Demographic, Dietary, and Urinary Factors and 24-h Urinary Calcium Excretion

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Background and objectives: Higher urinary calcium is a risk factor for nephrolithiasis. This study delineated associations between demographic, dietary, and urinary factors and 24-h urinary calcium.

Design, setting, participants, & measurements: Cross-sectional studies were conducted of 2201 stone formers (SF) and 1167 nonstone formers (NSF) in the Health Professionals Follow-up Study (men) and Nurses’ Health Studies I and II (older and younger women).

Results: Median urinary calcium was 182 mg/d in men, 182 mg/d in older women, and 192 mg/d in younger women. Compared with NSF, urinary calcium as a fraction of calcium intake was 33 to 38% higher in SF (P values <0.01). In regression analyses, participants were combined because associations with urinary calcium were similar in each cohort and in SF and NSF. After multivariate adjustment, participants in the highest quartile of calcium intake excreted 18 mg/d more urinary calcium than those in the lowest (P trend =0.01). Caffeine and family history of nephrolithiasis were positively associated, whereas urinary potassium, thiazides, gout, and age were inversely associated, with urinary calcium. After multivariate adjustment, participants in the highest quartiles of urinary magnesium, sodium, sulfate, citrate, phosphorus, and volume excreted 71 mg/d, 37 mg/d, 44 mg/d, 61 mg/d, 37 mg/d, and 24 mg/d more urinary calcium, respectively, than participants in the lowest (P values trend ≤0.01).

Conclusions: Intestinal calcium absorption and/or negative calcium balance is greater in SF than NSF. Higher calcium intakes at levels typically observed in free-living individuals are associated with only small increases in urinary calcium.


Higher urinary calcium is a major risk factor for calcium kidney stones, (1) the most common type of stone. However, the impact of many factors on urinary calcium excretion is unclear.

The relation between calcium intake and urinary calcium excretion remains incompletely defined. Previous studies reporting the nonlinear relation between calcium ingestion and urinary calcium compared low calcium intake to very high intake but did not determine the shape of the calcium intake/urinary calcium curve for intakes typically observed in free-living individuals. For example, in 13 healthy volunteers, Pak reported that a calcium intake of 198 mg/d resulted in urinary calcium excretion of 138 mg/d, whereas a calcium intake of 1878 mg/d resulted in urinary calcium of 202 mg/d (2). Despite metabolic studies reporting greater intestinal absorption of calcium in stone formers (SF), (3) no population-based study to date has compared the relation between calcium intake and urinary calcium in individuals with and without a history of kidney stones.

Substantial uncertainty also remains about associations between other factors (such as magnesium, potassium, fluid intake, and acid-base status) and urinary calcium. For example, although previous studies reported that magnesium administration and potassium deprivation increase urinary calcium, (4–6) the amounts of magnesium and potassium in these studies were not representative of typical diets. Complicating matters, calcium itself may impact other urinary constituents. For example, the calcium-sensing receptor is located in the medullary collecting duct (MCD), and animal studies report reductions of MCD water permeability with higher urinary calcium (7). Despite this, few population studies to date have examined the independent association between urinary calcium excretion and urinary volume (8). Finally, although alkali administration decreases urinary calcium, increases urinary citrate, and increases urinary pH, (9,10) urinary calcium (and/or other factors important in calcium homeostasis) may affect urinary citrate (11). Previous studies did not report the independent associations between urinary calcium, citrate, and pH.

To delineate associations between demographic, dietary, and urinary factors and 24-h urinary calcium excretion, we conducted a cross-sectional study of 3368 individuals, with and without a history of kidney stones, from three cohorts: the Health Professionals Follow-up Study and the Nurses’ Health Studies I and II.

Materials and Methods

Source Population

Health Professionals Follow-up Study (HPFS). In 1986, 51,529 male health professionals between the ages of 40 and 75 yr enrolled in

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HPFS by returning an initial questionnaire that provided detailed information on medical history, lifestyle, and medications.

Nurses’ Health Study I (NHS I). In 1976, 121,700 female registered nurses between the ages of 30 and 55 yr enrolled in NHS I by returning an initial questionnaire.

Nurses’ Health Study II (NHS II). In 1989, 116,671 female registered nurses between the age of 25 and 42 yr enrolled in NHS II by returning an initial questionnaire.

HPFS, NHS I, and NHS II are followed by biennial mailed questionnaires that ask about lifestyle practices and other exposures of interest, as well as newly diagnosed diseases. The follow-up for all three cohorts exceeds 90%.

Ascertainment of Diet
A semiquantitative food-frequency questionnaire asking about the average use of more than 130 foods and beverages during the previous year has been mailed to study participants every 4 yr. Intake of specific dietary factors was computed from the reported frequency of consumption of each specified unit of food and from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake to determine the nutrient composition of the diet independent of the total amount of food eaten (12,13). The intake of nutritional supplements in multivitamins or isolated form was determined by the brand, type, and frequency of reported use. The reproducibility and validity of the food-frequency questionnaires (FFQs) were documented previously (14,15).

Ascertainment of other Covariates
Information on age, weight, and height was obtained on the baseline questionnaire. Self-reported weight was updated every 2 yr. Self-reported weight has been validated in HPFS and NHS I (16). Information on kidney stones, hypertension, diabetes mellitus, and gout was obtained from biennial questionnaires. The validity of these self-reported diseases has been documented (17–21). Although we do not have stone composition reports from all SF in these cohorts, the majority of kidney stones likely were calcium oxalate (21). Information on the use of specific medications also was obtained on biennial questionnaires. Information on family history of kidney stones was obtained in 1994 in HPFS and in 1997 in NHS II.

Urine Collections
Twenty-four-hour urine samples were collected in two cycles as part of a study to compare the urine composition of SF to nonstone formers (NSF). In the first cycle, which spanned from 1994 to 1999, we obtained one 24-h urine collection from 1046 participants (22). The second cycle began in 2003, when we invited additional SF and randomly selected controls to perform two 24-h urine collections. In the first cycle, participants were ineligible if they were >70 yr of age in HPFS or >65 yr in NHS I or had a history of cancer or cardiovascular disease. In the second cycle, participants were ineligible if they were >75 yr of age or had a history of cancer (other than nonmelanoma skin cancer).

The rates of participation and completion among SF and NSF participants in each cohort were reported previously (23). The 24-h urine collection procedure used the system provided by Mission Pharmacal (San Antonio, TX) (23). The demographic characteristics and dietary intake of participants who collected urine and those who did not were similar (23).

In the present study, we excluded participants with missing information on diet or body mass index (BMI). To remove those with likely over- or undercollections, we also excluded participants with 24-h urinary creatinine values in the top 1% or bottom 1% of the urinary creatinine distribution of NSF in each cohort. After exclusions, 1037 HPFS participants, 1246 NHS I participants, and 1085 NHS II participants provided at least one 24-h urine collection, and 2354 participants completed two collections.

Analytic Procedures Used for the Urine Measurements
Calcium and magnesium were measured by an atomic absorption spectrophotometer. Creatinine, uric acid, citrate, and phosphorus were measured by a Cobas centrifugal analyzer. Oxalate was analyzed by ion chromatography. Sodium and potassium were determined directly by flame emission photometry. We previously sent blinded split samples to assess reproducibility; the coefficients of variation for all factors analyzed were <10%.

Statistical Analyses
In the primary analysis, we examined participants who provided a single 24-h urine collection. If a participant submitted more than one 24-h urine collection, we used the first sample. In secondary analyses, we studied participants who submitted two collections. Participants were included only if the creatinine value in each urine collection differed by <30% from the mean creatinine value of the two collections. Values for urinary factors were obtained by calculating the arithmetic mean of the collections.

We calculated urinary calcium as a fraction of calcium intake in individuals with and without a history of kidney stones and also in individuals with 24-h urinary calcium values above and below the cohort specific medians. Analysis of covariance was used to adjust mean values of urinary calcium as a fraction of intake for age, hypertension, diabetes, weight, and the 24-h urinary excretion of creatinine, sodium, potassium, magnesium, total volume, citrate, sulfate, and phosphorus.

To examine the independent relations between demographic, dietary, and urinary factors and the 24-h urinary excretion of calcium, we constructed linear regression models with 24-h urinary calcium as the dependent variable. Because we ascertained long-term dietary patterns with the FFQ but studied 24-h urine (which is likely to reflect short-term dietary intake), we used urinary factors to estimate dietary intake when possible. Independent variables considered in multivariate analyses were age (continuous); BMI (continuous); history of kidney stones, hypertension, diabetes, and gout (each yes or no); family history of kidney stones (yes or no); cohort (HPFS, NHS I, or NHS II); season of urine collection; smoking status (current, past, or never); menopausal status; use of medications (including thiazide diuretics, nonsteroidal anti-inflammatory drugs, postmenopausal hormones, oral contraceptives, bisphosphonates, and statins); 24-h urinary factors including volume, pH, magnesium, potassium, citrate, sodium, sulfate, phosphate, uric acid, oxalate, and creatinine (all in quartiles); and intakes of calcium, caffeine, total carbohydrates, sucrose, fructose, n-3 fatty acids, n-6 fatty acids, phytate, vitamin K, vitamin A, vitamin B12, vitamin B6, folate, copper, and zinc (all in quartiles). Cohort specific quartiles of urinary and dietary factors were determined before study participants were merged into a single data set.

All P values are two tailed. We calculated 95% confidence intervals (CI) for all estimates. Data were analyzed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). The research protocol for this study was approved by the institutional review board of Brigham and Women’s Hospital.

Results
Characteristics of men (HPFS), older women (NHS I), and younger women (NHS II) who provided a 24-h urine collection are displayed in Table 1. By design, the majority (>60%) of participants had a history of kidney stones. Thiazide use
ranged from 9% in men to 16% in older women. Men consumed less supplemental calcium than women and excreted more urinary magnesium, sodium, sulfate, phosphorus, potassium, and creatinine.

Unadjusted values for urinary calcium as a fraction of dietary and total calcium intake are displayed in Table 2. Urinary calcium as a fraction of dietary calcium was calculated only in participants not taking calcium supplements. Compared with NSF, urinary calcium as a fraction of total calcium intake was 38% higher in SF men and younger women and 33% higher in

Table 1. Characteristics of study participants by cohort

<table>
<thead>
<tr>
<th>Demographic and dietary factors</th>
<th>HPFS (n = 1037)</th>
<th>NHS I (n = 1246)</th>
<th>NHS II (n = 1085)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yr)</td>
<td>63.4 (58.8 to 69.3)</td>
<td>66.1 (61.3 to 71.3)</td>
<td>49.8 (45.3 to 53.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (23.7 to 28.0)</td>
<td>26.0 (22.9 to 29.8)</td>
<td>25.3 (22.5 to 30.7)</td>
</tr>
<tr>
<td>history of kidney stones</td>
<td>63.0%</td>
<td>69.1%</td>
<td>63.3%</td>
</tr>
<tr>
<td>history of hypertension</td>
<td>35.3%</td>
<td>48.8%</td>
<td>22.0%</td>
</tr>
<tr>
<td>thiazide use</td>
<td>8.8%</td>
<td>16.3%</td>
<td>14.9%</td>
</tr>
<tr>
<td>history of diabetes</td>
<td>5.7%</td>
<td>10.0%</td>
<td>4.5%</td>
</tr>
<tr>
<td>history of gout</td>
<td>7.0%</td>
<td>3.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>family history of kidney stones</td>
<td>18.1%</td>
<td>N/A</td>
<td>25.7%</td>
</tr>
<tr>
<td>calcium supplement use</td>
<td>48.1%</td>
<td>69.0%</td>
<td>63.3%</td>
</tr>
<tr>
<td>total calcium intake (mg/d)</td>
<td>890 (701 to 1180)</td>
<td>1196 (759 to 1684)</td>
<td>1239 (821 to 1731)</td>
</tr>
<tr>
<td>urinary magnesium (mg/d)</td>
<td>118 (94 to 147)</td>
<td>95 (74 to 122)</td>
<td>94 (74 to 121)</td>
</tr>
<tr>
<td>urinary sodium (mEq/d)</td>
<td>173 (134 to 224)</td>
<td>132 (99 to 172)</td>
<td>144 (109 to 182)</td>
</tr>
<tr>
<td>urinary sulfate (mmol/d)</td>
<td>22 (17 to 28)</td>
<td>16 (12 to 20)</td>
<td>16 (13 to 20)</td>
</tr>
<tr>
<td>urinary citrate (mg/d)</td>
<td>666 (480 to 889)</td>
<td>613 (427 to 817)</td>
<td>724 (544 to 910)</td>
</tr>
<tr>
<td>urinary phosphorus (mg/d)</td>
<td>1032 (852 to 1249)</td>
<td>732 (593 to 904)</td>
<td>808 (649 to 999)</td>
</tr>
<tr>
<td>urinary volume (L/d)</td>
<td>1.6 (1.2 to 2.1)</td>
<td>1.7 (1.3 to 2.2)</td>
<td>1.6 (1.2 to 2.2)</td>
</tr>
<tr>
<td>urinary potassium (mEq/d)</td>
<td>73 (58 to 91)</td>
<td>58 (45 to 73)</td>
<td>53 (42 to 66)</td>
</tr>
<tr>
<td>urinary creatinine (mg/d)</td>
<td>1627 (1379 to 1896)</td>
<td>1030 (886 to 1185)</td>
<td>1171 (1018 to 1359)</td>
</tr>
<tr>
<td>urinary calcium (mg/d)</td>
<td>182 (122 to 255)</td>
<td>182 (117 to 252)</td>
<td>192 (141 to 259)</td>
</tr>
</tbody>
</table>

Note: Data are presented as median (25th to 75th percentile) unless otherwise indicated. HPFS, Health Professionals Follow-up Study; NHS, Nurses’ Health Study; BMI, body mass index.

Table 2. Urinary calcium as a fraction of calcium intake for each cohort

<table>
<thead>
<tr>
<th>Stone Formers</th>
<th>Nonstone Formers</th>
<th>≥ Cohort Median</th>
<th>&lt; Cohort Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPFS (n = 1037)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urinary Ca²⁺ (mg/d)</td>
<td>194⁴</td>
<td>156</td>
<td>255⁵</td>
</tr>
<tr>
<td>urinary/dietary Ca²⁺ intake</td>
<td>27%⁴</td>
<td>19%</td>
<td>36%⁵</td>
</tr>
<tr>
<td>urinary/total Ca²⁺ intake</td>
<td>22%⁴</td>
<td>16%</td>
<td>31%⁵</td>
</tr>
<tr>
<td>NHS I (n = 1246)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urinary Ca²⁺ (mg/d)</td>
<td>188⁵</td>
<td>170</td>
<td>252⁶</td>
</tr>
<tr>
<td>urinary/dietary Ca²⁺ intake</td>
<td>25%⁵</td>
<td>21%</td>
<td>38%⁶</td>
</tr>
<tr>
<td>urinary/total Ca²⁺ intake</td>
<td>16%⁵</td>
<td>12%</td>
<td>22%⁶</td>
</tr>
<tr>
<td>NHS II (n = 1085)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urinary Ca²⁺ (mg/d)</td>
<td>204⁴</td>
<td>171</td>
<td>262⁵</td>
</tr>
<tr>
<td>urinary/dietary Ca²⁺ intake</td>
<td>25%⁴</td>
<td>18%</td>
<td>33%⁵</td>
</tr>
<tr>
<td>urinary/total Ca²⁺ intake</td>
<td>18%⁴</td>
<td>13%</td>
<td>22%⁵</td>
</tr>
</tbody>
</table>

Values are medians. Urinary/dietary Ca²⁺ values are calculated only in participants not taking calcium supplements (HPFS, n = 538; NHS I, n = 386; and NHS II, n = 398). ⁴P values <0.01 comparing stone formers to non-stone formers. ⁵P values <0.05 comparing stone formers to non-stone formers. ⁶P values <0.01 comparing high to low urinary Ca²⁺.
SF older women (P values ≤0.01). Urinary calcium as a fraction of intake was higher in participants with urinary calcium above the cohort specific median and was lower in participants taking calcium supplements. Differences between SF and NSF and between calcium supplement users and nonsupplement users remained after adjusting for age, hypertension, diabetes, weight, and 24-h urinary factors.

Because the relations between each demographic, dietary, and urinary factor and urinary calcium were similar in each cohort and in SF and NSF, we combined all participants in the linear regression analyses. Associations between body size, hypertension, and urinary calcium in these study populations were reported previously (24,25). Age, thiazide use, and history of gout were independently and inversely associated with urinary calcium. After multivariate adjustment, every five-year increase in age was associated with a 6 mg/d (95% CI 4 to 9 mg/d) decrease in urinary calcium. Participants taking thiazide diuretics excreted 25 mg/d (17 to 34) less urinary calcium than those not taking thiazides. Participants with a history of gout excreted 26 mg/d (11 to 40) less urinary calcium than those without gout. Men with a family history of nephrolithiasis excreted 17 mg/d (3 to 30) more, and women with a family history excreted 19 mg/d (7 to 32) more urinary calcium than individuals without a family history. Diabetes mellitus, smoking, season of urine collection, menopause, postmenopausal hormone use, oral contraceptive use, and other individual medications were not associated with urinary calcium.

Multivariate-adjusted differences in 24-h urinary calcium excretion by specific dietary and urinary factors are displayed in Table 3. In nonsupplement users, participants in the highest quartile of dietary calcium excreted 11 mg/d (−2 to 24; P trend = 0.05) more urinary calcium than those in the lowest. Participants in the highest quartiles of total calcium intake (including supplements) and caffeine excreted 18 mg/d (10 to 27; P trend = 0.01) and 10 mg/d (2 to 18; P trend = 0.004) more urinary calcium, respectively, than participants in the lowest quartiles. Higher levels of urinary magnesium, sodium, sulfate, citrate, phosphorus, and urinary volume all were independently associated with higher urinary calcium. Compared with participants in the lowest quartile of each urinary factor, the multivariate-adjusted increases in urinary calcium for those in the highest quartile were 71 mg/d (62 to 81; P trend <0.001) for urinary magnesium, 37 mg/d (27 to 47; P trend <0.001) for urinary sodium, 44 mg/d (33 to 55; P trend <0.001) for urinary sulfate, 61 mg/d (51 to 70; P trend <0.001) for urinary citrate, 37 mg/d (26 to 48; P trend <0.001) for urinary phosphorus, and 24 mg/d (14 to 33; P trend <0.001) for urinary volume. Participants in the highest quartile of urinary potassium excreted 49 mg/d (39 to 59; P trend <0.001) less urinary calcium. We previously reported the inverse association between urinary oxalate and urinary calcium (26).

We also examined factors as continuous variables if associations with urinary calcium appeared linear. After multivariate adjustment, for every 50 mg/d increase in urinary magnesium, 100 mEq/d increase in urinary sodium, 10 mmol/d increase in urinary sulfate, 100 mg/d increase in urinary citrate, and 100 mg/d increase in urinary phosphorus, urinary calcium increased by 33 mg/d, 23 mg/d, 31 mg/d, 8 mg/d, and 7 mg/d, respectively (P values <0.001). For every 20 mEq/d increase in urinary potassium, urinary calcium decreased by 17 mg/d (P < 0.001).

The intakes of total carbohydrate, sucrose, fructose, n-3 fatty acids, n-6 fatty acids, phytate, vitamin K, vitamin A, vitamin B12, vitamin B6, folic acid, copper, and zinc were not associated with urinary calcium. Urinary factors not associated with urinary calcium after multivariate adjustment included pH, uric acid, and creatinine. We observed similar relations with urinary calcium among participants who submitted two 24-h urine collections.

**Discussion**

We identified a wide variety of nondietary and dietary factors that impacted urinary calcium excretion in our study population. Nondietary factors such as older age and history of gout were associated independently with lower urinary calcium. The lower amount of urinary calcium in older participants may be secondary to decreases in calcium absorption, perhaps from intestinal resistance to 1,25-dihydroxyvitamin D (27). We are unaware of previous studies that specifically examined the effect of gout, independent of diet and body size, on urinary calcium excretion. Previously, we reported the lack of consistent, independent associations between hypertension, body size, and urinary calcium in these cohorts (24,25).

In study participants with and without a history of kidney stones, the magnitude of the association between calcium intake and urinary calcium was small. Although this may in part reflect the high rates of vitamin D insufficiency/deficiency in these cohorts, (28,29) it is also possible that our data underscore the nonlinearity of the relation between calcium intake and urinary calcium. Because previous studies reporting a “plateau effect” for calcium ingestion and urinary calcium compared only extreme values of calcium intake, the shape of the calcium intake urinary calcium curve at typical levels of intake is incompletely defined. For example, in a study of 13 healthy volunteers on controlled diets, Pak found that a calcium intake of 198 mg/d resulted in urinary calcium of 138 mg/d (an intestinal calcium absorption of 70%, assuming calcium balance), whereas a calcium intake of 1878 mg/d resulted in urinary calcium excretion of 202 mg/d (an intestinal calcium absorption of 11%, assuming calcium balance) (2). Overall, our data suggest that for free-living individuals consuming typical diets, even substantial reductions in calcium intake would not, on average, result in large reductions in urinary calcium. Given these findings, it is not surprising that lower calcium intake in these cohorts is not associated with reduced stone risk (30–33).

The greater impact of other factors relative to calcium intake on urinary calcium is illustrated by the following example. After multivariate adjustment, study participants in the fourth quartile of dietary calcium excreted 6 mg/d more urinary calcium than participants in the second quartile (Table 3). In theory, this suggests that a typical individual in the highest quartile of dietary calcium would need to reduce calcium intake by 50%, on average, to decrease urinary calcium by 6 mg/d. By contrast, the point estimate for change in urinary
Table 3. Multivariate-adjusted differences in 24-h urinary calcium excretion<sup>a</sup>

<table>
<thead>
<tr>
<th>Component</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>95% CI</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium intake</td>
<td>Referent</td>
<td>8</td>
<td>14</td>
<td>18</td>
<td>(−1 to 16)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dietary calcium intake</td>
<td>Referent</td>
<td>5</td>
<td>9</td>
<td>11</td>
<td>(−7 to 17)</td>
<td>0.05</td>
</tr>
<tr>
<td>Caffeine intake</td>
<td>Referent</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>(−8 to 8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Urinary magnesium</td>
<td>Referent</td>
<td>29</td>
<td>43</td>
<td>71</td>
<td>(21 to 37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary sodium</td>
<td>Referent</td>
<td>15</td>
<td>20</td>
<td>37</td>
<td>(6 to 23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary sulfate</td>
<td>Referent</td>
<td>11</td>
<td>22</td>
<td>44</td>
<td>(2 to 20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary citrate</td>
<td>Referent</td>
<td>21</td>
<td>34</td>
<td>61</td>
<td>(13 to 30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary phosphorus</td>
<td>Referent</td>
<td>6</td>
<td>19</td>
<td>37</td>
<td>(−3 to 14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary volume</td>
<td>Referent</td>
<td>17</td>
<td>21</td>
<td>24</td>
<td>(8 to 25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary potassium</td>
<td>Referent</td>
<td>−20</td>
<td>−30</td>
<td>−49</td>
<td>(−11 to −28)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age, kidney stone history, cohort, weight, calcium intake, caffeine intake, thiazide use, history of gout, 24-h urinary excretion of creatinine, and other urinary factors. See Table 1 for median and 25<sup>th</sup>-75<sup>th</sup> percentile values for each factor.
calcium by continuous unit of urinary sodium (Results section) and the distributions of urinary sodium in our study (Table 1) suggest that a typical individual in the 75th percentile of dietary sodium would need to reduce sodium intake between 12 and 15% (depending on cohort) to decrease urinary calcium excretion by the same amount (6 mg/d).

Urinary calcium as a fraction of calcium intake was higher in SF, higher in participants with urinary calcium above the cohort specific median, and lower in participants taking calcium supplements (Table 2). These relations were independent of age, body size, and other dietary factors. Although we did not assess intestinal calcium absorption, if we assume study participants were in calcium balance or in negative calcium balance at the time of urine collection, we can infer that intestinal absorption of calcium and/or net loss of total body calcium was greater in SF and individuals with higher urinary calcium excretion. The lower values of urinary calcium as a fraction of calcium intake in supplement users may reflect nonlinearity of intestinal calcium absorption or may reflect decreased bioavailability of supplemental calcium compared with dietary calcium. We did not have data on the timing of calcium supplement ingestion (i.e., with or between meals).

Higher urinary magnesium and lower urinary potassium were associated with markedly higher levels of urinary calcium. Although previous studies reported that magnesium administration and potassium deprivation increase urinary calcium, (4–6) the amounts of magnesium and potassium in those studies were not representative of typical diets. For example, in their study of magnesium and urine composition, Chesley and Tepper parenterally administered between 642 and 1284 mg of elemental magnesium over about 3 h (4). In a more recent study reporting associations between orally administered magnesium salts and increases in urinary calcium in participants from 17 metabolic trials, the magnesium dose ranged from 255 mg/d to 1000 mg/d (34). Potential mechanisms underly magnesium-mediated urinary calcium losses include magnesium inhibition of renal tubular calcium uptake by TRPV5 (34). Because bone represents a major site for total body stores of magnesium, calcium, and phosphorus, it is also possible that the positive association between the urinary excretions of these three minerals is an epiphenomenon related to increased bone resorption. Although Lemann reported that complete elimination of potassium from the diet of healthy volunteers resulted in a 25% increase in urinary calcium, (6) additional studies attempting to quantify the effect of more moderate potassium restriction have not been performed.

Our results underscore the complex role of acid-base status in urinary calcium and citrate excretion. Animal protein intake represents an acid load and increases urinary calcium, (35–37) whereas alkali administration decreases it (9,10). Thus, the positive association between urinary sulfate, a marker for animal protein intake, and urinary calcium was expected. However, we also observed a marked independent association between higher urinary citrate and higher urinary calcium. Because acidosis decreases and alkali administration increases urinary citrate, it would be reasonable to expect, a priori, an inverse association between urinary citrate and calcium. We cannot explain the positive relation between urinary citrate and calcium but speculate that factors regulating calcium homeostasis, such as vitamin D, also might modulate urinary citrate (11). It is also possible that filtered citrate may inhibit tubular calcium re-absorption, perhaps by forming calcium complexes. Finally, we did not observe an association between urinary pH and calcium after adjusting for citrate. Previous studies reporting associations between urinary pH and calcium did not account for differences in urinary citrate (34).

As expected from previous reports, (38,39) we observed a positive relation between sodium intake (as determined by 24-h urinary sodium) and urinary calcium excretion. Because the associations between urinary sodium and urinary calcium in our study were similar in individuals with and without a history of kidney stones, our results are not consistent with the hypothesis that SF have an exaggerated calciuric response to sodium (40).

Urinary volume and caffeine intake were associated with higher urinary calcium. The presence of the calcium-sensing receptor in the lumen of the MCD and in vitro animal studies reporting reductions of MCD water permeability with higher calcium concentrations (7) led to the hypothesis that higher urinary calcium diminishes urinary concentration as an adaptation to prevent calcium stone disease (41). Although some authorities maintain that calcium is unlikely to substantially impact urinary concentration in humans, (8) our data are consistent with the hypothesis that calcium plays a role in determining urinary volume. Although previous reports suggest caffeine increases urinary calcium losses, (42) we found the impact of caffeine to be relatively small.

The limitations of our study deserve mention. First, we studied 24-h urinary calcium excretion. Therefore, we could not identify factors influencing postprandial increases in urinary calcium, which may be important for kidney stone formation (43). Second, we ascertained long-term dietary patterns with the FFQ, whereas 24-h urine composition is likely to reflect short-term dietary intake. Thus, it is possible that some relations between specific dietary exposures and 24-h urinary calcium excretion are of greater magnitude than we describe. However, we used urinary factors (such as urinary sodium and potassium) to estimate dietary intake when possible. Finally, this study did not include urine collections from nonwhite participants.

Conclusions
Our study identified a large number of demographic, dietary, and urinary factors related to 24-h urinary calcium excretion. We observed previously unappreciated independent associations for age and gout. Compared with a wide array of other modifiable factors, higher calcium intakes in free-living individuals are associated with only small increases in urinary calcium. Our data highlight the need to further define the relation between calcium intake and urinary calcium and also suggest additional studies of calcium supplement bioavailability. Intestinal absorption of dietary calcium and/or negative calcium balance appears to be greater in SF than in NSF. Finally, our study provides clear impetus for additional research.
delineating the roles of magnesium and potassium in calcium handling and the effects of calcium homeostasis on citrate and water. Further investigation of factors with a large impact on urinary calcium may lead to novel approaches to prevent nephrolithiasis.

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Disclosures
None.

References


