.82), but the calibration improved modestly ($\chi^2 = 6.5$).
First, high phosphorus levels are known to inhibit 1,25-dihydroxyvitamin D synthesis in some studies. Lower levels of 1,25-dihydroxyvitamin D are hypothesized to decrease cardiac contractility and to increase coronary calcification. Additional research studies may be required to evaluate if lower 1,25-dihydroxyvitamin D levels in individuals with higher serum phosphorus levels contribute to a greater vascular risk.

Second, higher serum phosphorus levels may directly promote vascular injury. Investigators have reported that higher phosphorus levels increase the propensity of mineral deposition in vascular smooth muscle cells in vitro. This increased predisposition can be partly explained by increased osteopontin expression. Serum phosphorus may also directly increase vascular calcification, especially when levels of calcium-phosphorus product are high, and systolic blood pressure. Other investigators have reported similar cross-sectional correlates of serum phosphorus levels in patients with CKD and in people without CKD. Second, serum phosphorus levels (and the highly correlated calcium-phosphorus product) were associated with an increased risk of incident CVD in a continuous fashion in multivariable models adjusting for hsCRP and in a model incorporating established CVD risk factors as time-varying covariates. Values of serum phosphorus higher than 3.5 mg/dL (3.82 mmol/L) (defining the lower limit of the highest quartile and well within the reference range) were associated with a 55% increased CVD risk. Furthermore, these associations remained robust in a subgroup of individuals with an eGFR greater than 90 mL/min per 1.73 m² and without proteinuria. Of note, relations of serum phosphorus levels to CVD incidence strengthened in multivariable models compared with age- and sex-adjusted models, possibly because of confounding of the latter models by the inverse relations of serum phosphorus levels to select CVD risk factors. To our knowledge, the present investigation is the first to demonstrate a graded independent relation of serum phosphorus levels (within the reference range) to CVD risk in a community-based sample of men and women without either CKD or CVD at baseline. Third, serum calcium levels were not related to incident CVD in any of the models. Given the very high correlation of serum phosphorus levels and the calcium-phosphorus product, and the lack of any association of serum calcium with CVD risk, the association of the calcium-phosphorus product with CVD risk was likely driven by the association of serum phosphorus levels with CVD risk.

**MECHANISMS**

There are several potential mechanisms that may explain the association of serum phosphorus levels with greater CVD risk. First, high phosphorus levels are known to inhibit 1,25-dihydroxyvitamin D synthesis in some studies. Lower levels of 1,25-dihydroxyvitamin D are hypothesized to decrease cardiac contractility and to increase coronary calcification. Additional research studies may be required to evaluate if lower 1,25-dihydroxyvitamin D levels in individuals with higher serum phosphorus levels contribute to a greater vascular risk.

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as observed in patients with CKD\(^8\) or in individuals without CKD (referred to as dystrophic calcification).\(^{37}\) Most observational studies of patients with CKD have noted significant associations of vascular calcification with increased levels of serum phosphorus and calcium-phosphorus product. It is not clear, however, if higher serum phosphorus levels within the reference range are associated with increased vascular calcification.

Third, higher serum phosphorus levels may indicate subclinical renal dysfunction, with associated cardiovascular sequelae. Although our data lacked information on parathyroid hormone (PTH), we performed additional analyses excluding individuals with an eGFR of 90 mL/min per 1.73 m\(^2\) or less and/or proteinuria; the relations of serum phosphorus levels to CVD risk remained robust in these analyses. It is also important to note that none of the participants in our sample had a calcium-phosphorus product level of more than 55 mg\(^2\)/dL\(^2\) (a threshold above which adverse events have been reported to escalate in patients with CKD\(^9\)). Therefore, we do not believe that secondary hyperparathyroidism caused by renal dysfunction is a likely mechanism that would explain the observed relations in our study.

Fourth, higher serum phosphorus levels increase circulating PTH levels even in healthy individuals.\(^{40}\) Higher PTH levels may be proinflammatory; PTH has been reported to induce production of IL-6 (interleukin 6) via bone resorption\(^{39}\) or by increased hepatic synthesis.\(^{40}\) Higher levels of serum IL-6 and hsCRP have been associated with increased CVD risk. In our study, we adjusted for hsCRP and still observed a significant independent association of serum phosphorus levels and CVD risk.

### IMPLICATIONS

Surveys conducted by the US Department of Agriculture demonstrate an increase in the dietary intake of phosphorus among Americans, accompanied by a gradual decline in intake of calcium over the past 2 decades.\(^{41}\) Although the significance of increased consumption of phosphorus is unclear, limited data suggest that greater dietary intake of phosphorus may be associated with higher serum phosphorus levels.\(^{30,38,42,43}\)

The Institute of Medicine has formulated dietary reference guidelines for phosphorus intake for Americans that suggest higher phosphorus levels may not be associated with adverse health effects in the general population.\(^{34}\) These dietary references have been questioned because the rising dietary phosphorus intake is paralleled by a greater risk of fractures and lower bone density among children.\(^{45,46}\) In the present study, we did not assess dietary phosphorus intake. Further research is warranted, therefore, to evaluate if a higher dietary intake of phosphorus translates into a greater risk for CVD in the general population by contributing to higher serum phosphorus levels.

### STRENGTHS AND LIMITATIONS

The large, community-based sample of men and women; exclusion of individuals with CKD at baseline; adjustment for eGFR, proteinuria, and hsCRP; and the extended follow-up of 20 years strengthen our study.

Several limitations of our study deserve comment. We did not measure circulating PTH or 1,25-dihydroxyvitamin D levels in our sample to gain insights into mechanisms by which serum phosphorus levels may increase vascular risk. We attempted to control for secondary hyperparathyroidism by excluding individuals with CKD at baseline and by adjusting for eGFR and proteinuria in multivariable models. We also did not adjust for physical activity or other dietary determinants of CVD. In addition, we performed sex-pooled analyses and analyzed the composite outcome of first CVD events; we had limited power to evaluate the risk of individual CVD outcomes. Furthermore, we did not adjust for multiple statistical testing; however, all analyses were defined a priori. Finally, all of our participants were white, which may limit the generalizability of our results to nonwhite individuals.

In conclusion, in a large community-based sample of individuals free of baseline CKD and CVD, higher levels of serum phosphorus are associated with an increased risk of incident CVD in a graded fashion. Additional research is warranted to confirm or refute our findings and to elucidate the mechanisms underlying the potential link between phosphorus homeostasis and vascular risk.
and Wyeth Pharmaceuticals; has received honoraria from Bayer and Pfizer Pharmaceutical Co for speaking engagements; has served as a consultant for McNeil Consumer Products Co and Wyeth Pharmaceuticals; and has served as an expert witness for Merck & Co Inc, NutraQuest Inc, and GlaxoSmithKline.

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REFERENCES


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