Kidney Function Predicts the Rate of Bone Loss in Older Individuals: The Cardiovascular Health Study

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Background. Results of cross-sectional analyses of the association of kidney function with bone mineral density (BMD) have been conflicting. We examined the association of cystatin-C, a new marker of kidney function that is unrelated to lean mass, with initial and follow-up BMD, in an ancillary study of the Cardiovascular Health Study, a population-based cohort of individuals ≥65 years old.

Methods. Two years after measurement of cystatin-C and other covariates, the first BMD was measured in Pittsburgh, Pennsylvania and Davis, California, by using dual energy x-ray absorptiometry. Follow-up BMD was measured in Pittsburgh 4 years later. Associations of cystatin-C with initial BMD and the change in BMD (%/y) at the hip were examined with linear regression. Analyses were conducted separately for men and women.

Results. In 1519 participants who had cystatin-C and initial BMD assessed, 614 had follow-up BMD. The percent annual change in BMD at the total hip by cystatin-C quartiles was 0.24, 0.13, 0.40, and 0.66%/y (first to fourth quartile) in women and 0.02, 0.30, 0.18, and 0.94%/y in men. After adjusting for potential confounders, cystatin-C was marginally associated with initial BMD in men but not women. Cystatin-C was associated with bone loss in men; after adjustment for weight loss, cystatin-C was not associated with bone loss in women.

Conclusion. Kidney dysfunction, as assessed by cystatin-C, is associated with a more rapid loss of BMD at the hip, especially in men. Further studies are needed to confirm these findings and to determine whether this loss leads to an elevated risk of fracture.

Patients with end-stage renal disease (ESRD) have low bone mineral density (BMD), which may lead to an increased risk of hip fractures (1). Whether milder decrements in kidney function lead to lower BMD, however, is unclear. In one matched case–control study (matched on age, gender, and weight), individuals with kidney disease had lower BMD (2). In contrast, a study using data from the Third National Health and Nutrition Examination Survey (NHANES III) found that individuals with worse kidney function had lower femoral neck BMD; however, after adjusting for age, gender, and weight, kidney function was no longer an independent predictor (3).

Conflicting results may be due to correlations between creatinine and body mass. Creatinine levels are determined in part by muscle mass, which is also associated with age, gender, and weight. Although the use of estimated glomerular filtration rate (eGFR) can improve detection of kidney disease, it is still based on serum creatinine and can be affected by changes in muscle mass. A measure of kidney function that is not related to muscle mass may improve the assessment of whether mild-to-moderate kidney impairment is associated with lower BMD. Cystatin-C is a cysteine proteinase inhibitor that is produced in most nucleated cells (4). Cystatin-C is freely filtered by the glomerulus, reabsorbed, and metabolized by the proximal tubule. Prior studies have shown it to be a better estimate of GFR in the elderly population than are estimates based on serum creatinine (5). Serum cystatin-C is not influenced by body mass, age, or gender (6). We used data from the Cardiovascular Health Study (CHS), a prospective, longitudinal study of older community-dwelling adults, to test the hypothesis that kidney function was associated with low BMD and greater rates of bone loss.

Methods

Participants

The study methods for CHS have previously been described (7). In brief, CHS participants were recruited from Medicare eligibility lists at four locations: Forsyth
County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Individuals were invited to participate if they were community-dwelling adults, 65 years old or older, expecting to remain in the area for the next 3 years, were not receiving active treatment for cancer, and were able to give informed consent without a proxy. The initial cohort was recruited in 1989–1990, and a second cohort of 687 African Americans was recruited in 1992–1993, resulting in 5888 individuals.

Two sites (Pittsburgh and Sacramento County) measured BMD during 1995–1996 (1566 complete data sets). In Pittsburgh, follow-up BMD was measured in 1998–1999 (a mean of 3.98 ± 0.11 years between examinations).

**BMD**

BMD for total hip, femoral neck, and trochanter was measured by dual-energy x-ray absorptiometry (DXA; QDR 2000 or 2000+; Hologic, Inc., Bedford, MA). For each participant, the same scanner was used at each visit, and all scans were completed using the array beam mode. Standardized positioning and utilization of QDR software was based on the manufacturer’s recommended protocol. Scans were read blindly at the University of California, San Francisco reading center with Hologic software version 7.10. Data from the DXA measurements were monitored for quality control by the University of California, San Francisco. The coefficient of variation (CV) for the total hip BMD was <0.75%. Annualized percentage change in BMD at each site was calculated by the following formula: \[ \frac{(\text{Follow-up BMD (g/cm}^2) - \text{initial BMD (g/cm}^2)/\text{initial BMD})/\text{duration of follow-up}}{100} \] and was expressed as percent change per year (8).

**Kidney Function**

Detailed methods for blood drawing, quality assurance, and assay performances have been described previously (9). Cystatin-C was measured using a BN1 nephelometer (Dade Behring Inc., Deerfield, IL) that utilized a particle enhanced immunonephelometric assay (N Latex Cystatin-C) (10). The assay range is 0.195–7.330 mg/L, with the reference range for young, healthy individuals reported as 0.53–0.95 mg/L. Intra-assay CVs range from 2.0% to 2.8%, and inter-assay CVs range from 2.3% to 3.1%.

Serum creatinine was measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY), a colorimetric method. We estimated GFR using the four-variable version of the Modification of Diet in Renal Disease equation: \[ \text{GFR} = 186.3 \times (\text{serum creatinine}^{1.154} \times \text{age}^{-0.203} \times 1.212 \times 0.742) \] for women (11). Chronic kidney disease was defined as a GFR < 60 ml/min/1.73 m².

**Covariates**

Covariates were selected if they were felt to be related to kidney function and BMD. Total mass, lean body mass, and fat mass were calculated by the QDR software using whole-body DXA data. Lean mass values exclude bone mineral content. Diabetes was defined as the use of insulin, oral hypoglycemic agents, or fasting glucose level ≥ 126 mg/dL. Blood pressure was measured in the sitting position in the right arm, after a 5-minute rest, using an appropriately sized cuff. Hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of antihypertensive medications. Race was categorized as white or non-white. The non-white category includes the following: black (n = 303), American Indian/Alaskan Native (n = 1), Asian/Pacific Islander (n = 2), and other (n = 3). Body weight was measured using a calibrated balance beam scale. Height was measured with a wall-mounted stadiometer. Smoking status was defined as current smoking. Physical activity was calculated using the Minnesota Leisure Time Activities questionnaire (12) as kilocalories from activities, including housework and exercise.

Medication use was defined as prescription use of thiazide diuretics, oral corticosteroids, and (for women) hormone use, based on review of prescription bottle labels by interviewers. Medication use, creatinine, cystatin-C, weight, height, diabetes, smoking status, and physical activity were evaluated at the 1993–1994 visit.

**Statistical Analysis**

Test of trend across cystatin-C quartiles was performed using linear regression for continuous variables and the Cochran–Armitage trend test for categorical variables. Linear regression was used to assess the association of kidney function with initial and percent change in BMD at the total hip, trochanter, and femoral neck. All analyses were stratified by gender. To account for regression to the mean, analyses of change in BMD accounted for initial BMD values, although excluding initial BMD did not affect the results. The initial models adjusted for age, race, total lean body mass, and total fat mass. Subsequent models adjusted for age, race, initial BMD at site, diabetes, total lean mass, total fat mass, change in total body mass, physical activity, smoking status, use of thiazides, use of oral steroids, and use of estrogen (women). SAS version 8.1 (SAS Institute, Cary, NC) was used for the analyses. Our primary analyses examined the association of cystatin-C with BMD and change in BMD. Secondary analyses examined serum creatinine and chronic kidney disease (CKD) as markers of kidney function.

**RESULTS**

Of the 1566 individuals with full DXA data sets, 1519 had both cystatin-C and initial BMD available and 614 had a second measure of BMD. Overall, 51% were women and 81% were white. The mean initial BMD for the total hip was 0.94 ± 0.17 g/cm² for men and 0.75 ± 0.15 g/cm² for women. The mean eGFR was 67.2 ml/min/1.73 m². The mean serum creatinine level was 1.22 ± 0.25 mg/dL in men and 0.96 ± 0.23 mg/dL in women. The mean cystatin-C level was 1.11 ± 0.25 mg/L in men and 1.04 ± 0.27 mg/L in women. Participant characteristics by cystatin-C quartile are shown in Table 1. Individuals with higher cystatin-C levels were older, had higher fat mass, were more likely to be hypertensive, and more likely to be white. Women with higher cystatin-C levels had lower levels of physical activity, were more likely to be on thiazide diuretics, but less likely to be on estrogens. When we evaluated those participants who had BMD measurements at...
Table 1. Participant Characteristics, by Gender and Cystatin-C Quartile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Quartile 1 &lt;0.9 mg/L</th>
<th>Quartile 2 0.91–1.01 mg/L</th>
<th>Quartile 3 1.02–1.17 mg/L</th>
<th>Quartile 4 ≥1.18 mg/L</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>n = 885</td>
<td>n = 257</td>
<td>n = 218</td>
<td>n = 214</td>
<td>n = 196</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>75.9 ± 4.5</td>
<td>74.7 ± 3.8</td>
<td>75.0 ± 4.1</td>
<td>76.1 ± 4.3</td>
<td>78.4 ± 5.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race, % white</td>
<td>89.0</td>
<td>62.5</td>
<td>83.7</td>
<td>53.4</td>
<td>82.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.5</td>
<td>10.7</td>
<td>9.3</td>
<td>13.6</td>
<td>12.9</td>
<td>.28</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>9.2</td>
<td>9.3</td>
<td>10.0</td>
<td>9.7</td>
<td>7.9</td>
<td>.67</td>
</tr>
<tr>
<td>Estrogen use, %</td>
<td>16.2</td>
<td>12.6</td>
<td>17.4</td>
<td>9.0</td>
<td>5.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thiazide use, %</td>
<td>16.0</td>
<td>13.4</td>
<td>8.7</td>
<td>20.2</td>
<td>23.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral steroid use, %</td>
<td>2.0</td>
<td>0.9</td>
<td>0</td>
<td>3.4</td>
<td>5.2</td>
<td>.06</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 ± 5.0</td>
<td>26.0 ± 4.6</td>
<td>26.6 ± 4.5</td>
<td>27.9 ± 4.9</td>
<td>28.3 ± 6.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight, lbs</td>
<td>150.4 ± 30.0</td>
<td>143.4 ± 26.4</td>
<td>149.1 ± 27.4</td>
<td>155.2 ± 29.3</td>
<td>160.6 ± 35.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity in kcal, median (IQ range)</td>
<td>810</td>
<td>945</td>
<td>980</td>
<td>807</td>
<td>536</td>
<td></td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>29.3 ± 10.2</td>
<td>27.3 ± 8.6</td>
<td>28.7 ± 9.0</td>
<td>31.1 ± 10.0</td>
<td>30.9 ± 11.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>37.3 ± 5.4</td>
<td>37.0 ± 5.4</td>
<td>37.4 ± 5.4</td>
<td>37.8 ± 5.1</td>
<td>37.2 ± 5.9</td>
<td>.55</td>
</tr>
<tr>
<td>Change in total mass, kg/y, median (IQ range)</td>
<td>−0.23</td>
<td>−0.15</td>
<td>−0.33</td>
<td>−0.14</td>
<td>−0.59</td>
<td>.05</td>
</tr>
<tr>
<td>Creatinine, mg/dL (range)</td>
<td>0.96 ± 0.23</td>
<td>0.83 ± 0.12</td>
<td>0.89 ± 0.13</td>
<td>0.98 ± 0.13</td>
<td>1.17 ± 0.35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m² (range)</td>
<td>67.1 ± 15.7</td>
<td>78.4 ± 15.2</td>
<td>70.4 ± 11.7</td>
<td>62.8 ± 9.4</td>
<td>53.3 ± 13.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total hip BMD (baseline), g/cm²</td>
<td>0.75 ± 0.14</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.14</td>
<td>0.76 ± 0.14</td>
<td>0.74 ± 0.14</td>
<td>.25</td>
</tr>
<tr>
<td>Change in total hip BMD, %/y</td>
<td>−0.34 ± 0.12</td>
<td>−0.24 ± 0.19</td>
<td>−0.13 ± 0.11</td>
<td>−0.40 ± 0.15</td>
<td>−0.66 ± 0.12</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>n = 634</td>
<td>n = 104</td>
<td>n = 153</td>
<td>n = 179</td>
<td>n = 198</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>76.8 ± 5.0</td>
<td>74.5 ± 4.0</td>
<td>76.3 ± 4.5</td>
<td>76.9 ± 5.0</td>
<td>78.2 ± 5.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race, % white</td>
<td>82.7</td>
<td>59.6</td>
<td>79.1</td>
<td>89.8</td>
<td>92.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>16.7</td>
<td>17.3</td>
<td>15.8</td>
<td>14.1</td>
<td>19.3</td>
<td>.62</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>7.9</td>
<td>13.0</td>
<td>6.0</td>
<td>5.7</td>
<td>8.4</td>
<td>.44</td>
</tr>
<tr>
<td>Thiazide use, %</td>
<td>10.6</td>
<td>11.5</td>
<td>7.2</td>
<td>7.8</td>
<td>15.2</td>
<td>.14</td>
</tr>
<tr>
<td>Oral steroid use, %</td>
<td>2.8</td>
<td>1.9</td>
<td>1.3</td>
<td>3.4</td>
<td>4.0</td>
<td>.14</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 ± 3.6</td>
<td>26.4 ± 3.5</td>
<td>26.5 ± 3.6</td>
<td>26.6 ± 3.4</td>
<td>26.9 ± 3.9</td>
<td>.63</td>
</tr>
<tr>
<td>Weight, lbs</td>
<td>174.2 ± 25.8</td>
<td>172.8 ± 25.1</td>
<td>174.4 ± 25.5</td>
<td>176.1 ± 24.3</td>
<td>173.0 ± 27.8</td>
<td>.81</td>
</tr>
<tr>
<td>Physical activity in kcal, median (IQ range)</td>
<td>1275</td>
<td>1048</td>
<td>1568</td>
<td>1538</td>
<td>958</td>
<td>.11</td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>22.9 ± 8.1</td>
<td>21.5 ± 8.0</td>
<td>22.4 ± 7.8</td>
<td>23.7 ± 7.9</td>
<td>23.5 ± 8.5</td>
<td>.02</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>54.1 ± 6.8</td>
<td>55.1 ± 5.9</td>
<td>54.8 ± 6.6</td>
<td>54.5 ± 6.5</td>
<td>52.7 ± 7.5</td>
<td>.003</td>
</tr>
<tr>
<td>Change in total mass, kg/y, median (IQ range)</td>
<td>−0.20</td>
<td>−0.16</td>
<td>−0.09</td>
<td>−0.21</td>
<td>−0.49</td>
<td>.008</td>
</tr>
<tr>
<td>Creatinine, mg/dL (range)</td>
<td>0.71 ± 0.3</td>
<td>0.78 ± 0.12</td>
<td>0.79 ± 0.36</td>
<td>0.81 ± 0.31</td>
<td>1.15 ± 0.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m² (range)</td>
<td>67.3 ± 15.1</td>
<td>83.8 ± 15.6</td>
<td>72.2 ± 10.4</td>
<td>66.8 ± 9.3</td>
<td>55.4 ± 11.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total hip BMD (baseline), g/cm²</td>
<td>0.94 ± 0.17</td>
<td>0.97 ± 0.18</td>
<td>0.95 ± 0.15</td>
<td>0.95 ± 0.16</td>
<td>0.92 ± 0.17</td>
<td>.03</td>
</tr>
<tr>
<td>Change in total hip BMD, %/y</td>
<td>−0.37 ± 1.12</td>
<td>−0.02 ± 0.79</td>
<td>−0.30 ± 1.06</td>
<td>−0.18 ± 1.03</td>
<td>−0.94 ± 1.24</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Notes: *Test of trend across quartiles.
†Calculated only in participants with both initial and follow-up bone mineral density.
IQ = interquartile; eGFR = estimated glomerular filtration rate; BMD = bone mineral density.

initial but not follow-up visit, there were no differences in creatinine or cystatin-C for women; for men, there was no 0.23 versus difference in creatinine, but those men with follow-up BMD had somewhat lower cystatin-C levels: 1.07 ± 0.23 versus 1.13 ± 0.27 mg/L (p = .001).

In women, higher cystatin-C quartiles were not associated with initial BMD (p > .10 for test of linear trend at all sites). In men, higher cystatin-C quartiles were associated with lower BMD at the femoral trochanter (p = .008) and at the total hip (p = .03), but there was not a significant association at the femoral neck. The association of lower BMD at the trochanter in men remained after multivariate adjustment (Table 2). There was no association of CKD (low GFR) with initial BMD (Table 3). Similar results were seen when serum creatinine was used instead of cystatin-C or CKD (data not shown).

In contrast to the initial BMD results, cystatin-C was associated with a greater loss of bone over time (Table 2). This was true for both men and women, although the association of cystatin-C with loss of BMD was stronger in men. The association of cystatin-C with bone loss remained after adjustment for age, race, initial BMD, lean mass, and
fat mass (Table 2). Further adjustment did not appreciably affect the association of cystatin-C with bone loss in men. Among women, after adjustment, cystatin-C was not a significant predictor of bone loss (Table 2). As change in body weight might mediate the relationship between cystatin-C and loss of bone, the models were repeated without loss of total body mass as a variable. In these models, cystatin-C was a predictor of bone loss in women at the total hip (β = 0.15 ± 0.07%/y per standard deviation cystatin-C, p = .04) and at the femoral neck (β = 0.20 ± 0.08%/y per standard deviation cystatin-C, p = .02), but was not a significant predictor at the trochanter (β = 0.10 ± 0.09%/y per standard deviation cystatin-C, p = .27). In unadjusted models and models adjusted for age, race, gender, and body composition, CKD was associated with a significantly greater loss at the femoral neck in both men and women and in men was associated with greater loss at the trochanter (Table 3). With further adjustment, CKD was only associated with bone loss at the femoral neck in women. The creatinine results were similar to the results for CKD, and were weaker per standard deviation difference compared with cystatin-C.

**DISCUSSION**

To our knowledge, this is the first longitudinal community-based study to examine the association of kidney function with rate of bone loss. We found that higher cystatin-C levels were associated with greater bone loss at the hip. The loss increased across cystatin-C quartiles, and was apparent in individuals with mild-to-moderate kidney impairment. Notably, individuals in the highest cystatin-C quartile had a rate of bone loss that was twice as high as the rate in the placebo arms of treatment trials with bisphosphonates (13–15). The unadjusted results showed that cystatin-C predicted bone loss in both men and women, although after adjustment the results were stronger in men. We did not find that initial BMD was lower in individuals with kidney dysfunction. This finding is in contrast to that from the study by Hsu and colleagues (3), which used NHANES III data and found that individuals with decreased kidney function had lower BMD before adjustment for other cofactors. After adjustment for age, race, and gender they did not find a significant relationship. Differences in study population may have explained the difference in results. Our study was restricted to older individuals who had lower initial BMD than the NHANES III population had. Our study also showed that cystatin-C was a stronger predictor of bone loss than was serum creatinine. This may reflect detection of mild kidney impairment that is not detected by serum creatinine. Cystatin-C may be particularly useful in identifying individuals with low GFR but normal creatinine levels (5,16). Older individuals with higher levels of comorbidity and lower functional status often have decreased muscle mass, which leads to a decrease in serum creatinine and falsely elevated eGFR (17).

Our study also found that cystatin-C was a stronger predictor of bone loss in men than in women. As with women, the prevalence of osteoporosis increases with age in men, although the overall prevalence in men is lower.
(18). Our results are consistent with the observation that secondary causes of osteoporosis are more common in men (19). In women, postmenopausal bone loss may overwhelm the effect of mild kidney disease on BMD. In contrast, the effect of mild kidney dysfunction in men may help to explain low BMD measurements or fractures. The prevalence of osteoporosis in men increases over the age 70 (19,20); this increase could reflect declining kidney function.

Kidney disease can affect bone metabolism in a number of ways. With decreasing GFR, parathyroid hormone levels increase and 1,25 vitamin D levels decrease, leading to the development of secondary hyperparathyroidism (21,22). Individuals with kidney disease are also more likely to have risk factors associated with bone loss, e.g., diabetes, decreased physical activity, and increased cytokine levels (21–25). In our study, the association of cystatin-C with bone loss in women was weakened and became non-significant when weight loss was added to the models. This finding suggests that weight loss could be a mediator of bone loss in CKD. Weight loss has been found in other studies to be a predictor of bone loss and hip fracture in older adults (26,27). Mild kidney dysfunction may also be one of the explanations for why two recent studies found that homocysteine predicted hip fractures (28,29). Our study suggests that older individuals with mild-to-moderate kidney dysfunction may be at increased risk for hip fracture.

This study has a number of limitations. Our endpoint of change in BMD is a surrogate outcome, rather than an event such as hip fracture. Although cystatin-C has been shown to be a more accurate measure of kidney function, we do not have a direct measure of GFR. The gold standard is inulin clearance, but this is impractical for epidemiologic studies. We therefore cannot be sure whether the stronger results of cystatin-C with bone loss compared with CKD or creatinine reflect a more accurate determination of kidney function or are due to an association with an uncontrolled confounder. Cystatin-C was measured 2 years before the first DXA scan, and it is possible that kidney function changed during that period of time. We also do not have measures of potential mediators of the bone loss, e.g., calcium, phosphorus, vitamin D levels, or parathyroid hormone levels. Knowing which mediator is important has implications for prevention. Low 1,25 vitamin D levels or acidosis is readily treatable. Supplementation with 1,25 vitamin D has been shown to decrease the loss of BMD in persons with advanced CKD (30). Bisphosphonates can be used in individuals with mild-to-moderate renal insufficiency, but the prescribing information recommends avoiding use in individuals with a creatinine clearance <30–35 ml/min because of inadequate safety data (31).

**Summary**

We found that decreased kidney function is associated with a more rapid loss of BMD, especially in older men. Decreased kidney function rises with age and kidney disease is common (11). This finding suggests that the increased recognition of renal impairment could identify individuals at increased risk of bone loss. Further studies are needed to confirm our findings and to prevent accelerated bone loss in the setting of CKD.
ACKNOWLEDGMENTS

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A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

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