Relation of Ascorbic Acid to Coronary Artery Calcium

The Coronary Artery Risk Development in Young Adults Study

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Ascorbic acid is an antioxidant nutrient possibly related to the development of atherosclerosis. To examine the relation between ascorbic acid and coronary artery calcium, an indicator of subclinical coronary disease, the authors analyzed data from 2,637 African-American and White men and women aged 18–30 years at baseline who were enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study (1985–2001). Participants completed diet histories at enrollment and year 7, and plasma ascorbic acid levels were obtained at year 10. Coronary artery computed tomography was performed at year 15. The authors calculated odds ratios in four biologically relevant plasma ascorbic acid categories, adjusting for possible confounding variables. When compared with men with high plasma ascorbic acid levels, men with low levels to marginally low levels had an increased prevalence of coronary artery calcium (multivariate odds ratio = 2.68, 95% confidence interval: 1.31, 5.48). Among women, the association was attenuated and nonsignificant (multivariate odds ratio = 1.50, 95% confidence interval: 0.58, 3.85). Ascorbic acid intakes from diet alone and diet plus supplements were not associated with coronary artery calcium. Low to marginally low plasma ascorbic acid levels were associated with a higher prevalence of coronary artery calcium among men but not among women.

antioxidants; ascorbic acid; calcium; cardiovascular diseases

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; NHANES II, Second National Health and Nutrition Examination Survey; OR, odds ratio; YALTA, Young Adult Longitudinal Trends in Antioxidants.

Because ascorbic acid, an essential water-soluble antioxidant, protects endogenous lipid-soluble antioxidants from oxidative damage and affects the production of vascular collagen, endothelial prostacyclin, nitric oxide, and the catabolism of cholesterol to bile acids (1, 2), it has been hypothesized that low plasma ascorbic acid levels may be a risk factor for cardiovascular disease (1). A number of prospective studies have reported, at least in some populations, that low blood levels of vitamin C are independently associated with the risk of coronary heart disease, stroke, cardiovascular disease death, and all-cause mortality (3–9).

We undertook this study to examine the relation of ascorbic acid status (assessed at enrollment and year 7 by diet plus supplement intake and at year 10 by plasma ascorbic acid levels) to coronary artery calcium among participants enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Coronary artery calcium, the calcified component of atherosclerosis in the coronary arteries, is an indicator of subclinical atheroscle-
rotic coronary artery disease that was assessed at year 15 of follow-up by computed tomography. To our knowledge, this report is the first study to examine the relation between ascorbic acid status and coronary artery calcium.

MATERIALS AND METHODS

Subjects

The CARDIA Study is a prospective study designed to document levels of risk factors for coronary disease and potential determinants of these risk factors in a cohort of young adults approximately equally divided among men and women and among African Americans and Whites. Beginning in 1985, 5,115 participants aged 18–30 years were recruited from four clinical sites located in Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota, and Oakland, California. This analysis is based on data collected from participants who were enrolled in the Young Adult Longitudinal Trends in Antioxidants (YALTA) Study, an ancillary study of the CARDIA Study.

All YALTA Study participants attended the CARDIA Study follow-up examinations performed at years 10 and 15. The YALTA Study was designed to examine the relation between antioxidant nutrients and cardiovascular disease. Because of missing data on key variables, this report is based on information obtained from 2,637 YALTA Study participants. Of the 3,042 CARDIA Study participants who had a coronary artery computed tomographic scan at year 15 to assess the presence of coronary artery calcium, we excluded two participants who had undergone a sex change, 22 who were pregnant at year 10 or year 15, and other participants with missing or questionable data on dietary ascorbic acid intake (n = 49), plasma ascorbic acid levels (n = 292), and adjustment variables (n = 67). The CARDIA Study was approved by the institutional review board at each clinical center, and informed consent was obtained from all participants prior to enrollment.

Measurements

CARDIA Study participants completed a diet history at baseline and year 7 modeled on the Chicago Western Electric Study questionnaire and designed to assess usual intake over a typical month (10). The development, implementation, and evaluation of the CARDIA Study dietary history, an interviewer-assisted questionnaire, have been described in detail elsewhere (11). Nutrient intakes were based on the average intake recorded at baseline and year 7 or on one of these for participants who had only one dietary assessment. Nutrient and energy intakes were recomputed in 2002 using updated information from the Nutrition Coordinating Center at the University of Minnesota. We excluded women with averaged year 0 and year 7 daily dietary intakes below 600 or above 6,000 kcal and men with reported daily intakes below 800 and above 8,000 kcal (1 kcal = 4.19 kJ). Data collected at baseline and at the periodic follow-up examinations included self-reported age, race, sex, years of education completed, usual level of physical activity (reported in exercise units) (12, 13), history of smoking (never/past/current, divided into <15 cigarettes/day and ≥15 cigarettes/day), hypertension (defined as either self-reported history of hypertension, mean of the second and third blood pressure measurements of >140/90 taken while seated, or use of antihypertensive medication), diabetes (defined as either self-reported history of diabetes, elevated fasting serum level of glucose (≥126 mg/dl), or use of medication for diabetes), alcohol intake, and use of vitamin C and vitamin E supplements. Body mass index (weight (kg)/height (m)^2) was calculated using weight and height measurements obtained during the physical examination performed at year 10. Because plasma ascorbic acid levels were ascertained at year 10, covariate data from year 10 were also used whenever possible. A more detailed description of the study procedures has been published previously (14).

Fasting lipid and lipoprotein measurements were performed at the Northwest Lipid Research Center in Seattle, Washington. The low density lipoprotein cholesterol level was calculated using the Friedewald equation. Plasma levels of ascorbic acid were measured at the Molecular Epidemiology and Biomarker Laboratory at the University of Minnesota using high performance liquid chromatography. Specimens were collected at year 10 in vials containing metaphosphoric acid and frozen for up to 1 year at −70°C. Plasma levels of ascorbic acid ranged from 5.6 μmol/liter (0.10 mg/dl) to 211.2 μmol/liter (3.72 mg/dl). Levels of carotenoids (including lycopene, α-carotene, β-carotene, β-cryptoxanthin, and zeaxanthin plus lutein) and tocopherols (α-tocopherol and γ-tocopherol) were assayed by high performance liquid chromatography from baseline and year 7 plasma samples stored at −70°C. Plasma levels of carotenoids and tocopherols from baseline and year 7 were averaged and included as adjustment variables in some multivariable models.

Coronary artery computed tomography was used to assess the presence or absence of coronary artery calcium. All CARDIA Study participants underwent computed tomography testing at year 15 of follow-up using tomographic scanners, with the Oakland, California, and Chicago, Illinois, sites having the Imatron (South San Francisco, California) electron beam tomographic scanner and the Birmingham, Alabama, and Minneapolis, Minnesota, sites having GE Lightspeed (General Electric Medical System, Milwaukee, Wisconsin) and Siemens AG (Erlangen, Germany) multidetector computed tomographic scanners, respectively. The computed tomography scanning protocol included two scans, use of a hydroxyapatite phantom for the monitoring of image brightness and noise, and adjustment of scanner differences in brightness levels during reading. Use of the phantom allowed for the comparability of scans between sites. A single reader was blinded to the order of duplicate scans and to the image data in the scan pair. A radiologist identified the courses of the coronary arteries using specially developed image-processing software that was programmed to define a calcific focus as four adjacent pixels comprising an area of at least 1.87 mm^2. Calcium scores were summed across all lesions within a given artery (left main, left anterior descending, left circumflex, and right coronary artery) and across all arteries to obtain the total calcium score for the scan, expressed as an Agatston score.
Ascorbic Acid and Coronary Artery Calcium

RESULTS

Plasma ascorbic acid levels and other relevant variables were available from 2,637 participants, aged 28–40 years at year 10 of follow-up. A comparison of variables relevant to cardiovascular disease and coronary artery calcium is presented in table 1. Approximately 11 percent of participants had low or marginally low plasma ascorbic acid levels, whereas 23 percent had levels consistent with tissue saturation. Participants with low or marginally low plasma ascorbic acid levels were more likely to be current smokers, African American, and male and to have hypertension and diabetes. Low or marginally low plasma ascorbic acid levels were also associated with higher energy intake, greater body mass index, lower fiber intake, lower serum levels of high density lipoprotein cholesterol, and higher serum levels of low density lipoprotein cholesterol and triglycerides.

We examined four models to assess the relation between plasma ascorbic acid status and coronary artery calcium. In the simple race-, age-, and clinical site-adjusted models, men and women with the lowest plasma levels of ascorbic acid had the highest prevalence of coronary artery calcium. Compared with participants who had plasma levels of ascorbic acid consistent with tissue saturation, participants with low to marginally low plasma ascorbic acid levels had an approximately threefold higher prevalence of coronary artery calcium (table 2). Across categories of plasma ascorbic acid levels in men, there was a trend toward higher prevalence of coronary artery calcium as plasma levels decreased, even after adjustment for other cardiovascular disease risk factors, plasma carotenoids, and plasma tocopherols (p_trend < 0.01). We also analyzed the relation between plasma ascorbic acid and coronary artery calcium by quintile of plasma ascorbic acid level, adjusting for sex. When analyzed in this fashion and with all covariates included, lower levels of plasma ascorbic acid were associated with a higher prevalence of coronary artery calcium (model 4 odds ratios (ORs) = 1.77 (95 percent confidence interval (CI): 1.05, 2.98), 1.26 (95 percent CI: 0.74, 2.12), 1.36 (95 percent CI: 0.81, 2.28), 1.31 (95 percent CI: 0.78, 2.19), and 1.00, respectively; p_trend = 0.06).

Because smoking lowers plasma ascorbic acid levels, we conducted additional analyses after stratifying by year 10 smoking status. Among the 1,525 never smokers, there was a nonsignificant 41 percent higher prevalence of coronary artery calcium in the lowest compared with the highest plasma ascorbic acid level group (model 4 OR = 1.41, 95 percent CI: 0.58, 3.41; p = 0.45). Among the 564 current smokers at year 10, low to marginally low plasma ascorbic acid levels were also not significantly associated with coronary artery calcium (model 4 OR = 1.28, 95 percent CI: 0.43, 3.84; p = 0.66). The smaller sample sizes available in these two subgroups may have limited the power to observe a significant association. We also examined whether sex, race, or smoking modified the relation of plasma ascorbic acid to coronary artery calcium and did not find evidence for such interactions (all p > 0.05).

We also examined the relation of dietary ascorbic acid intake (table 3) and total ascorbic acid intake (that included supplements) to coronary artery calcium (table 4). The

Statistical methods

We used analysis of variance to compare the mean values of continuous variables adjusted for differences in age, race, and sex and chi-square tests to compare categorical variables across categories of plasma or dietary markers of ascorbic acid. We used simple age-, race-, and clinical center-adjusted logistic models and multivariable-adjusted logistic models stratified by sex to examine the relation of plasma ascorbic acid and vitamin C intake to coronary artery calcium. We entered into the multivariable models variables previously reported to be associated with cardiovascular disease risk, including age (in years), race (White, African American), sex, hypertension (yes/no), diabetes mellitus (yes/no), smoking (≥15 cigarettes/day, <15 cigarettes/day, former, never), and serum lipid levels (mg/dl), as well as other selected plasma antioxidants that might be associated with plasma ascorbic acid levels and coronary artery calcium, including lycopene, α-carotene, β-carotene, β-cryptoxanthin, zeaxanthin plus lutein, α-tocopherol, and γ-tocopherol. Because the relation between serum high density lipoprotein, tocopherols, and carotenoids and coronary artery calcium was not linear, these variables were entered into the multivariable models in quartile categories. The relation between plasma ascorbic acid status and coronary artery calcium was examined using four biologically relevant plasma ascorbic acid category levels (low to marginal: ≤22.7 µmol/liter (<0.4 mg/dl), low normal: 22.8–45.4 µmol/liter (0.4–0.8 mg/dl), high normal: 45.5–62.5 µmol/liter (0.8–1.1 mg/dl), and levels consistent with tissue saturation: >62.5 µmol/liter (>1.1 mg/dl)) (1).

To test for monotonic trends, we entered the absolute plasma and dietary ascorbic acid values for each participant as a continuous variable in the regression models and report the p value derived from these analyses. In addition, we examined the relation of dietary ascorbic acid intake, including vitamin C supplement use, modeled as a continuous variable, to the presence of coronary artery calcium. In additional models, we also analyzed the relation between plasma ascorbic acid (by quartile) and coronary artery calcium. Smoking was analyzed as a categorical variable (never/past/current <15 cigarettes per day/current ≥15 cigarettes per day) in the multivariate models. Additional models examined the relation of plasma ascorbic acid to coronary artery calcium among year 10 smokers and nonsmokers. We used cross-product interaction terms (i.e., plasma ascorbic acid × sex and plasma ascorbic acid × race) to test for effect modification. We used logistic regression to calculate odds ratios and the 95 percent confidence intervals. Two-tailed p values of <0.05 were considered statistically significant.
dietary estimates were based on the average ascorbic acid intake from baseline and year 7 of follow-up. In the simple model that adjusted for the effects of age, race, sex, clinical center, and energy intake, there was no significant relation between dietary ascorbic acid intake and coronary artery calcium ($p_{trend} = 0.07$) (table 3). Likewise, in models that adjusted for the same variables used in the analyses of plasma ascorbic acid, there was no evidence of an association between quartile of dietary or dietary plus supplementary ascorbic acid intake and prevalence of coronary artery calcium (model 4; $p_{trend} = 0.44$). Restricting the analyses to the 1,353 participants who were not using a vitamin C supplement did not change the results.

### DISCUSSION

Overall, our study produced mixed findings. The main positive finding was that low to marginally low plasma ascorbic acid levels (measured at year 10) were associated with an approximately threefold higher prevalence of coronary artery calcium (ascertained at year 15) among men independently of other cardiovascular disease risk factors, including smoking. We did not, however, observe a similar relation among women, perhaps because fewer women had coronary artery calcium, thereby limiting our statistical power to detect such an association. We also cannot exclude the possibility that our findings resulted from chance or residual confounding. The findings among men concur with
findings from cross-sectional and longitudinal analyses of participants in the Second National Health and Nutrition Examination Survey (NHANES II) (7, 15). Simon et al. (15) reported previously that NHANES II participants with low to marginally low serum ascorbic acid levels had an increased prevalence of self-reported coronary heart disease. In the NHANES II Mortality Study, which followed participants for a mean of 14 years, Simon et al. (7) found a trend toward increased cardiovascular disease mortality among individuals with low to marginally low serum ascorbic acid levels. Similar to our current findings, those from the NHANES II Mortality Study did not reflect a relation between dietary intake of ascorbic acid and cardiovascular disease endpoints (7).

Our current findings are also consistent with results from some observational studies that also reported low blood ascorbic acid levels to be a risk factor for coronary heart disease (3–5, 8, 16, 17). Not all observational studies have reported such an association (6, 18), and the few randomized trials examining the effect of vitamin C supplementation on coronary heart disease endpoints, typically in combination with other antioxidants, have produced inconsistent results, ranging from decreased risk to no effect to increased risk (19–22). Specifically determining whether marginal vitamin C deficiency is a factor in the development of atherosclerotic coronary disease would be of considerable public health importance, since blood levels consistent with marginal deficiency are prevalent in the population (7) and readily modifiable.

Conclusions based on our findings are qualified by limitations in the study design. We collected information on plasma levels of ascorbic acid 5 years before the coronary artery calcium measurement, but we do not have coronary artery calcium scores before year 15. Therefore, we cannot be certain that differences in plasma ascorbic acid preceded the development of coronary artery calcium since we cannot exclude the possibility that subclinical coronary disease lowered plasma ascorbic acid levels. The concern about the direction of causality is underscored in part because we were unable to find an association between dietary ascorbic acid intake (measured at baseline and year 7) and coronary artery calcium; that is, since blood levels of ascorbic acid are generally correlated with intake, a similar association between lower ascorbic acid intakes and coronary artery calcium would have been expected.
**TABLE 3. Prevalence of coronary artery calcium across quartiles of dietary ascorbic acid intake among 2,637 participants, Coronary Artery Risk Development in Young Adults Study, 1985–2001**

<table>
<thead>
<tr>
<th>Quartile of dietary ascorbic acid intake</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>$p_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with coronary artery calcium (no.)</td>
<td>70 (11)*</td>
<td>65 (10)</td>
<td>60 (9)</td>
<td>57 (9)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>SD†</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Dietary intake of ascorbic acid (mg/day)</td>
<td>65</td>
<td>17</td>
<td>114</td>
<td>13</td>
<td>163</td>
</tr>
<tr>
<td>OR†</td>
<td>95% CI†</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Model 1‡</td>
<td>1.49</td>
<td>0.96, 2.33</td>
<td>1.17</td>
<td>0.77, 1.79</td>
<td>1.07</td>
</tr>
<tr>
<td>Model 2§</td>
<td>1.31</td>
<td>0.84, 2.06</td>
<td>1.09</td>
<td>0.71, 1.67</td>
<td>1.02</td>
</tr>
<tr>
<td>Model 3¶</td>
<td>1.37</td>
<td>0.86, 2.17</td>
<td>1.10</td>
<td>0.72, 1.70</td>
<td>1.03</td>
</tr>
<tr>
<td>Model 4#</td>
<td>1.22</td>
<td>0.70, 2.12</td>
<td>1.04</td>
<td>0.64, 1.70</td>
<td>1.05</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage.  
† SD, standard deviation; OR, odds ratio; CI, confidence interval.  
‡ Model 1 adjusted for age, race, sex, clinical center, and energy intake.  
§ Model 2 adjusted for age, race, sex, clinical center, hypertension, diabetes, smoking, and energy intake.  
¶ Model 3 adjusted for age, race, sex, clinical center, hypertension, diabetes, smoking, serum high density lipoprotein and low density lipoprotein cholesterol, triglycerides, and energy intake.  
# Model 4 adjusted for all the variables noted in table 1 plus clinical center, mean serum levels of tocopherols, and carotenoids (including $\alpha$- and $\beta$-carotene, zeaxanthin/lutein, lycopene, and $\beta$-cryptoxanthin) by quartile measured at baseline and year 7 ($n = 2,515$).

**TABLE 4. Prevalence of coronary artery calcium across quartiles of total ascorbic acid intake (diet plus supplements) among 2,637 participants, Coronary Artery Risk Development in Young Adults Study, 1985–2001**

<table>
<thead>
<tr>
<th>Quartile of total ascorbic acid intake</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>$p_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with coronary artery calcium (no.)</td>
<td>71 (11)*</td>
<td>57 (9)</td>
<td>60 (9)</td>
<td>64 (10)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>SD†</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Dietary intake of ascorbic acid (mg/day)</td>
<td>88</td>
<td>24</td>
<td>150</td>
<td>22</td>
<td>229</td>
</tr>
<tr>
<td>OR†</td>
<td>95% CI†</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Model 1‡</td>
<td>1.42</td>
<td>0.94, 2.16</td>
<td>0.93</td>
<td>0.63, 1.39</td>
<td>1.05</td>
</tr>
<tr>
<td>Model 2§</td>
<td>1.33</td>
<td>0.88, 2.03</td>
<td>0.91</td>
<td>0.61, 1.37</td>
<td>1.04</td>
</tr>
<tr>
<td>Model 3¶</td>
<td>1.37</td>
<td>0.93, 2.04</td>
<td>0.93</td>
<td>0.62, 1.38</td>
<td>1.02</td>
</tr>
<tr>
<td>Model 4#</td>
<td>1.30</td>
<td>0.78, 2.15</td>
<td>0.90</td>
<td>0.57, 1.42</td>
<td>1.04</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage.  
† SD, standard deviation; OR, odds ratio; CI, confidence interval.  
‡ Model 1 adjusted for age, race, sex, clinical center, and energy intake.  
§ Model 2 adjusted for age, race, sex, clinical center, hypertension, diabetes, smoking, and energy intake.  
¶ Model 3 adjusted for age, race, sex, clinical center, hypertension, diabetes, smoking, serum high density lipoprotein and low density lipoprotein cholesterol, triglycerides, and energy intake.  
# Model 4 adjusted for all the variables noted in table 1 plus clinical center, mean serum levels of tocopherols, and carotenoids (including $\alpha$- and $\beta$-carotene, zeaxanthin/lutein, lycopene, and $\beta$-cryptoxanthin) by quartile measured at baseline and year 7 ($n = 2,515$).
There are several potential explanations for these findings. Because the dietary assessments were performed at baseline and year 7 and plasma ascorbic acid levels were assayed at year 10, we cannot exclude the possibility that dietary and supplement use changed during the intervening period, although we did find a weak, albeit statistically significant, correlation between dietary ascorbic acid intake and plasma ascorbic acid levels \((r = 0.14; p < 0.0001)\). It is also possible that the dietary assessments were not sufficiently accurate or precise to permit the detection of the association. Prospective studies that examined dietary intake of ascorbic acid as a predictor of cardiovascular disease have produced contradictory results. An analysis of data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study found that individuals with the highest intakes of ascorbic acid had 25–50 percent lower cardiovascular disease mortality \((23)\). Dietary ascorbic acid intake was also associated with a lower risk of coronary heart disease death among Finnish women \((24)\) and a group of 747 noninstitutionalized elderly Massachusetts residents \((25)\). The Nurses’ Health Study \((26)\), the Health Professionals Follow-up Study \((27)\), and others \((28,29)\), however, found no significant association between ascorbic acid intake and risk of coronary heart disease.

Ascorbic acid may reduce the risk of cardiovascular disease by a number of mechanisms. Antioxidant status has been hypothesized to be an important factor in atherogenesis, and ascorbic acid is a highly effective water-soluble antioxidant capable of inhibiting lipid peroxidation \((30,31)\). In some studies, ascorbic acid blood levels and dietary intake have been associated with increased levels of high density lipoprotein cholesterol and decreased levels of total cholesterol \((1,32,33)\). The inverse relation between plasma ascorbic acid levels and coronary artery calcium that we observed, however, was independent of cholesterol levels. Ascorbic acid promotes endothelial prostacyclin production \((34)\), improves endothelium-dependent vasodilation \((2)\), and is essential for vascular collagen formation, all factors that may be associated with cardiovascular disease risk. Despite the potential for ascorbic acid to lower the risk for cardiovascular disease, recent clinical trials using antioxidant cocktails that contain ascorbic acid have failed to lower cardiovascular disease risk \((19–22)\). We are unaware, however, of clinical trials using ascorbic acid supplementation specifically among individuals with low to marginally low blood levels, our postulated high-risk group.

In addition to the limitations discussed, we were also limited by having only a single measurement of plasma ascorbic acid, which may not reflect long-term plasma concentrations optimally. However, plasma ascorbic acid levels reflect at least the previous several months of dietary intake, even during periods of seasonal variation \((35)\), and are strongly correlated with leucocyte ascorbic acid levels, an indicator of tissue ascorbic acid levels \((36,37)\). We cannot exclude the possibility that our findings were affected by residual confounding (especially from smoking) or that plasma ascorbic acid levels were simply a healthy diet or lifestyle marker. The association of low plasma ascorbic acid levels with higher prevalence of coronary artery calcium among men was, however, independent of the effects of other lifestyle-related variables, such as education and exercise.

In conclusion, we found that low to marginally low plasma ascorbic acid levels were independently associated with a higher prevalence of coronary artery calcium in young adult men but not in young adult women. Because we cannot exclude chance or residual confounding as an explanation of our findings, our results need to be confirmed by other investigators.

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REFERENCES