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SERUM FIBROBLAST GROWTH FACTOR-23 AND INCIDENT HYPERTENSION: THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

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Abstract

Elevated serum fibroblast growth factor-23 (FGF23), an endogenous hormone, is associated with disturbed mineral homeostasis, cardiovascular disease, and chronic kidney disease. It is unclear whether FGF23 impacts the development of incident hypertension. We investigated the association of serum FGF23 measured at baseline (1990–92) with incident hypertension at two follow-up visits (1993–95 and 1996–98) in 7,948 middle-aged men and women without hypertension at baseline participating in the Atherosclerosis Risk in Communities Study. Incident hypertension was determined by measured blood pressure (DBP ≥ 90 mm Hg, or SBP ≥ 140 mm Hg) and/or self-reported hypertension medication use at follow-up exams. Complementary log-log models that accounted for interval censoring were used to model the association between FGF23 and incident hypertension. During a median follow-up of 5.9 years, 27% (2,152/7,948) participants developed hypertension. A nonlinear association between serum FGF23 and incident hypertension was observed; only persons in the highest decile of serum FGF23 had an increased risk of incident hypertension. After adjustment for demographics, behaviors, and adiposity the hazard ratio for incident hypertension was 1.24 (95% CI: 1.11, 1.39) for the highest decile of FGF23 compared to the lowest quintile. The association was further attenuated in the final model after adjusting for renal function (hazard ratio: 1.21, 95% CI: 1.08, 1.35). In conclusion, high levels (≥ 60.6 pg/mL) of FGF23 are associated with a modestly increased risk of incident hypertension in the general population, independent of kidney function.

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Fibroblast growth factors; fibroblast growth factor-23; hypertension; Atherosclerosis Risk in Communities Study; risk factors

INTRODUCTION

Approximately 78 million Americans adults have hypertension¹; the age-adjusted prevalence approaches 65–75% among persons aged 65 years or older.^{2,3} Hypertension frequently underlies cardiovascular disease; evidence suggests that hypertension is present in 69% of adults with incident myocardial infarction, 77% with incident stroke, and 74% diagnosed with incident heart failure.^{1,3} Development of hypertension occurs in conjunction with, (i) the inability of the renal system to maintain mineral homeostasis, and (ii) changes in cardiac and vascular structure.⁴

Fibroblast growth factor-23 (FGF23) is a protein produced by osteocytes and osteoblasts. It is principally involved in kidney function and mineral metabolism;^{5,6} elevated levels have been linked to cardiovascular morbidity and mortality in both the general population^{7–9} and those with chronic kidney disease.^{10–12} It is unclear whether FGF23 impacts the development of hypertension, and if so whether the biological mechanism involves mineral metabolism, changes to cardiac or vascular structure, or another explanation. Recent work demonstrates that elevated FGF23 is associated with mineral homeostasis disruption, plasma volume, and hypertension in animal models.^{13,14} Importantly, in individuals with normal kidney function, FGF23 is a risk factor for mortality, heart failure, and cardiovascular disease events.^{15,16} Therefore, it appears that FGF23 may have cardiovascular consequences in conjunction with and independent of mineral metabolism.

The objective of the current study was to evaluate the association between FGF23 and incident hypertension in the prospective, community-based Atherosclerosis Risk in Communities (ARIC) Study. We hypothesized that elevated serum FGF23 would be positively associated with risk of incident hypertension independent of traditional cardiovascular (CVD) risk factors in the ARIC cohort.

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a longitudinal prospective cohort study initiated in 1987–89. Originally, 15,792 men and women ages 45–64 years of age were recruited from 4 U.S. communities: Minneapolis suburbs, Minnesota; Jackson, Mississippi; Washington County, Maryland; and Forsyth County, North Carolina.¹⁷ Five follow-up visits were conducted: visit 2 (1990–92), visit 3 (1993–95), visit 4 (1996–98), and visit 5 (2011–13). FGF23 was first measured at visit 2, thus visit 2 is baseline for the present analysis. Of the 14,348 participants attending visit 2, we excluded participants with prevalent hypertension (defined as measured systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or self-reported antihypertensive medication use) at visit 2 (n=5,163), individuals who were neither African American nor white, and African

Americans from the Minnesota and Maryland centers due to small sample sizes (n=91), individuals with FGF23 values >200 pg/mL (n=12) or missing FGF23 values (n=751), and those missing hypertension classification at visits 3 and 4 (n=383). Our final sample size was 7,948 observations. No exclusions were made for missing covariates. Written informed consent was collected from all study participants; all affiliated institutional review boards approved the study protocol.

FGF23 and other covariates

FGF23—All participants were instructed to fast overnight prior to blood specimen collection at study visit 2 (1990–92). Blood samples were processed, shipped, and stored at -70°C until laboratory assays were performed.¹⁷ In 2012–2013, intact serum FGF23 was measured in stored specimens collected at ARIC visit 2 by enzyme-linked immunosorbent assay (Kainos Laboratories, Inc., Tokyo, Japan). Serum samples were incubated in microtiter plates previously coated with a capture antibody. A detection antibody was then added to form a sandwich complex between serum FGF23 that had bound to the detection antibody on the plate. The microtiter plate was then washed and incubated with a tetramethylbenzidine substrate solution. Finally, a spectrophotometric plate reader determined the optical density of each well and sample intact FGF23 concentrations were calculated from a standard curve. The inter-assay (process) coefficient of variation for FGF23 based on ARIC blind duplicate samples (split-specimens collected at the time of blood draw) was 16.6% and the coefficient of variation from internal laboratory quality control samples was 8.8%; internal lab quality control was based on a standard blood pool which had a serum FGF23 concentration of 41.4 pg/mL. Blind duplicates were performed over the full range of ARIC participants.

Self-reported variables—Questionnaires were administered to all participants at each ARIC visit. Age, sex, and race were determined based on self-report. Education was categorized as less than a high school diploma, a high school diploma, or beyond a high school diploma; physical activity was calculated using the Baecke questionnaire for sports during leisure time (both carried forward from visit 1).¹⁸ Smoking status and alcohol intake were categorized as current, former, or never users.

Objectively measured variables—Body mass index (kg/m^2) and waist-to-hip ratio (cm) were calculated from objective height (meters), weight (kg), and girth of waist and hip (cm) collected by trained ARIC study staff using standardized protocols.¹⁷ High-density lipoprotein cholesterol (HDL, mg/dL), low-density lipoprotein cholesterol (LDL, Friedewald equation, mg/dL),¹⁹ and triglycerides (mg/dL) were measured as previously reported.¹⁷ High-sensitivity C-reactive protein, parathyroid hormone, phosphorous, sodium, and calcium were measured in 2012–2013 in stored visit 2 serum (all mg/dL, Roche Diagnostics, Indianapolis, IN). Cystatin C was measured using a Roche Modular P Chemistry analyzer and Gentian cystatin C reagent; serum creatinine was determined using a modified kinetic Jaffé reaction. Kidney function (estimated glomerular filtration rate; eGFR) was derived using the CKD-EPI 2012 equation which incorporates both creatinine and cystatin C²⁰. We modeled eGFR in two ways: continuously $\text{ml}/\text{min}/1.73\text{m}^2$ and categorically as 90, 60 to <90, and 15 to <60 $\text{ml}/\text{min}/1.73\text{m}^2$. Prevalent coronary heart disease, heart failure, stroke,

and diabetes definitions have been previously described.^{9,17} Finally, all medication use was ascertained by a medication inventory conducted at the baseline study visit.

Incident hypertension—Seated blood pressure was measured using a random zero sphygmomanometer. All participants rested for 5 minutes prior to blood pressure ascertainment; three measurements were collected at visit 3 (mean of final two calculated for analysis), whereas at visit 4 only two measurements were collected (mean calculated for analysis). Incident hypertension was defined as mean systolic blood pressure (SBP) of ≥ 140 mmHg, and/or diastolic blood pressure (DBP) ≥ 90 mmHg, and/or antihypertensive medication use reported at ARIC visits 3 or 4.²¹ For our secondary analysis, incident self-reported hypertension was identified through ARIC annual follow-up phone calls through 2012. At each phone call, participants were asked: (i) “Since we last contacted you, has a doctor said you had high blood pressure?” and (ii) “Did you take any medications during the past two weeks for high blood pressure?” Participants who answered affirmatively to either of these questions were classified as having incident self-reported hypertension.²²

Statistical analysis

Baseline characteristics of participants are described using means and proportions stratified by categories of FGF23. For the primary analysis, complementary log-log (cloglog) regression models were used to explore the relationship between serum FGF23 and risk of incident hypertension. Cloglog models account for data that are collected in intervals but originate continuously; beta coefficients are interpreted as log hazard ratio (HR) providing ease of interpretation.²³ For the secondary analysis, Cox regression models were used to examine the association between serum FGF23 and risk of self-reported incident hypertension. Restricted cubic splines using 5 knots at 5%, 25%, 50%, 75%, and 95% were used to visually depict the associations, and aid in selecting the most appropriate representation. The spline models suggested an exponential nonlinear relationship between FGF23 and incident hypertension. To elucidate the association more thoroughly, the upper FGF23 quintile was split into deciles 9 and 10.

The primary analysis included only objectively measured hypertension at study visits; a secondary analysis included self-reported hypertension obtained through study visits and annual follow-up telephone calls. Model 1 included adjustment for demographic characteristics (age, race, sex, ARIC field center, and educational attainment). Model 2 additionally adjusted for lifestyle variables (cigarette smoking, physical activity, body mass index, alcohol consumption, and serum phosphorus). Model 3 further adjusted for kidney function (eGFR). Interaction terms were used to evaluate whether race, sex, age, and kidney function (eGFR) modified the relationship between serum FGF23 and risk of incident hypertension. Sensitivity analyses explored excluding individuals with: (i) prevalent coronary heart disease (CHD), and (ii) prehypertension to evaluate the robustness of the association. Further sensitivity analyses examined the impact of adding serum parathyroid hormone, calcium, sodium, 25-hydroxyvitamin D and baseline cardiovascular medication use (cholesterol lowering medications, anticoagulants, and aspirin) to Model 3. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina); we used a conventional threshold of $\alpha=0.05$ (a 5% Type I error rate).

RESULTS

The 7,948 participants who were free of hypertension at baseline (visit 2, 1990–1992) were on average 56.3 years old, 56% were female, and 17% African American. Mean (SD) serum FGF23 was 43.6 (± 15.1) pg/mL. Serum FGF23 was positively associated with some traditional cardiovascular risk factors and prevalent cardiovascular diseases. These results were most evident in the upper deciles of FGF23. In particular, participants with high FGF23 were more likely to have elevated LDL, HDL, and triglycerides, serum calcium and phosphorus, impaired estimated glomerular filtration rate (eGFR), and prevalent diabetes (Table 1). Differences in kidney function were notable: 4.9% of participants in the top decile of FGF23 compared with 0.4% of participants in the first quintile of FGF23 had an eGFR < 60 ml/min/1.73m² (Table 1). Mean age of participants was similar across FGF23 quantiles: 56.8 ± 5.8 years in decile 10 and 55.8 ± 5.6 years in quintile 1. Likewise, no significant differences were observed between FGF23 category and race, education, physical activity (sport index), prevalent heart failure, prevalent stroke, or serum sodium.

Incident Hypertension at Study Visits

Over a median follow-up of 5.9 years, 27% of the sample ($n=2,152$) developed incident hypertension. A nonlinear association between serum FGF23 and incident hypertension was observed using restricted cubic splines; only persons in the highest decile of serum FGF23 had an increased risk of incident hypertension (Table 2). After adjustment for demographics (Model 1), the hazard ratio for incident hypertension was 1.27 (95% CI: 1.14, 1.42) for the highest decile of FGF23 compared to the lowest quintile. After additional adjustment for behaviors and adiposity (Model 2) the HR was 1.24 (95% CI: 1.11, 1.39). The association was further attenuated in the final model (Model 3) after adjusting for renal function 1.21 (95% CI: 1.08, 1.35) (Table 2). There was no evidence of meaningful multiplicative interaction with age, race, sex, or eGFR category.

Incident self-reported Hypertension

Of the original 7,644 participants free of hypertension at visit 2, 55% of the sample ($n=4,128$) developed incident hypertension over a mean of 12.3 years (through visit 5). FGF23 was positively associated with incident self-reported hypertension in a dose-response manner (Table 3). Relative to quintile 1, the demographic-adjusted (Model 1), hazard ratios for incident self-reported hypertension were 1.33 (95% CI: 1.20, 1.48) for decile 10, 1.21 (95% CI: 1.09, 1.34) for decile 9, and 1.16 (95% CI: 1.07, 1.27) for quintile 4. After additional adjustment for behaviors and adiposity (Model 2) the hazard ratios were attenuated: 1.23 (95% CI: 1.11, 1.37) for decile 10, 1.14 (95% CI: 1.03, 1.27) for decile 9, and 1.11 (95% CI: 1.02, 1.21) Final adjustment for renal function using Model 3 revealed similar results to Model 2 (Table 3).

Sensitivity Analyses

Sensitivity analyses excluding: (i) individuals with prevalent CHD (self-reported physician diagnosis of myocardial infarction (MI) or coronary revascularization (coronary artery bypass surgery or angioplasty), prevalent MI diagnosed from ECG at visit 1, or an incident adjudicated CHD event between ARIC visits 1 and 2), and (ii) individuals with pre-

hypertension (systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg) resulted in a higher risk of incident hypertension compared to the primary analysis (Table 4). When excluding individuals with CHD, individuals in the upper decile of FGF23 had a 30% higher risk of incident hypertension (HR: 1.30 95% CI: 1.11, 1.54) compared with analyses not excluding these individuals (HR: 1.21, 95% CI: 1.08, 1.35) in the fully adjusted model (Model 3). When excluding individuals with pre-hypertension, individuals in the upper decile of FGF23 had a 42% higher incidence of hypertension (HR: 1.42 95% CI: 1.06, 1.90) in the fully adjusted model. Results were nearly identical when additionally adjusting for serum parathyroid hormone, calcium, sodium, 25-hydroxyvitamin D and baseline cardiovascular medication use (in separate models, and a model with all biomarkers included; data not shown).

DISCUSSION

In this large community-based cohort, a non-linear association was found between FGF23 and risk of incident hypertension, independent of traditional cardiovascular risk factors and indicators of kidney function. Participants in the highest decile of FGF23 were at approximately 21% greater risk of incident hypertension after adjustment for demographics, health behaviors, and traditional cardiovascular risk factors. These associations were independent of kidney function. Furthermore, the results were similar regardless of whether incident hypertension was defined through objective measurements or by self-report, with the highest decile of FGF23 being associated with an elevated risk of incident hypertension for both methods of measurement. These findings provide human evidence in a large cohort study that FGF23 is associated with the development of incident hypertension, thereby extending the current understanding of the role of FGF23 on cardiovascular risk. Our findings are supported by a recent study which reported that FGF23 was correlated with prevalent hypertension in children and adolescents.²⁴

Recent evidence from human and animal studies provides insight into the mechanisms through which elevated FGF23 may increase the risk of incident hypertension. Specifically, FGF23 has been found to initiate mineral homeostasis disruption, and a consequent increase in blood pressure. In mouse models, FGF23 was found to increase calcium and sodium reabsorption, as well as renal phosphate excretion.^{13,14} Though the literature are complex, it is hypothesized that calcium reabsorption may lead to serum calcium accumulation, vascular calcification, and consequent elevated blood pressure.^{25,26} A recent cross-sectional analysis of National Health and Nutrition Examination Survey data demonstrated a positive association between serum calcium and prevalent hypertension; individuals in the highest quartile of serum calcium had a 1.49 higher odds of hypertension (95% CI: 1.15–1.93, $p=0.005$) than those in the lowest quartile.²⁷ The effects of sodium on blood volume have been extensively documented independent of FGF23.^{28–33} In a randomized controlled trial using the Dietary Approaches to Stop Hypertension (DASH) diet, blood pressure was reduced by 11.5 and 7.1 mm Hg in participants with and without hypertension respectively.³⁴ Researchers recently found that FGF23 is an influential regulator of sodium reabsorption in the kidney and overall plasma volume, an important contributor to blood pressure. Mice that were lacking the FGF23 gene excreted more sodium in their urine, whereas mice with elevated FGF23 levels had higher plasma sodium and blood pressure.¹³

Furthermore, though a rise in serum phosphorus precedes FGF23 elevation,³⁵ data from epidemiological studies are equivocal in establishing the relationship between serum phosphate levels and blood pressure.³⁶ In our analyses, the impact of adjusting for serum phosphorus, sodium, and calcium (in separate models, and a model with all biomarkers included) was negligible. To further complicate matters, markers of mineral metabolism are highly correlated; there is a paucity of data available on the combined effects of phosphorus, calcium, and sodium on blood pressure. As a result, the ability to specify the impact of one mineral on blood pressure in isolation is limited.³⁷

Additional mechanisms exist linking FGF23 and hypertension independent of mineral homeostasis. It is possible that FGF23 is an early indicator of impaired kidney function, an established risk factor for incident hypertension.³⁸ Although the current analyses adjusted for kidney function, FGF23 may be elevated prior to frank changes in the kidney. In addition, a positive association has been found between FGF23 and atherosclerosis,³⁹ though it is unclear whether it acts independently of phosphorus.^{25,40} Finally, high circulating FGF23 has been associated with endothelial dysfunction and arterial wall stiffness,^{41–43} and inflammation^{44,45} - factors which may contribute to the increased peripheral resistance typical of essential hypertension.

Strengths of this study include the prospective design with ample long-term follow-up, a community-based bi-racial cohort, a large sample size, and a comprehensive collection of cardiovascular risk factors for confounding adjustment. Importantly, biologically active and intact FGF23 and incident hypertension were both objectively measured for our primary analyses. Secondary analyses using self-reported hypertension with much longer follow-up (mean 12.3 vs. 5.9 years) yielded similar results. Limitations of this study include that FGF23 was measured at a single point in time. Any associated measurement error, however, was likely non-differential therefore attenuating the results of the analyses towards the null. Second, Klotho, a co-receptor for FGF23, was not measured in the present study. Klotho is necessary for FGF23 to have biological activity;⁵ elevated FGF23 levels are considered more informative when presence of Klotho is verified. Third, the possibility of selection bias exists. It is possible that those who participated in the present study differ in their association of FGF23 and hypertension compared to those lost to follow-up. Finally, despite our attempts to statistically adjust for known confounders, residual confounding may be present.

Identification of new biomarkers that contribute to hypertension provides the opportunity to identify individuals at high risk, develop pharmacologic agents for intervention, and improve our understanding of hypertension physiology. Clinical identification of patients who are high risk for hypertension could aid in earlier identification, risk classification, and more targeted treatment. Furthermore, pharmacologic interventions to reduce the production or biological activity of FGF23 – which are primarily being created with the goal of preventing both cardiovascular and kidney disease – are in various stages of development. Oral phosphate binders, FGF23 monoclonal antibodies, and FGF receptor agonists are treatment options being considered, particularly in the chronic kidney disease population.^{25,36} Oral phosphate binders are the only therapeutic agent currently available, and have been shown to effectively reduce FGF23 levels after 6 weeks of treatment.^{25,35,46–49} Additional

investigations with longer follow-up times are needed. Clinical trials with hard endpoints are of utmost importance to determine whether these agents hold therapeutic value.

In conclusion, in this large community-based cohort elevated FGF23 levels were associated with a greater risk of incident hypertension, independent of traditional hypertension and cardiovascular risk factors and abnormal kidney function. These data suggest FGF23 as a possible risk marker for incident hypertension. Next steps include replication in other cohorts and further exploration of the biological mechanisms underlying this association.

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Table 1

Baseline (visit 2) participant characteristics by FGF23 category, ARIC, 1990–92 (n=7,948).

Category	Serum FGF23 (pg/mL) Categories								P trend ¹	Missing (n)
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Decile 9	Decile 10				
Median	25.9	34.7	40.7	47.8	55.9	73.2				
Range	2.9 – 31.3	31.4 – 37.8	37.9 – 43.8	43.9 – 52.4	52.5 – 60.5	60.6 – 181.8				
N total	1,589	1,590	1,590	1,590	795	794				
N incident hypertension	405	424	426	416	215	266				
Demographics										
Age, mean years ± SD	55.8 ± 5.6	56.1 ± 5.6	56.2 ± 5.6	56.3 ± 5.6	56.5 ± 5.7	56.8 ± 5.8		0.09		0
Female n (%)	974 (61.3)	938 (59.0)	881 (55.4)	842 (53.0)	427 (53.7)	434 (54.7)		<0.0001		0
African American, n (%)	301 (18.9)	261 (16.4)	271 (17.0)	256 (16.1)	130 (16.3)	125 (15.7)		0.25		0
Education, > High school	635 (40.0)	641 (40.4)	659 (41.5)	666 (42.0)	303 (38.2)	321 (40.5)		0.61		11
Behavioral Variables										
Sport Index, mean ± SD	2.5 ± 0.8	2.5 ± 0.8	2.5 ± 0.8	2.5 ± 0.8	2.5 ± 0.8	2.5 ± 0.8		0.26		24
Smoking, current, n (%)	425 (26.8)	365 (23.0)	333 (21.0)	325 (20.5)	154 (19.4)	144 (18.2)		<0.0001		8
Alcohol, current, n (%)	1016 (64.0)	967 (60.9)	959 (60.4)	975 (61.4)	472 (59.4)	449 (56.5)		0.04		7
Prevalent Disease										
Diabetes, n (%)	134 (8.4)	124 (7.8)	140 (8.8)	145 (9.2)	87 (10.9)	91 (11.5)		0.03		18
Heart failure, n (%)	14 (0.9)	24 (1.5)	23 (1.5)	25 (1.6)	18 (2.3)	18 (2.3)		0.07		133
Stroke, n (%)	8 (0.5)	6 (0.4)	10 (0.6)	12 (0.8)	10 (1.3)	42 (5.4)		0.14		15
CHD, n (%)	47 (3.0)	49 (3.1)	73 (4.7)	61 (3.9)	37 (4.8)	8 (1.0)		0.01		150
Physiologic Variables										
BMI, kg/m ² ± SD	26.1 ± 4.7	26.8 ± 4.7	27.1 ± 4.7	27.2 ± 4.6	27.6 ± 4.8	27.9 ± 5.0		<0.0001		6
LDL, mg/dL ± SD	127 ± 37	131 ± 35	133 ± 35	133 ± 35	138 ± 37	135 ± 37		<0.0001		115
HDL, mg/dL ± SD	54.0 ± 17.5	51.9 ± 16.9	50.4 ± 16.8	49.6 ± 17.0	48.4 ± 15.9	48.0 ± 16.6		<0.0001		32
Triglycerides, mg/dL ± SD	113.7 ± 73.1	119.9 ± 65.9	126.4 ± 75.6	132.1 ± 80.9	137.2 ± 75.3	148.4 ± 95.4		<0.0001		11
Phosphorous, mg/dL ± SD	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5		<0.0001		53
Calcium, mg/dL ± SD	9.2 ± 0.4	9.3 ± 0.4	9.3 ± 0.4	9.3 ± 0.4	9.4 ± 0.4	9.4 ± 0.4		<0.0001		51
Sodium	140 ± 2.2	141 ± 2.2	141 ± 2.3	141 ± 2.1	141 ± 2.1	141 ± 2.2		0.68		0
eGFR, ml/min/1.73m ² ± SD	101.4 ± 14.6	99.1 ± 14.0	97.8 ± 14.3	95.9 ± 14.3	94.0 ± 15.0	90.8 ± 17.3		<0.0001		104

Category	Serum FGF23 (pg/mL) Categories						P trend ¹	Missing (n)
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Decile 9	Decile 10		
eGFR Creatinine level, n (%) [‡]								
>90 ml/min/1.73m ²	1239 (78.9)	1192 (75.7)	1119 (71.5)	1062 (67.8)	488 (61.9)	429 (55.1)	<0.0001	0
60–90 ml/min/1.73m ²	325 (20.7)	376 (23.9)	437 (27.9)	495 (31.6)	287 (36.4)	312 (40.0)	<0.0001	0
<60 ml/min/1.73m ²	6 (0.4)	7 (0.4)	9 (0.6)	10 (0.6)	13 (1.7)	38 (4.9)	<0.0001	104

Abbreviations: Fibroblast growth factor 23, FGF23; Atherosclerosis Risk in Communities Study, ARIC; standard deviation, SD; coronary heart disease, CHD; body mass index, BMI; low-density lipoprotein cholesterol, LDL; high-density lipoprotein cholesterol, HDL; estimated glomerular filtration rate, eGFR.

* Overall P test for linear trend.

[‡] Kidney function (estimated glomerular filtration rate; eGFR) was derived using the CKD-EPI 2012 equation which incorporates both creatinine and cystatin C.

Table 2

Adjusted HRs and 95% CIs for objectively measured incident hypertension by FGF23 category, ARIC, 1990–98 (total n=7,948; total developing hypertension = 2,152).

Serum FGF-23 (pg/mL) Categories						
Category	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Decile 9	Decile 10
Median	25.9	34.7	40.7	47.8	55.9	73.2
Range	2.9 – 31.3	31.4 – 37.8	37.9 – 43.8	43.9 – 52.4	52.5 – 60.5	60.6 – 181.8
N total	1,589	1,590	1,590	1,590	795	794
N events	405	424	426	416	215	266
Model						
Model 1	1	0.97 (0.88, 1.06)	0.97 (0.89, 1.06)	0.96 (0.87, 1.05)	0.95 (0.85, 1.07)	1.27 (1.14, 1.42)
Model 2	1	0.97 (0.89, 1.07)	0.97 (0.89, 1.06)	0.95 (0.87, 1.04)	0.93 (0.83, 1.05)	1.24 (1.11, 1.39)
Model 3	1	0.98 (0.90, 1.07)	0.98 (0.89, 1.07)	0.96 (0.87, 1.05)	0.94 (0.83, 1.05)	1.21 (1.08, 1.35)

Model 1: Adjusted for age, race, sex, ARIC field center, and educational attainment.

Model 2: Adjusted for Model 1 + cigarette smoking, alcohol intake, physical activity, body mass index, and serum phosphorus.

Model 3: Adjusted for Model 2 + eGFR category.

Table 3

Adjusted HRs and 95% CIs for self-reported incident hypertension by FGF23 category, ARIC, 1990–2012 (total n=7,644; total developing hypertension = 4,128).

Category	Quintile 1	Serum FGF-23 (pg/mL) Categories					Decile 9	Decile 10
		Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 6		
Median	25.1	35.3	42.9	47.9	53.8	74.1		
Range	2.8 – 31.1	31.2 – 39.1	39.2 – 44.8	44.9 – 53.9	54.0 – 60.6	60.7 – 181.9		
N total	1,529	1,529	1,529	1,529	764	764		
N events	803	831	828	839	399	428		
Model								
Model 1	1	1.10 (1.00, 1.19)	1.11 (0.98, 1.19)	1.16 (1.07, 1.27)	1.21 (1.09, 1.34)	1.33 (1.20, 1.48)		
Model 2	1	1.09 (0.99, 1.16)	1.09 (0.99, 1.16)	1.11 (1.02, 1.21)	1.14 (1.03, 1.27)	1.23 (1.11, 1.37)		
Model 3	1	1.09 (1.00, 1.16)	1.09 (0.99, 1.16)	1.10 (1.02, 1.20)	1.13 (1.03, 1.26)	1.21 (1.10, 1.37)		

Model 1: Adjusted for age, race, sex, ARIC field center, and educational attainment.

Model 2: Adjusted for Model 1 + cigarette smoking, alcohol intake, physical activity, body mass index, and serum phosphorus.

Model 3: Adjusted for Model 2 + eGFR category.

Table 4

Adjusted HRs and 95% CIs for incident hypertension by FGF23 category, ARIC, sensitivity analyses for individuals without coronary heart disease (CHD) ^{*} and pre-hypertension. [†]

Model	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Decile 9	Decile 10
Main Results						
Model 1	1	0.97 (0.88, 1.06)	0.97 (0.89, 1.06)	0.96 (0.87, 1.05)	0.95 (0.85, 1.07)	1.27 (1.14, 1.42)
Model 2	1	0.97 (0.89, 1.07)	0.97 (0.89, 1.06)	0.95 (0.87, 1.04)	0.93 (0.83, 1.05)	1.24 (1.11, 1.39)
Model 3	1	0.98 (0.90, 1.07)	0.98 (0.89, 1.07)	0.96 (0.87, 1.05)	0.94 (0.83, 1.05)	1.21 (1.08, 1.35)
Sensitivity Analysis: Individuals without CHD [*]						
Model 1	1	1.08 (0.94, 1.24)	1.08 (0.94, 1.24)	1.04 (0.91, 1.20)	1.02 (0.86, 1.21)	1.43 (1.22, 1.68)
Model 2	1	1.04 (0.90, 1.19)	1.02 (0.89, 1.18)	0.99 (0.86, 1.14)	0.95 (0.80, 1.13)	1.33 (1.13, 1.57)
Model 3	1	1.04 (0.91, 1.20)	1.03 (0.89, 1.18)	1.00 (0.86, 1.15)	0.96 (0.80, 1.14)	1.30 (1.11, 1.54)
Sensitivity Analysis: Individuals without pre-hypertension [†]						
Model 1	1	1.23 (0.96, 1.56)	1.13 (0.89, 1.44)	1.11 (0.87, 1.42)	1.54 (1.18, 2.02)	1.58 (1.20, 2.10)
Model 2	1	1.19 (0.93, 1.51)	1.08 (0.84, 1.38)	1.07 (0.83, 1.37)	1.49 (1.14, 1.95)	1.51 (1.13, 2.00)
Model 3	1	1.21 (0.95, 1.54)	1.09 (0.85, 1.40)	1.07 (0.83, 1.38)	1.49 (1.14, 1.96)	1.42 (1.06, 1.90)

^{*} CHD defined as self-reported physician diagnosis of myocardial infarction (MI) or coronary revascularization (coronary artery bypass surgery or angioplasty), prevalent MI diagnosed from ECG at visit 1, or an incident adjudicated CHD event between ARIC visits 1 and 2.

[†] Pre-hypertension defined as systolic blood pressure 120–139 mm Hg or diastolic blood pressure of 80–89 mm Hg.

Model 1: Adjusted for age, race, sex, ARIC field center, and educational attainment.

Model 2: Adjusted for Model 1 + cigarette smoking, alcohol intake, physical activity, body mass index, and serum phosphorus.

Model 3: Adjusted for Model 2 + eGFR category.