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 gene2 (that regulates renal and intestinal phosphorus absorption) or the Klotho gene3 (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-sectionally5-8 and with an elevated risk of all-cause mortality and cardiovascular disease (CVD) mortality longitudinally.9-11 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.

For editorial comment see page 873

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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. 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. The Modification of Diet in Renal Disease equation was used to calculate an estimated glomerular filtration rate (eGFR): 186.3 × (serum creatinine)\(^{-1.104}\) × age\(^{-0.203}\) × (0.742 for women). Individuals with an eGFR of less than 60 mL/min per 1.73 m\(^2\) 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. 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). 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 (Ames Labs; Ames Co Inc, Elkhart, Ind) and coded as none, trace, 1+, or 2+ or more. For analytical purpose, 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. 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.

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. 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. 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. 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.
Table 1. Baseline Characteristics of 3368 Participants According to Quartiles of Serum Phosphorus Levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphorus, mg/dL</td>
<td>1.6-2.8</td>
<td>2.9-3.1</td>
<td>3.2-3.4</td>
<td>3.5-6.2</td>
<td></td>
</tr>
<tr>
<td>Subjects, No.</td>
<td>815</td>
<td>868</td>
<td>915</td>
<td>770</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>45.1 ± 9.6</td>
<td>44.1 ± 9.7</td>
<td>43.4 ± 10.2</td>
<td>44.0 ± 10.4</td>
<td>.007</td>
</tr>
<tr>
<td>Women, %</td>
<td>35.3</td>
<td>46.2</td>
<td>55.4</td>
<td>67.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>26.5 ± 4.5</td>
<td>26.3 ± 4.4</td>
<td>25.4 ± 4.3</td>
<td>24.9 ± 4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7.1</td>
<td>5.5</td>
<td>2.7</td>
<td>2.7</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125.9 ± 16.5</td>
<td>123.0 ± 16.4</td>
<td>119.6 ± 15.5</td>
<td>118.7 ± 15.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80.4 ± 9.5</td>
<td>78.7 ± 9.7</td>
<td>76.7 ± 9.2</td>
<td>75.8 ± 9.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>29.2</td>
<td>23.2</td>
<td>17.3</td>
<td>17.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>9.8</td>
<td>9.9</td>
<td>6.4</td>
<td>7.9</td>
<td>.13</td>
</tr>
<tr>
<td>Alcohol, mean ± SD, drinks/wk</td>
<td>4.22 ± 6.17</td>
<td>4.07 ± 5.66</td>
<td>3.39 ± 4.82</td>
<td>3.44 ± 4.36</td>
<td>.27</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio, mean ± SD</td>
<td>4.61 ± 1.59</td>
<td>4.60 ± 1.57</td>
<td>4.39 ± 1.52</td>
<td>4.34 ± 1.54</td>
<td>.19</td>
</tr>
<tr>
<td>Triglycerides, mean ± SD, mg/dL</td>
<td>115.0 ± 86.6</td>
<td>108.5 ± 94.2</td>
<td>98.0 ± 69.8</td>
<td>98.0 ± 76.2</td>
<td>.23</td>
</tr>
<tr>
<td>eGFR, mean ± SD, mL/min per 1.73 m²†</td>
<td>106.7 ± 50.6</td>
<td>104.3 ± 43.5</td>
<td>110.3 ± 51.9</td>
<td>118.4 ± 92.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum creatinine, mean ± SD, mg/dL</td>
<td>1.17 ± 0.23</td>
<td>1.16 ± 0.22</td>
<td>1.12 ± 0.22</td>
<td>1.07 ± 0.22</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum albumin, mean ± SD, g/dL</td>
<td>4.42 ± 0.30</td>
<td>4.44 ± 0.30</td>
<td>4.47 ± 0.31</td>
<td>4.46 ± 0.29</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemoglobin, mean ± SD, g/dL</td>
<td>14.9 ± 1.3</td>
<td>14.8 ± 1.4</td>
<td>14.5 ± 1.3</td>
<td>14.3 ± 1.3</td>
<td>.02</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein, mean ± SD, mg/L</td>
<td>2.72 ± 5.94</td>
<td>2.38 ± 4.21</td>
<td>2.11 ± 3.78</td>
<td>2.46 ± 4.89</td>
<td>.10</td>
</tr>
<tr>
<td>Proteinuria, mean ± SD, %</td>
<td>3.0 ± 0.16</td>
<td>2.0 ± 0.13</td>
<td>1.0 ± 0.11</td>
<td>1.0 ± 0.12</td>
<td>.20</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

SI conversion factors: To convert serum phosphorus levels to millimoles per liter, multiply by 0.3229; to convert HDL cholesterol and triglycerides to millimoles per liter, multiply by 0.0259 and 0.0113, respectively; to convert serum creatinine to micromoles per liter, multiply by 88.4.

†The eGFR is calculated by using the Modification of Diet in Renal Disease equation (see “Study Sample” subsection of the “Methods” section).

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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.
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.

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.

**Table 3. Cox Proportional Hazard Models Examining the Relations of Serum Phosphorus and Serum Calcium Levels to Incidence of CVD**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Incident CVD, No.</th>
<th>Subjects at Risk, No.</th>
<th>Serum Phosphorus Level</th>
<th>Serum Calcium Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137</td>
<td>815</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>868</td>
<td>1.10 (0.87-1.39)</td>
<td>1.23 (0.95-1.59)</td>
</tr>
<tr>
<td>3</td>
<td>129</td>
<td>915</td>
<td>1.08 (0.84-1.37)</td>
<td>1.27 (0.97-1.67)</td>
</tr>
<tr>
<td>4</td>
<td>116</td>
<td>770</td>
<td>1.32 (1.02-1.71)</td>
<td>1.55 (1.16-2.07)</td>
</tr>
</tbody>
</table>

*P value for trend* .004 .04 .01

**HR for CVD (95% CI)**

<table>
<thead>
<tr>
<th>Serum Phosphorus Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1.23 (0.95-1.59)</td>
</tr>
<tr>
<td>1.41 (1.04-1.90)</td>
</tr>
<tr>
<td>1.87 (1.20-2.89)</td>
</tr>
</tbody>
</table>

**Table 3. Cox Proportional Hazard Models Examining the Relations of Serum Phosphorus and Serum Calcium Levels to Incidence of CVD**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Incident CVD, No.</th>
<th>Subjects at Risk, No.</th>
<th>Serum Phosphorus Level</th>
<th>Serum Calcium Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>816</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>1023</td>
<td>0.83 (0.66-1.06)</td>
<td>0.86 (0.66-1.12)</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>698</td>
<td>0.88 (0.68-1.14)</td>
<td>0.95 (0.71-1.26)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>831</td>
<td>1.03 (0.82-1.31)</td>
<td>1.06 (0.80-1.40)</td>
</tr>
</tbody>
</table>

*P value for trend* .09 .47 .48 .29

**Figure.** Multivariable-adjusted relations of serum phosphorus levels to the incidence of cardiovascular disease (CVD) on follow-up. Estimated multivariable hazard ratios for CVD (y-axis) in relation to serum phosphorus levels (x-axis) as a function of penalized regression splines are shown. Vertical lines indicate quartiles of phosphorus levels. The dotted lines indicate confidence intervals. To convert serum phosphorus levels to millimoles per liter, multiply by 0.3229.
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.\(^{38}\) 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.\(^{30,38,42,45}\)

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.\(^{44}\) 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.

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**Author Contributions:** Dr Vasan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Dhingra and Vasan. **Acquisition of data:** Dhingra, Sullivan, and Vasan. **Analysis and interpretation of data:** Dhingra, Sullivan, Fox, Wang, Gaziano, and Vasan. **Drafting of the manuscript:** Dhingra, Sullivan, Fox, and Vasan. **Critical revision of the manuscript for important intellectual content:** Dhingra, Sullivan, Fox, Wang, D’Agostino, Gaziano, and Vasan. **Statistical expertise:** Sullivan, D’Agostino, and Vasan. **Administrative, technical, or material support:** D’Agostino and Vasan. **Study supervision:** Dhingra, Fox, Sullivan, D’Agostino, Gaziano, and Vasan. **Financial Disclosure:** Dr Gaziano has received funding from McNeil Consumer Products Co and Pliva; has received research support in the form of pills or packaging from BASF Group, DMS Pharmaceuticals Group Inc,
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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