Fibroblast growth factor 23 (FGF23) is a hormone secreted by bone cells that regulates vitamin D and phosphorus metabolism. Elevated FGF23 concentrations are associated with excess risk of cardiovascular disease. Associations of FGF23 with stroke outcomes are less clear.

Methods—Using a case–cohort study design, we examined the association of baseline plasma FGF23 concentrations with incident stroke in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a cohort of black and white adults aged ≥45 years. FGF23 was measured in 615 participants who developed incident stroke (cases) and in 936 participants randomly selected from the REGARDS cohort (comparison subcohort).

Results—In multivariable-adjusted models, higher calcium and phosphorus concentrations, lower estimated glomerular filtration rate and higher urine albumin excretion were independently associated with higher FGF23. There was no statistically significant association of FGF23 with risk of all-cause stroke in Cox models adjusted for demographic factors and established stroke risk factors (hazard ratio comparing fourth with first quartile 1.19; 95% confidence interval, 0.78–1.82). In prespecified models stratified by stroke subtypes, there was a graded association of FGF23 with risk of cardioembolic stroke in fully adjusted models (quartile 1, reference; quartile 2 hazard ratio, 1.48; 95% confidence interval, 0.63–3.47; quartile 3 hazard ratio, 1.99; 95% confidence interval, 0.89–4.44; quartile 4 hazard ratio, 2.52; 95% confidence interval, 1.08–5.91). There were no statistically significant associations of FGF23 with other ischemic stroke subtypes or with hemorrhagic strokes.

Conclusions—Higher FGF23 concentrations were associated with higher risk of cardioembolic but not with other stroke subtypes in community-dwelling adults. Additional studies should delineate reasons for these findings. (Stroke. 2015;46:322-328. DOI: 10.1161/STROKEAHA.114.007489.)

Key Words: cardiovascular disease • fibroblast growth factors • stroke

Fibroblast growth factor 23 (FGF23) is a hormone secreted by bone cells that regulates vitamin D and phosphorus homeostasis. Higher FGF23 concentrations have been associated with greater prevalence of cardiovascular and kidney disease independently of traditional risk factors. Higher FGF23 concentrations have also been linked to greater risk of incident cardiovascular disease events and death, establishing increased circulating FGF23 as a novel cardiovascular risk factor. Experimental data showing that FGF23 directly induces cardiac hypertrophy in animal models and provides biological plausibility for a direct association of excess FGF23 with cardiovascular disease.

Most of the studies that examined the association of FGF23 with incident cardiovascular disease risk used a composite of events as the primary outcome, but there is evidence that the strength of the association of FGF23 with cardiovascular disease events substantially varies by outcome. For example, higher FGF23 concentrations have been more strongly associated with cardiovascular events linked to heart failure than those linked to atherosclerotic disease. Few studies examined the association of FGF23 with stroke as a distinct end point, and those that did were limited by a low number of events or did not examine the association of FGF23 with different ischemic stroke subtypes. This is important in that a recent study showed that higher FGF23 concentrations were independently associated with higher risk of incident atrial fibrillation, a major risk factor for cardioembolic strokes. As such, it is possible that the association between FGF23 and stroke risk may differ by pathogenic subtype. The primary focus of the current study was to examine the association of FGF23 with incident stroke events overall and by pathogenic subtypes in participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Methods

The REGARDS study is a population-based investigation of stroke incidence in black and white US adults aged ≥45 years. Details of the
study design have been reviewed elsewhere. Briefly, the study was designed to provide approximately equal representation of men and women and oversampled individuals who were black and individuals living in the US stroke belt/buckle. Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants’ sociodemographics, cardiovascular risk factors, and the use of antihypertensive, antilglycemic, and cholesterol-lowering medication. After this call, health professionals conducted an in-home study visit that included an electrocardiogram (ECG) recording, blood pressure, height and weight measurements, inventory of medications and collection of blood and urine samples. Overall, 30,239 individuals were enrolled between January 2003 and October 2007 (42% black; 55% women). The REGARDS study protocol was approved by the institutional review boards governing research in human subjects at the participating centers, and all participants provided informed consent.

Primary Exposure
The exposure of interest was FGF23 concentrations measured in baseline plasma samples using a second generation, C-terminal ELISA (Immutopics, Santa Clara, CA) with coefficients of variation <10%.

Outcome of Interest
The outcome of interest was incident stroke. Suspected strokes were reported via telephone follow-up with participants every 6 months. Medical records were requested for stroke events and reviewed by ≥2 physician members of a committee of stroke experts to validate and classify potential strokes. Stroke events were defined according to the World Health Organization definition of stroke.29 Events not meeting this definition but characterized by symptoms lasting <24 hours, with neuroimaging consistent with acute ischemia or hemorrhage were classified as clinical strokes and included as stroke events. Cases in which adjudicators agreed that the event was likely a stroke or stroke-related death but information was incomplete for World Health Organization or clinical classification were classified as probable strokes and also included as stroke events. Strokes were further subclassified into pathogenic subtypes of small-vessel occlusion, large-vessel atherosclerosis, cardioembolic, or unclassified.20 Ischemic stroke subtype classifications were based on the potential stroke pathogenesis discovered during poststroke evaluation as per other stroke epidemiology studies.21-25

Covariates of Interest
Age, race, sex, smoking history, annual family income, and educational attainment were determined by self-report. Systolic and diastolic blood pressure were defined as the average of 2 seated measurements taken after a 5-minute rest. History of coronary heart disease was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a history of a cardiac procedure (coronary artery bypass surgery or percutaneous coronary intervention), or self-reported history of myocardial infarction. Diabetes mellitus was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose concentration ≥26.9 mmol/L, or a nonfasting blood glucose concentration of ≥11.1 mmol/L. History of atrial fibrillation was ascertained from self-report or by detection in ECG recordings obtained during the baseline study visit. Left ventricular hypertrophy was classified using ECG criteria.24 Phosphorus and calcium concentrations were measured in baseline plasma samples using standard assays. N-terminal pro-B-type natriuretic peptide concentrations were measured using an electrochemiluminescence immunoassay (Roche Elecsys 2010 analyzer; Roche Diagnostics, Indianapolis, IN). High-sensitivity C-reactive protein was measured by particle-enhanced immunonephelometry (BNII nephelometer, Dade Behring). Estimated glomerular filtration rate (eGFR) was determined from serum creatinine measurements using the chronic kidney disease (CKD) Epidemiology Collaboration equation.25 Urine albumin measured by the BNII ProSpec nephelometer (Siemens AG) and urine creatinine measured by the rate Jaffé method (Roche/Hitachi, Basel, Switzerland) were used to calculate urine albumin:creatinine ratio (ACR).

Derivation of Case Cohort
We used a case–cohort study design. This approach provides an unbiased estimate of the relative hazard of an outcome(s) without requiring measurement of biomarkers in all participants and is considered a gold standard for minimizing the cost of expensive assays without compromising the power advantage of large cohort studies.26 Cases included all participants who developed an incident stroke during follow-up through September 2011. The cohort random sample (comparison group) was selected using stratified sampling to ensure sufficient representation of high-risk groups. All participants with ≥1 follow-up contact (n=29653) were categorized into 20 strata based on age (45–54, 55–64, 65–74, 75–84, and ≥85 years), race (black or white), and sex (men or women).27 In each stratum, participants were randomly selected to fulfill the desired distribution: 50% black, 50% white, 50% women, 50% men, 20% age 45 to 54 years, 20% age 55 to 64 years, 25% age 65 to 74 years, 25% age 75 to 84 years, and 10% age ≥85 years. Given a random cohort size of ≥1000 individuals and 615 stroke events, we estimated that we would be able to detect a minimal effect size (hazard ratio [HR]) of 1.6 when comparing the highest with the lowest quartile of FGF23.

Statistical Analysis
Descriptive statistics were used to compare participant characteristics across quartiles of FGF23 within the cohort random sample using appropriate weights to account for the stratified sampling design. Factors that were associated with FGF23 concentrations in unadjusted analyses were then entered into a multivariable linear regression model to identify independent predictors of FGF23 in the cohort random sample. After confirming the proportionality of hazards, Cox regression models for case–cohort studies28 were used to estimate the HR of incident stroke as a function of baseline FGF23 in sequential models. Model 1 adjusted for age, sex, race, and an age-race interaction term because associations of race with stroke are greater at younger ages, as previously reported.29 Model 2 adjusted for variables in model 1 plus systolic blood pressure and clinical factors (history of diabetes mellitus, history of heart disease, atrial fibrillation, current smoking, and left ventricular hypertrophy). Model 3 further adjusted for laboratory factors (eGFR, natural log-transformed urine ACR, phosphorus, and calcium concentrations). In all models, FGF23 was analyzed in quartiles, with the lowest quartile serving as the referent group. Because a previous study showed that the association of FGF23 with incident cardiovascular disease events differed by CKD status,3 we examined the effect modification by CKD (defined as an eGFR <60 mL/min per 1.73 m² or an ACR≥30 mg/g) by testing the statistical significance of a multiplicative interaction term in the model. In pre-specified analyses, we examined the association of FGF23 with stroke risk in models stratified by ischemic versus hemorrhagic strokes and in models further stratified by ischemic stroke subtypes. For the latter analyses, when >1 pathogenic subtype was considered present, that case was counted in each subtype group. A 2-tailed P value <0.05 was considered statistically significant. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results
Baseline Characteristics of Study Participants
A total of 619 participants who developed a stroke during follow-up and 1104 participants randomly selected from the REGARDS study cohort were included in the study. After excluding 93 participants who reported a history of stroke at the baseline visit and 79 participants who had missing FGF23 concentrations, a total of 1551 participants constituted the final analyzed sample (615 cases and 936 participants in the
cohort random sample). In general, when compared with individuals who were stroke free during follow-up, individuals who developed a stroke were older, more likely to be men, have less than a high school education, make <$20,000 a year, be a current smoker, and have diabetes mellitus, hypertension, coronary heart disease, atrial fibrillation, and CKD.

Table 1 reports the baseline characteristics of participants in the cohort random sample by quartiles of FGF23. Higher concentrations of FGF23 were associated with older age, female sex, residence in US stroke belt/buckle states, lower diastolic blood pressure, lower educational achievement, lower annual income, current smoking, diabetes mellitus, coronary heart disease, left ventricular hypertrophy, atrial fibrillation, lower eGFR, higher urine ACR, higher calcium, phosphorus, high-sensitivity C-reactive protein, and N-terminal pro–B-type natriuretic peptide concentrations. In a linear regression model adjusted for variables significantly associated with FGF23 in Table 1, only higher calcium and phosphorus concentrations, higher urine ACR, and lower eGFR remained independently associated with higher FGF23 concentrations.

**Table 1. Baseline Characteristics of Study Participants in the Cohort Random Sample by Quartiles of FGF23**

<table>
<thead>
<tr>
<th>FGF23 Quartile 1 (&lt;53 RU/mL)</th>
<th>FGF23 Quartile 2 (53–70 RU/mL)</th>
<th>FGF23 Quartile 3 (70.5–100 RU/mL)</th>
<th>FGF23 Quartile 4 (&gt;100 RU/mL)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted n*</td>
<td>6561</td>
<td>6565</td>
<td>6589</td>
<td>6577</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.1 (0.5)</td>
<td>63.6 (0.5)</td>
<td>65.9 (0.6)</td>
<td>66.9 (0.6)</td>
</tr>
<tr>
<td>Women, %</td>
<td>43</td>
<td>54</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>Black, %</td>
<td>45</td>
<td>36</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Region, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belt</td>
<td>39</td>
<td>31</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>Buckle</td>
<td>14</td>
<td>20</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Nonbelt</td>
<td>47</td>
<td>49</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2 (0.4)</td>
<td>29.5 (0.5)</td>
<td>29.7 (0.4)</td>
<td>29.6 (0.5)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>93.6 (1.0)</td>
<td>96.1 (1.3)</td>
<td>97.2 (0.9)</td>
<td>95.8 (1.1)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128.0 (1.4)</td>
<td>126.6 (1.1)</td>
<td>127.5 (1.3)</td>
<td>127.2 (1.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.6 (0.7)</td>
<td>76.9 (0.7)</td>
<td>76.4 (0.8)</td>
<td>75.0 (0.7)</td>
</tr>
<tr>
<td>Less than high school education, %</td>
<td>11</td>
<td>9</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Annual income &lt;$20,000 per y, %</td>
<td>14</td>
<td>11</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>11</td>
<td>9</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17</td>
<td>15</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>13</td>
<td>11</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>5</td>
<td>5</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>93.3 (1.2)</td>
<td>89.3 (1.2)</td>
<td>85.7 (1.3)</td>
<td>77.2 (1.6)</td>
</tr>
<tr>
<td>UACR, mg/g</td>
<td>6.5 (4.2–11.5)</td>
<td>6.6 (4.2–11.5)</td>
<td>6.9 (4.9–13.8)</td>
<td>9.3 (5.1–26.6)</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.2 (0.04)</td>
<td>9.1 (0.09)</td>
<td>9.1 (0.05)</td>
<td>9.4 (0.04)</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>3.4 (0.04)</td>
<td>3.4 (0.04)</td>
<td>3.5 (0.04)</td>
<td>3.7 (0.05)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.6 (0.7–3.8)</td>
<td>2.0 (0.9–4.3)</td>
<td>2.4 (0.9–5.1)</td>
<td>2.7 (1.1–5.9)</td>
</tr>
<tr>
<td>NT-pro-BNP, pg/mL</td>
<td>44.7 (27.2–101.2)</td>
<td>56.3 (29.9–100.5)</td>
<td>73.3 (36.9–160.5)</td>
<td>87.8 (41.1–244.0)</td>
</tr>
<tr>
<td>FGF23, RU/mL</td>
<td>44.1 (39.2–48.4)</td>
<td>60.8 (56.9–64.7)</td>
<td>78.9 (73.4–86.4)</td>
<td>140.5 (115.1–219.0)</td>
</tr>
</tbody>
</table>

*eGFR indicates estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; NT-pro-BNP, N-terminal pro–B-type natriuretic peptide; and UACR, urine albumin:creatinine ratio.

*Analysis weighted to the full cohort.

**Associations of FGF23 With Incident Stroke**

Table 2 depicts the HRs of incident stroke by quartiles of FGF23. Higher quartiles of FGF23 were associated with higher risk of incident stroke in models adjusted for age, race, age×race interaction, and sex (quartile 1, reference; quartile 2 HR, 1.42; 95% confidence interval [CI], 1.01–1.99; quartile 3 HR, 1.35; 95% CI, 0.97–1.88; quartile 4 HR, 1.84; 95% CI, 1.31–2.58; \( P_{\text{trend}}=0.001 \)). The magnitude and strength of the associations were modestly attenuated after adjustment for systolic blood pressure, diabetes mellitus, cigarette smoking, coronary heart disease, atrial fibrillation, and left ventricular hypertrophy (HR comparing fourth with first quartile, 1.59; 95% CI, 1.09–2.35; \( P_{\text{trend}}=0.04 \)). After further adjustment for phosphorus, calcium, eGFR, and natural log-transformed urine ACR, the association of higher FGF23 with higher incident stroke risk was completely attenuated (HR comparing the highest with lowest quartile of FGF23, 1.19; 95% CI, 0.78–1.82; \( P_{\text{trend}}=0.77 \)). Estimated GFR and urine ACR were the variables that were primarily responsible for this attenuation. The association of FGF23 with stroke risk was not modified by CKD status (\( P_{\text{interaction}}=0.24 \)).
Associations of FGF23 With Stroke Subtypes

A total of 540 strokes were classified as ischemic in pathogenesis and 75 as hemorrhagic. There were no statistically significant associations of FGF23 with risk of hemorrhagic stroke in unadjusted or adjusted analyses (data not shown). When the analysis was restricted to ischemic strokes, the results were similar to analyses using all-cause strokes—higher FGF23 quartiles were not associated with higher risk of incident stroke in fully adjusted models (HR comparing the fourth with first quartile 1.28; 95% CI, 0.81–2.01; \( P_{\text{trend}} = 0.56 \); Figure).

A total of 136 ischemic strokes were further subclassified as being cardioembolic in pathogenesis, 85 as being because of large-vessel atherosclerosis, 104 as being because of small-vessel occlusion, and 245 were unclassified (the total was >1540 because >1 pathogenic subtype was identified for some events). In prespecified analyses restricted to cardioembolic stroke subtypes, higher quartiles of FGF23 were associated with higher risk of incident stroke after adjustment for demographic characteristics, clinical factors, and laboratory measures including indices of kidney function (HR comparing the fourth with first quartile, 2.52; 95% CI, 1.08–5.91; \( P_{\text{trend}} = 0.04 \); Figure). When the model was further adjusted for N-terminal pro–B-type natriuretic peptide concentrations as a surrogate measure of volume overload/left ventricular wall stress, the association between higher FGF23 and higher risk of cardioembolic stroke was no longer statistically significant, but the magnitude of the association only minimally changed (HR comparing the fourth with first quartile, 2.47; 95% CI, 0.98–6.22; \( P_{\text{trend}} = 0.08 \)). In contrast, in analyses restricted to large- or small-vessel disease subtypes, there were no statistically significant associations of FGF23 with stroke risk in fully adjusted models. Similarly, there was no statistically significant association of FGF23 with unclassified stroke subtypes in the fully adjusted model.

Discussion

FGF23 is a hormone that regulates phosphorus and vitamin D metabolism. In states of phosphorus excess, such as high dietary phosphorus intake or CKD, FGF23 secretion is stimulated to help maintain normal phosphorus balance by increasing urinary phosphorus excretion and reducing dietary phosphorus absorption via inhibition of vitamin D activation. Although this helps to preserve phosphorus homeostasis in the short term, a growing body of literature suggests that chronic elevations in circulating FGF23 have long-term cardiovascular consequences. In the current study, we found no statistically significant association of FGF23 concentrations with risk of all-cause incident stroke when accounting for established stroke risk factors, particularly baseline CKD. However, in prespecified analyses, higher FGF23 was associated with greater risk of incident cardioembolic stroke but not of other ischemic stroke subtypes or hemorrhagic stroke in models adjusted for established stroke risk factors and other parameters of mineral metabolism.

Previous studies have examined the association of FGF23 with stroke risk, but their results were inconsistent. The Heart and Soul Study reported that higher FGF23 was associated with higher risk of incident stroke or transient ischemic attack (total n=36) independently of other risk factors (HR per doubling of FGF23, 1.50; 95% CI, 1.11–2.04), whereas Kendrick et al found no statistically significant association of FGF23 with stroke (n=43) in individuals with advanced CKD. A Cardiovascular Health Study (CHS) report found that FGF23 was independently associated with higher risk of incident stroke among individuals with CKD (total events=168; HR per doubling of FGF23, 1.29; 95% CI, 1.08–1.54) but not among individuals with preserved kidney function (total events=218; HR per doubling of FGF23, 0.99; 95% CI, 0.81–1.20). Consistent with the results of the current study, the Northern Manhattan Study (NOMAS) reported no association of FGF23 with ischemic strokes (n=212) after adjusting for traditional stroke risk factors. Unlike our study, however, they found an independent association of FGF23 with hemorrhagic strokes (n=26). Importantly, none of the aforementioned studies examined the association of FGF23 with ischemic stroke subtypes. Thus, the results of the current study help to extend these previous findings by demonstrating that the magnitude and strength of the association of FGF23 with ischemic stroke are greater for strokes because of cardioembolism than for those linked to large-vessel atherosclerosis or small-vessel ischemic disease, potentially explaining the inconsistency in the association of FGF23 with stroke in these previous studies.

The reason why FGF23 was associated with higher risk of cardioembolic but not of other subtypes of ischemic stroke is unclear. Nonetheless, given the strong link between heart failure and cardioembolic stroke events, these results are broadly consistent with previous studies showing that higher FGF23 more strongly associates with cardiovascular disease events linked to heart failure than with large- or small-vessel atherosclerotic
In line with this, increased FGF23 has been independently associated with increased left ventricular mass, increased prevalence of left ventricular hypertrophy, and reduced ejection fraction, but not vascular calcification or peripheral arterial disease. Furthermore, FGF23 was shown to induce cardiomyocyte hypertrophy in vitro and stimulate adverse left ventricular remodeling in vivo, providing biological plausibility for a direct toxic effect of FGF23 on the myocardium. Higher FGF23 concentrations were also associated with higher risk of incident atrial fibrillation independently of potential confounders in 2 large community-based cohorts.

Given the tight association of FGF23 with kidney disease, it is also conceivable that the association of FGF23 with cardioembolic stroke may reflect known associations of kidney injury with left ventricular hypertrophy, heart failure, and atrial fibrillation. Studies with more direct measures of kidney function or with longitudinal measures of eGFR and urinary ACR are needed to determine the role of kidney disease in explaining the results observed herein.

We did not have direct measurements of left ventricular size or function in REGARDS participants or clinical examination findings to delineate who did or did not have prevalent heart failure at the time of FGF23 measurement, and so we were not able to determine the association of FGF23 with heart failure at baseline or whether heart failure may have mediated an association of FGF23 with cardioembolic stroke risk. Similarly, because we had to rely on self-report or detection on baseline ECG to determine whether individual participants had atrial fibrillation, we could not reliably determine whether the association of FGF23 with cardioembolic stroke risk was explained in whole or in part by an association of FGF23 with atrial fibrillation, as has been reported previously. Additional studies will need to examine the association of FGF23 with the development of atrial fibrillation after the baseline visit to examine this possibility. Other limitations of our study included having only one baseline measure of FGF23 and inclusion of only black or white adults limiting our ability to extrapolate these findings to other races/ethnicities.

Our study also had several strengths including standardized collection of baseline data and prospective data including physician-adjudicated stroke events and ischemic stroke subtypes.
Conclusions

Higher FGF23 was an independent risk factor for cardioembolic strokes but not for other stroke subtypes in this large national cohort of community-dwelling adults. Additional studies are needed to delineate reasons for the differential association of FGF23 by stroke subtype in this study and potential implications of these findings for clinical practice.

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Disclosures

None.

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Fibroblast Growth Factor 23 and Risk of Incident Stroke in Community-Living Adults
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