Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate homeostasis and when elevated increases cardiovascular disease and stroke risk and mortality. However, most studies of FGF23 have focused on those with chronic kidney disease (CKD). Less data are available from the general population, especially with respect to stroke. We previously reported elevated FGF23 increased stroke risk independent of CKD in the race/ethnically diverse community–based Northern Manhattan Study (NOMAS).7 The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study reported an association between FGF23 and cardioembolic stroke.8 We also reported that FGF23 was positively associated with carotid plaque presence and area, but FGF23’s role in subclinical cerebrovascular damage (SCVD), especially cerebral small vessel disease, is still unknown.9

Background and Purpose—Elevated fibroblast growth factor 23 (FGF23) regulates phosphate homeostasis and is linked with mortality, cardiovascular events, and stroke. However, the role of FGF23 as a risk factor for subclinical cerebrovascular damage is unclear.

Methods—We used multivariable linear and logistic regression to evaluate associations between FGF23, continuously and by quartiles, with white matter hyperintensity volume, expressed as percent intracranial volume (%ICV), and subclinical brain infarction (SBI) in a community-based stroke-free sample.

Results—There were 1170 stroke-free Northern Manhattan Study (NOMAS) participants with FGF23 levels and quantitative magnetic resonance imaging data on white matter hyperintensity volume and SBI. Participants with FGF23 levels in the top quartile (range=85–1425 RU/mL) had greater white matter hyperintensity volume (β=0.19 %ICV; 95% CI, 0.04–0.33 %ICV; P=0.01) compared with those in the lowest quartile (range=15–49 RU/mL), adjusted for demographics, vascular risk factors, and estimated glomerular filtration rate. These findings remained significant in those without evidence of chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m²). Elevated FGF23 was not associated with SBI overall after adjusting for demographic factors and estimated glomerular filtration rate, but sex modified the effect of FGF23 on odds of SBI (P for interaction=0.03). FGF23 was associated with significantly greater odds of SBI only in men (odds ratio, 1.7; 95% CI, 1.1–2.7; P=0.03) after full adjustment.

Conclusions—These cross-sectional community-based data from a diverse urban sample show an association between elevated FGF23 and small vessel disease and magnetic resonance imaging–defined brain infarction in men, independent of chronic kidney disease. Data on elevated FGF23 and subclinical cerebrovascular damage progression are needed. (Stroke. 2016;47:923-928. DOI: 10.1161/STROKEAHA.115.012379.)

Key Words: chronic kidney disease ■ cohort studies ■ fibroblast growth factor 23 ■ leukoaraiosis ■ magnetic resonance imaging (MRI)
Our previous finding that elevated FGF23 was associated with hemorrhagic stroke risk in the NOMAS sample suggested that FGF23 may be a risk factor for cerebral small vessel disease, but we did not find an association with incident lacunar stroke. White matter hyperintensities (WMH) and subclinical brain infarctions (SBI) are subclinical markers of cerebral small vessel disease that have been associated with traditional vascular risk factors and increased stroke risk. Both WMH and SBI are common, and identifying novel risk factors for these lesions is a priority. We performed the current study to test the hypothesis that elevated FGF23 is associated with a greater burden of SCVD.

Methods

Cohort

The NOMAS included 3298 participants at baseline who were identified through random digit dialing using dual-frame sampling to identify published and nonpublished numbers. People were eligible if they were never diagnosed with stroke, were >40 years of age, and were residents of Northern Manhattan for >3 months in a household with a telephone. Participants were recruited for in-person assessments (overall response rate of 68%) and underwent complete neurological examinations between 1993 and 2001.

Baseline Evaluation

Trained bilingual research assistants and study physicians collected demographic, medical, and laboratory data at enrollment using standardized data collection techniques and risk factor questions based on the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Study definitions for race/ethnicity, diabetes mellitus, cardiac disease, and other risk factors have been previously described. Subjects were contacted annually via telephone after enrollment to gather information regarding illnesses, hospitalizations, vital status, and cardiovascular events. Race-ethnicity was based on self-identification. Smoking status was categorized as never (reference), past, or current. Body mass index was calculated as kg/m². Hypertension was defined as blood pressures ≥140/90 mmHg (based on the average of 2 measurements with a mercury sphygmomanometer), a self-reported history of hypertension, or antihypertensive medication use. Diabetes mellitus was defined by self-reported history, use of hypoglycemic medications, or fasting blood sugar ≥126 mg/dL. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL or use of lipid-lowering medication.

MRI Substudy

Between 2003 and 2008, NOMAS participants were recruited for MRI sequentially during annual telephone follow-up if they met the following criteria: (1) still clinically stroke-free; (2) ≥50 years of age; and (3) no contraindications to MRI. To reach the planned sample size (N=1300), an additional 199 stroke-free household members of the original NOMAS participants, meeting the above criteria, were added to the prospective cohort from 2006 to 2008. The Institutional Review Board approved the study, and all participants provided written informed consent.

Imaging was performed on a 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Columbia University Medical Center. Quantification of WMH has been previously described. Briefly, we removed nonbrain elements manually using operator-guided tracing of the dura matter within the cranial vault, including the middle cranial fossa but above the posterior fossa and cerebellum, to define the total intracranial volume. Segmentation of WMH required the identification of brain matter, removal of image intensity nonuniformities, and modeling of Gaussian probability functions to determine the segmentation threshold. A single Gaussian distribution was then fitted to image data, and a segmentation threshold for WMH volume (WMHV) was determined a priori as 3.5 standard deviations (SDs) in pixel intensity above the mean of the fitted distribution of brain parenchyma, with morphometric erosion of 2 exterior image pixels to remove the effects of partial volume cerebrospinal fluid pixels on WMH determination. We used a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation). All analyses were performed blind to participant identifying or risk factor data.

Determination of the presence or absence of SBIs has been previously published. A superimposed image of the subtraction, fluid-attenuated inversion recovery, and T2-weighted images at 3x magnified view was used to assist in the interpretation of lesion characteristics. Vessels were indicated via signal void, best seen on T2-weighted images. Other imaging characteristics required for interpretation included cerebrospinal fluid density on the subtraction image and, if stroke was in the basal ganglia area, distinct separation from the circle of Willis and perivascular spaces. Infarcts were counted for total number and characterized by location (cortical, subcortical, and specific region) and size (small: <1 cm or large: >1 cm). Two raters were used to determine the presence of infarcts, and agreement among them has been generally good (previously published kappa values: 0.73–0.90).

Statistical Analysis

Known risk factors for SCVD and potential confounders of the association between FGF23 and MRI markers of SCVD were selected as covariates for multivariable analysis. We defined estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula as: GFR = 186.3×(serum Cr)−1.154×age−0.203×(0.742 if female)×(1.21 if African American). We used multivariable linear and logistic regression to evaluate associations between FGF23, continuously (natural log transformed) and by quartiles, with WMHV, expressed as percent intracranial volume, and SBI. First we examined the unadjusted association between FGF23 and both WMHV and SBI (model 1). Next we fit sequential models adjusting for age, sex, race/ethnicity, and eGFR (model 2), then smoking, body mass index, hypertension, diabetes mellitus, and hypercholesterolemia (model 3). We also conducted several sensitivity analyses: (1) further adjusting for phosphate and parathyroid hormone levels, (2) excluding those with evidence of CKD, and (3) excluding those with evidence of primary hyperparathyroidism. We tested for effect modifiers by including interaction terms for each covariate in the full model and did stratified analyses for significant interactions. Analyses were conducted using SAS (version 9.4, SAS Institute, NC).

Results

There were 1170 stroke-free NOMAS participants with FGF23 levels and quantitative MRI data on WMHV and SBI (Table 1). From the original cohort, 1150 participants had strokes or died before MRI and 1057 did not participate in the substudy (578 refused, 329 ineligible or other, and 150 lost to follow-up). There were minor differences comparing MRI substudy participants in the study sample to those lacking blood markers (Table 1 in the online-only Data Supplement).

We found a positive association between FGF23 and WMHV. Each unit increase in natural log-transformed FGF23 was associated with significantly greater WMHV, with sociodemographic factors and eGFR explaining a substantial proportion of the variance. Still, the association remained statistically significant in models 2 and 3 (Table 2). Dividing FGF23 levels into quartiles, we found a linear increase in WMHV across FGF23 quartiles (P for trend=0.02) even after adjusting for sociodemographic and vascular risk factors as well as eGFR, but most of the effect was driven by people in the upper FGF23 quartile (Table 2).
Also, eGFR was not significantly associated with WMHV with FGF23 in the model. To further minimize potential confounding by prevalent CKD, we restricted the sample to participants without evidence of CKD, defined as eGFR $\geq 60 \text{ mL/min per 1.73 m}^2$. The association between natural log-transformed FGF23 and WMHV remained similar in the fully adjusted model ($\beta = 0.11$; 95% CI, 0.01–0.21; $P=0.03$) and modeling WMHV adjusting for intracranial volume (instead of as a proportion of intracranial volume, data not shown). Associations remained significant in other sensitivity analyses (Table II in the online-only Data Supplement).

In an unadjusted model, each unit increase in natural log-transformed FGF23 was associated with greater odds of having SBI (Table 2), but the effect was attenuated after adjusting for sociodemographic factors and eGFR ($P=0.08$) and vascular risk factors ($P=0.21$). The trend for increasing odds of SBI across quartiles of FGF23, and comparing the top quartile of FGF23 to the lowest, showed a significant association with SBI only in the unadjusted model, with a trend toward significance after adjusting for sociodemographics and eGFR ($P=0.06$).

We found that sex modified the association between FGF23 and the odds of having SBI ($P$ for interaction=0.03). Stratified

Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=1170)</th>
<th>FGF23 Quartiles 1–3 (n=878)</th>
<th>FGF23 Quartile 4 (n=292)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (15.4–84.5)</td>
<td>Range (84.9–1424.6)</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>701 (59.9)</td>
<td>487 (55.5)</td>
<td>214 (73.3)</td>
</tr>
<tr>
<td>Men</td>
<td>469 (40.1)</td>
<td>391 (44.5)</td>
<td>78 (26.7)</td>
</tr>
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<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>170 (14.5)</td>
<td>126 (14.4)</td>
<td>44 (15.1)</td>
</tr>
<tr>
<td>Black</td>
<td>196 (16.8)</td>
<td>133 (15.1)</td>
<td>63 (21.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>779 (66.6)</td>
<td>599 (68.2)</td>
<td>180 (61.6)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (2.1)</td>
<td>20 (2.3)</td>
<td>5 (1.7)</td>
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<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>561 (47.9)</td>
<td>423 (48.2)</td>
<td>138 (47.3)</td>
</tr>
<tr>
<td>Former</td>
<td>504 (43.1)</td>
<td>384 (43.7)</td>
<td>120 (41.1)</td>
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<tr>
<td>Current</td>
<td>105 (9.0)</td>
<td>71 (8.1)</td>
<td>34 (11.6)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>842 (72.0)</td>
<td>611 (69.6)</td>
<td>231 (79.1)</td>
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<tr>
<td>No</td>
<td>328 (28.0)</td>
<td>267 (30.4)</td>
<td>61 (20.9)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>269 (23.0)</td>
<td>185 (21.1)</td>
<td>84 (28.8)</td>
</tr>
<tr>
<td>No</td>
<td>901 (77.0)</td>
<td>693 (78.9)</td>
<td>208 (71.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>459 (39.2)</td>
<td>321 (36.6)</td>
<td>138 (47.3)</td>
</tr>
<tr>
<td>No</td>
<td>711 (60.8)</td>
<td>557 (63.4)</td>
<td>154 (52.7)</td>
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<tr>
<td>SBI, n (%)*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>166 (14.7)</td>
<td>116 (13.7)</td>
<td>50 (17.9)</td>
</tr>
<tr>
<td>No</td>
<td>960 (85.3)</td>
<td>730 (86.3)</td>
<td>230 (82.1)</td>
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<td>Age, mean (SD)</td>
<td>70 (9)</td>
<td>69 (9)</td>
<td>73 (9)</td>
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<tr>
<td>BMI, mean (SD)</td>
<td>29 (5)</td>
<td>28 (5)</td>
<td>29 (6)</td>
</tr>
<tr>
<td>FGF23, mean (SD)</td>
<td>88.8 (119.2)</td>
<td>56.0 (14.2)</td>
<td>187.6 (208.4)</td>
</tr>
<tr>
<td>PO4, mean (SD)</td>
<td>3.0 (0.5)</td>
<td>3.0 (0.4)</td>
<td>3.1 (0.5)</td>
</tr>
<tr>
<td>PTH, mean (SD)</td>
<td>56.9 (26.3)</td>
<td>54.2 (21.3)</td>
<td>64.9 (36.4)</td>
</tr>
<tr>
<td>eGFR, mean (SD)</td>
<td>77.4 (20.3)</td>
<td>80.5 (18.8)</td>
<td>68.3 (21.9)</td>
</tr>
<tr>
<td>WMHV, 1/TCV %, mean (SD)</td>
<td>0.7 (0.8)</td>
<td>0.6 (0.7)</td>
<td>0.9 (1.0)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PO4, phosphate; PTH, parathyroid hormone; SBI, subclinical brain infarction; and WMHV, white matter hyperintensity volume.

*Forty-four with missing data.
Elevated FGF23 has been associated with incident hemorrhagic stroke suggests a role for rupture of both medium-sized and small vessels, especially given the high prevalence of hypertension in the NOMAS sample. Moreover, we have previously demonstrated an association of kidney function with WMHV in NOMAS, but the association of eGFR with WMHV was not significant with FGF23 in the model. These data suggest that elevated FGF23 may be a key driving factor underlying the association between CKD and white matter disease. With the caveat that our observational data are cross-sectional, the combination of our previous finding that elevated FGF23 is associated with carotid plaque presence, and now, more severe white matter disease, suggest that FGF23 may be a risk factor for arterial disease across small to large calibers.

### Table 2. Association of FGF23 With WMHV and SBI

<table>
<thead>
<tr>
<th>FGF23 Level</th>
<th>WMHV, 1/TCV*</th>
<th>Per unit lnFGF23</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
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<tr>
<td>Quar tile 1</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quar tile 2</td>
<td>0.13 (−0.02–0.28)</td>
<td>0.10</td>
<td>0.03 (−0.11–0.16)</td>
<td>0.69</td>
<td>0.01 (−0.12–0.15)</td>
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<tr>
<td>Quar tile 3</td>
<td>0.23 (0.07–0.38)</td>
<td>0.004</td>
<td>0.02 (−0.12–0.16)</td>
<td>0.79</td>
<td>0.01 (−0.13–0.15)</td>
</tr>
<tr>
<td>Quar tile 4</td>
<td>0.50 (0.35–0.66)</td>
<td>&lt;0.0001</td>
<td>0.21 (0.06–0.35)</td>
<td>0.005</td>
<td>0.19 (0.04–0.33)</td>
</tr>
</tbody>
</table>

*Log-transformed. Results presented as β (95% CI), P value.
†Results presented as OR (95% CI), P value.

### Discussion

In this cross-sectional community-based study from a race/ethnically diverse urban sample, we found that participants with greater FGF23 levels had a greater burden of white matter lesions after accounting for demographics, vascular risk factors, and renal function. Although FGF23 was not associated with MRI-defined subclinical infarction overall, greater FGF23 was associated with a greater odds of SBI among men.

Although FGF23 has been studied in carotid and coronary artery atherosclerosis, we are aware of no prior studies of FGF23 and small arterial disease. Community-based studies of the role of FGF23 in atherosclerosis have shown mixed and controversial results, despite some histopathologic studies demonstrating FGF23’s presence within atheromas of the carotid and coronary arteries. Elevated FGF23 has been associated with large vessel disease in CKD patients not on dialysis as well as in this community-based NOMAS cohort, but links with large vessel disease have not been reported in other community-based studies. Elevated FGF23 has been implicated indirectly in damage to peripheral arteries through its association with ankle-brachial index in the Cardiovascular Health Study.

We were unable to find previous studies showing a link between FGF23 and small vessel disease other than through its association with CKD. Our previous finding that elevated FGF23 was associated with MRI-defined subclinical infarction overall, greater factors, and renal function. Although FGF23 was not associated with greater FGF23 levels had a greater burden of white matter disease, suggest that FGF23 may be a risk factor for arterial disease across small to large calibers.
replacement therapy have greater FGF23 levels than men, or women on hormone replacement therapy.29 This may help explain the high proportion of women compared with men with FGF23 levels in the upper quartile in NOMAS. Estrogens act indirectly on parathyroid hormone and reduced phosphate levels and FGF23 in both in vivo and in vitro studies.30 In a cross-sectional analysis of the National Health and Nutrition Examination Survey, postmenopausal women had greater phosphate levels independent of parathyroid hormone, dietary intake, and eGFR.31 Higher phosphate levels in postmenopausal women could increase FGF23, but phosphate levels did not differ by sex in this sample (data not shown). Even though most women were postmenopausal at the time FGF23 was measured in NOMAS, a lag in SCVD and SBI development in women compared with men might be expected and is one plausible explanation for sex differences.

This study has several limitations. Our FGF23 and MRI data are cross-sectional, and no causal conclusions can be made about the temporal relationship between FGF23 and SBI or WMHV. In addition, the MRI subsample was somewhat healthier than the 3298 participants enrolled into NOMAS at baseline. However, this would be likely to minimize any association and bias our study toward the null.16 Also, not all lesions labeled as SBI or WMH are caused by vascular damage. For example, perivascular spaces can be misclassified as SBI, and WMH can be caused by any process that results in intrstitial water. Further, some vascular lesions are below the resolution of our protocol and scanner and could have gone undetected, limiting our ability to detect associations.32–34 Although WMHV often represents small vessel disease, there may be nonvascular and genetic causes.35 Strengths of our study include its population-based design, the race/ethnically diverse urban sample, and the quantitative measurements of markers of subclinical vascular brain injury.

Conclusions

Our study shows a cross-sectional association between elevated FGF23 and cerebral small vessel disease and with MRI-defined infarction in men. These findings were independent of exposure to key sociodemographic and potentially modifiable vascular risk factors in a stroke-free and race-ethnically diverse urban community–based sample. However, prospective data examining elevated FGF23 and incident SCVD are needed.

Sources of Funding

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Disclosures

Dr DeCarli consults on a clinical trial sponsored by Novartis. The other authors report no conflicts.

References


Fibroblast Growth Factor 23 Is Associated With Subclinical Cerebrovascular Damage: The Northern Manhattan Study
Clinton B. Wright, Nirav H. Shah, Armando J. Mendez, Janet T. DeRosa, Mitsuhiro Yoshita, Mitchell S.V. Élkind, Ralph L. Sacco, Charles DeCarli, Tatjana Rundek, Shonni Silverberg, Chuanhui Dong and Myles Wolf

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/03/08/STROKEAHA.115.012379.DC1
**SUPPLEMENTAL MATERIAL**

**Supplemental Table I.** Characteristics of MRI Sub-study participants included and not included in analysis

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<th>Included (N=1,170)</th>
<th>Not Included (N=120)</th>
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<td>73.5 ± 9.0</td>
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<td>Male, n (%)</td>
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<td>Race-ethnicity, n (%)</td>
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<td>Black</td>
<td>196 (16.8)</td>
<td>27 (22.5)</td>
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<td>Hispanic</td>
<td>779 (66.6)</td>
<td>68 (56.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>25 (2.1)</td>
<td>4 (3.3)</td>
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<td>Smoking, n (%)</td>
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<td>561 (47.9)</td>
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<tr>
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<tr>
<td>Hypertension, n (%)</td>
<td>842 (72.0)</td>
<td>94 (78.3)</td>
<td>0.14</td>
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<tr>
<td>Diabetes, n (%)</td>
<td>269 (23.0)</td>
<td>23 (19.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>459 (39.2)</td>
<td>47 (39.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>28.5 ± 5</td>
<td>28.2 ± 5.4</td>
<td>0.50</td>
</tr>
<tr>
<td>eGFR, mean ± SD</td>
<td>77.4 ± 20.3</td>
<td>75 ± 20.9</td>
<td>0.35</td>
</tr>
<tr>
<td>FGF23, mean ± SD*</td>
<td>88.8 ± 119.2</td>
<td>72.4 ± 49.5</td>
<td>0.55</td>
</tr>
<tr>
<td>PO4, mean ± SD</td>
<td>3 ± 0.5</td>
<td>2.9 ± 0.6</td>
<td>0.66</td>
</tr>
<tr>
<td>PTH, mean ± SD*</td>
<td>56.9 ± 26.3</td>
<td>43.7 ± 11.4</td>
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* t test was based on unadjusted log-transformed data
Supplemental Table II. Sensitivity Analyses

<table>
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<td>Beta (95% CI)</td>
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<td>WHMV, 1/TCV%*</td>
<td>per lnFGF23</td>
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<td>p for trend</td>
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<tr>
<td>SBI</td>
<td>per lnFGF23</td>
<td>1.22 (0.89, 1.66)</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>p for trend</td>
<td>0.14</td>
<td>p for trend</td>
</tr>
</tbody>
</table>

* log-transformed

WMHV=white matter hyperintensity volume; SBI=MRI-defined subclinical infarction

Model 3a: adjusted covariates in model 3 plus PTH and PO4

Model 3b: adjusted covariates in model 3, excluding subjects with Ca>10.3 mg/dL and PTH>65 pg/ml (n=9)