Title

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Authors

Ong, Kwok-Leung
McClelland, Robyn L
Allison, Matthew A
et al.

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Association of elevated circulating fibroblast growth factor 21 levels with prevalent and incident metabolic syndrome: The Multi-Ethnic Study of Atherosclerosis

Kwok-Leung Ong[a,*], **Robyn L. McClelland**[b], **Matthew A. Allison**[c], **John Kokkinos**[a], **Ben J. Wu**[a], **Philip J. Barter**[a], and **Kerry-Anne Rye**[a]

[a]Lipid Research Group, School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia

[b]Department of Biostatistics, University of Washington, Seattle, WA, United States

[c]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, United States

Abstract

Background and aims: Fibroblast growth factor 21 (FGF21) plays an important role in glucose and lipid metabolism. We have investigated the relationship of plasma FGF21 levels with both prevalent and incident metabolic syndrome (MetS) in participants from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: 5783 participants from four major ethnic groups (non-Hispanic white, African American, Hispanic American, and Chinese American) were included in the cross-sectional analysis. Longitudinal analysis involved 3479 participants without MetS at baseline, of whom 1100 participants developed incident MetS over 9.2 years.

Results: Elevated FGF21 levels were found in participants with prevalent MetS (median [interquartile range] = 189.4 [114.4–302.1] vs. 123.7 [65.9–210.3] pg/mL, $p < 0.001$) or incident MetS (145.6 [84.9–240.8] vs 112.0 [57.0–194.5] pg/mL, $p < 0.001$), compared to those without. After adjusting for baseline demographic, socioeconomic and lifestyle factors, as well as cardiovascular risk factors and biomarkers, and compared to the lowest quartile, the highest FGF21 quartile was associated with prevalent MetS (odds ratio 2.80; 95% confidence interval, 2.30–3.40, $p < 0.001$). Among participants without MetS at baseline, the highest FGF21 quartile was associated with higher risk of incident MetS (hazards ratio 1.76; 95% confidence interval, 1.46–2.12, $p < 0.001$). Similar results were obtained when assessing ln-transformed FGF21 levels.

[*]Corresponding author. School of Medical Sciences, University of New South Wales, Sydney, NSW, 2052, Australia. oklws@yahoo.com.hk (K.-L. Ong).

Author contributions

K.L.O. participated in data analysis and wrote the manuscript; R.L.M. participated in data analysis. K.L.O., R.L.M., M.A.A., and K.A.R. participated in the study design. K.L.O. and J.K. participated in acquisition of the data. All authors participated in data interpretation and critical revision of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi.org/10.1016/j.atherosclerosis.2018.10.011.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Overall, no significant interaction was found with age, sex, and race/ethnicity for both prevalent and incident MetS.

Conclusions: Higher FGF21 levels significantly predict the development of MetS in an ethnically diverse population followed long term. Further studies are needed to confirm the potential role of FGF21 as a biomarker for MetS.

Keywords

Biomarker; Cardiovascular disease risk factors; Fibroblast growth factor 21; Metabolic syndrome; Multi-ethnic study of atherosclerosis

1. Introduction

Fibroblast growth factor 21 (FGF21) is a novel metabolic regulator that improves tissue sensitivity to insulin, lowers blood glucose levels, and plays an important role in glucose and lipid metabolism [1–3]. Its circulating levels are often elevated in obesity, dyslipidemia, type 2 diabetes, and coronary artery disease [4]. Therefore, FGF21 has been implicated as a potential biomarker for the early detection of these cardiometabolic disorders [4].

The metabolic syndrome (MetS) describes the clustering of closely related cardiovascular risk factors, including abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), moderately elevated blood pressure (BP) and moderately elevated fasting glucose [5]. Individuals with the metabolic syndrome are at increased risk of developing cardiovascular disease (CVD) and diabetes. Previous studies have suggested FGF21 as a biomarker of MetS [6–8]. However, these studies are limited by their small sample size. It is not known whether there is an ethnic or gender difference in the association of FGF21 levels and incident MetS, or whether such an association is independent of other CVD risk factors. Therefore, we investigated whether higher FGF21 levels were associated with both prevalent and incident MetS and individual MetS components, independent of non-MetS CVD risk factors or other relevant biomarkers.

2. Materials and methods

2.1. Study participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort of 6814 men and women aged 45–84 years, and free of clinically apparent CVD at baseline [9]. At baseline, none of the participants reported a history of physician-diagnosed CVD or had undergone procedures related to CVD. Participants were recruited from four major ethnic groups (38.5% non-Hispanic white, 27.8% African American, 22.0% Hispanic American, and 11.8% Chinese American) in six United States communities between July 2000 and August 2002. After the baseline exam, participants attended up to four additional clinic visits over a 10-year period. The study was approved by the institutional review boards at all participating centers and undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Informed written consent was obtained from all participants. Details of the study objectives, design, and protocol have been described previously [9].

Among 6814 participants at baseline, data on FGF21 levels were available in 5792 participants. After further excluding 9 participants with missing data on MetS status at baseline, a total of 5783 participants were included in the cross-sectional analysis. Among these 5783 participants, 3672 (63.5%) did not have the MetS at baseline. After excluding 193 participants with missing data on MetS status in followup visits, a total of 3479 participants were included in the longitudinal analysis of incident MetS, and 1100 of them (31.6%) developed incident MetS during follow-up period (Supplementary Fig. 1). The median follow-up period of these participants was 9.2 years.

2.2. Laboratory measurement

At baseline, venous blood samples were collected after a 12-h fast by certified technicians using standardized venipuncture procedures. FGF21 levels were measured from stored plasma samples using enzyme-linked immunosorbent assay kits as described previously [10,11]. The intra-assay and inter-assay coefficients of variation were < 10%.

Using the same samples, serum glucose was measured by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method. HDL-C was measured using the cholesterol oxidase method after precipitation of non-HDL-C with magnesium/dextran sulphate. Triglyceride levels were measured using a glycerol-blanked enzymatic method. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics Inc, Rochester, NY). Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation [12]. High-sensitivity C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), N-terminal pro B-type natriuretic peptide (NT-proBNP), γ-glutamyltransferase (GGT) levels were measured in all participants at the baseline exam as described previously [13–16]. Insulin resistance was estimated using the homeostasis model assessment index of insulin resistance (HOMA-IR), according to the updated computer model as described previously [17].

2.3. Other variables of interest

Information on age, ethnicity, education, health insurance, smoking, alcohol use, total gross family income, physical activity, medical history and medication use were obtained using standardized questionnaires. Body mass index (BMI) was measured as the weight in kilograms divided by height in meters squared. A standard flexible tape measure was used to measure hip and waist circumferences. Resting BP was measured three times in a seated position and the average of the last two BP readings was used in the analysis. Physical activity was measured as the total number of hours of self-reported moderate and vigorous activity per week, multiplied by metabolic equivalent (MET) level as described elsewhere [18]. Sedentary behavior was defined as time spent on watching television and reading.

2.4. MetS definition

Participants were defined to have MetS if they met three or more of the following components: abdominal obesity (waist circumference > 102 cm in men or > 88 cm in

women); triglycerides ≥150 mg/dL (1.7 mmol/L); HDL cholesterol < 40 mg/dL (1.0 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women; BP ≥ 130/85 mmHg, or on anti-hypertensive medication; and fasting glucose ≥100 mg/dL (5.6 mmol/L) or on anti-diabetic medication [5].

2.5. Statistical analysis

Descriptive data are presented as mean (standard deviation), percentage (number), or median (interquartile range), where appropriate. Comparison of baseline clinical characteristics between participants with and without prevalent or incident MetS was performed by Chi-square test for categorical variables and independent *t*-test for continuous variables. For skewed variables, data were analyzed after natural log (ln) transformation. Correlations between FGF21 levels and other continuous clinical characteristics and biomarkers were analyzed with Spearman correlation.

In cross-sectional analysis, the association of baseline FGF21 levels with prevalent metabolic syndrome and its individual components was assessed using multivariable logistic regression analysis. Odds ratios (OR) were estimated in several adjustment models. In model 1, data were adjusted for age, sex, and ethnicity. In model 2, data were further adjusted for socioeconomic and lifestyle factors, including education, family income, smoking, pack-years of smoking, current alcohol use, physical activity, and sedentary behavior. In model 3, data were further adjusted for other cardiovascular risk factors (not included in the MetS definition), including LDL-C, use of lipid-lowering medication, and eGFR. In model 4, data were further adjusted for BMI and other CVD biomarkers, including CRP, fibrinogen, IL-6, NT-proBNP, and GGT, to investigate if the association between baseline FGF21 levels with MetS is independently of these biomarkers.

As FGF21 and NT-proBNP levels were very highly skewed, data were ln-transformed in the Cox regression analysis to prevent unstable estimates of the regression coefficient since extreme values may have an undue influence on the estimate of the regression coefficient. FGF21 quartiles were also modeled in a separate analysis. In a separate analysis, the association of ln-transformed FGF21 levels with the number of the individual MetS components (i.e. 0, 1, 2, 3, 4, and 5) present in the participants was assessed using multivariable linear regression analysis with the same adjustment models as mentioned above. No multi-collinearity was detected (variance inflation factors < 3.0 in all the analyses).

For longitudinal analysis, cumulative incidence of MetS was estimated by the Kaplan-Meier method and compared by the log-rank test. The association of baseline FGF21 levels with incident MetS and the incidence of its individual components over the follow-up period was assessed using Cox proportional hazard regression analysis. For each participant who developed the metabolic syndrome, the time to event was considered as the time interval between the exact date of the visit at which the metabolic syndrome was ascertained and the exact date of the baseline visit 1. For participants who remained event-free, the follow-up time was censored at their last available visit. Hazards ratios (HR) were estimated after adjusting for the same set of variables as in the cross-sectional analysis. The proportional hazards assumption was checked using Schoenfeld residuals and we found violations for

age, race/ethnicity, FGF21 levels, and number of MetS components present at baseline in the analysis of incident MetS, but not the incidence of individual MetS components. Subsequent exploratory analysis led to treatment of age, race/ethnicity, and FGF21 levels as time-dependent variables (i.e. HRs for these variables changed as a function of time). For incidence of individual MetS components, participants with MetS at baseline as well as those with that component present at baseline were excluded from the analysis. The incremental value of the addition of ln-transformed FGF21 levels in the Cox regression model was assessed by the change in Harrell's C-statistic using a method adapted for survival models [19].

In all analysis, we also investigated whether there was an interaction by age, sex, and race/ethnicity. p for interaction was estimated by including the interaction term in the regression models in the full sample after adjustment for the main effects of the covariates. Moreover, as FGF21 levels have been reported to be affected by lipid-lowering medications [10,20] and lipid-lowering medication also affect triglycerides and HDL-C, we excluded participants on lipid-lowering medications at baseline in a sensitivity analysis. A two-tailed $p < 0.05$ was considered statistically significant. Data analysis was performed using SPSS 24 (IBM, Armonk, NY) or STATA 14.0 (StataCorp, College Station, TX).

3. Results

3.1. Baseline clinical characteristics

Table 1 shows the baseline characteristics of participants with and without prevalent MetS. Participants with prevalent MetS were more likely to be older, women, Hispanic American and less educated, with lower family income and physical activity than those without prevalent MetS at baseline. As expected, participants with prevalent MetS had poorer cardiovascular risk profile than those without prevalent MetS. Similar trends were also found between participants with and without incident MetS among those who did not have prevalent MetS at baseline (Table 1).

3.2. Association of FGF21 levels with prevalent MetS at baseline

At baseline, higher FGF21 levels correlated with poorer cardiovascular risk profile (Supplementary Table 1). As shown in Table 1, baseline FGF21 levels were elevated in participants with prevalent MetS (both $p < 0.001$). In multivariable logistic regression analysis, the association of higher ln-transformed FGF21 levels with prevalent MetS remained significant after adjusting for demographic, socioeconomic and lifestyle factors, as well as other traditional CVD risk factors and relevant biomarkers (OR 1.52 per SD increase in ln-transformed FGF21 levels, $p < 0.001$, Table 2). Similar results were obtained when FGF21 quartiles were analyzed (OR 1.73, 2.11, and 2.80 for quartiles 2, 3, and 4 respectively, compared to quartile 1, $p < 0.001$, Table 2). In a separate analysis, higher ln-transformed FGF21 levels were also associated with a larger number of MetS components present at baseline (an average increase of 0.17 component per SD increase in ln-transformed FGF21 levels, $p < 0.001$, Supplementary Table 2). In all these analyses, no significant interaction with age, sex, and race/ethnicity was found. In a sensitivity analysis, the association of baseline FGF21 levels with prevalent MetS remained significant after

excluding participants taking any lipid-lowering medication at baseline (Supplementary Table 3).

When assessing the individual MetS components separately, higher ln-transformed FGF21 levels were associated with higher odds of abdominal obesity, elevated triglycerides, reduced HDL-C, elevated BP, and elevated blood glucose (OR 1.24, 1.70, 1.27, 1.18 and 1.25 respectively per SD increase in ln-transformed FGF21 levels, all $p < 0.001$, Supplementary Table 4). Similar results were obtained when FGF21 quartiles were analyzed (OR 1.42, 3.55, 1.93, 1.63, and 2.06 respectively for quartile 4 vs quartile 1, all $p \leq 0.01$, Supplementary Table 4). No robust and meaningful interactions with age, sex, and race/ethnicity were found for all MetS components.

3.3. Association of FGF21 levels with incident MetS

As shown in Table 1, participants with incident MetS had significantly higher FGF21 levels at baseline than those without incident MetS ($p < 0.001$). Supplementary Fig. 2 shows the Kaplan-Meier cumulative curves for incident MetS over time across quartiles of FGF21 levels at baseline. Participants with higher FGF21 quartile levels at baseline had a higher risk of MetS (log-rank test $p < 0.001$). In multivariable Cox regression analysis, the association of higher ln-transformed FGF21 levels with incident MetS remained significant after adjusting for baseline demographic, socioeconomic and lifestyle factors, as well as other CVD risk factors and relevant biomarkers (HR 1.21 per SD increase in ln-transformed FGF21 levels, $p < 0.001$, Table 3). Similar results were obtained when FGF21 quartiles were analyzed (HR 1.16, 1.39, and 1.55 for quartiles 2, 3, and 4 respectively, compared to quartile 1, $p < 0.001$, Table 3). Similar results were also obtained after further adjusting for the number of MetS component present at baseline in a separate analysis (Supplementary Table 5). In a sensitivity analysis, the association of baseline FGF21 levels with incident MetS remained significant after excluding participants taking any lipid-lowering medication at baseline (Supplementary Table 3). No significant interaction was found for age, sex, and race/ethnicity. However, a significant interaction was found with time, in which the HR of baseline ln-transformed FGF21 levels for incident MetS was attenuated by about 3% per year during the follow-up period (p for time interaction = 0.033, Table 4). Similar results were obtained when FGF21 quartiles were analyzed (p for time interaction = 0.005).

When assessing the individual incident MetS components, higher ln-transformed FGF21 levels were significantly associated with higher risk of incident hypertriglyceridemia (HR 1.26 per SD increase in ln-transformed FGF21 levels, $p = 0.003$, Table 5). Similar results were obtained when FGF21 quartiles were analyzed (HR 1.23, 1.36, and 2.21 for quartiles 2, 3, and 4 respectively, compared to quartile 1, $p < 0.001$). No significant interaction was found for age, sex, and race/ethnicity. FGF21 levels were not significantly associated with incident abdominal obesity, reduced HDL-C, elevated BP, and elevated blood glucose.

In a separate analysis, we assessed the incremental predictive value of FGF21 by using C-statistics. In a model with age, sex, race/ethnicity, education, family income, smoking, pack-years of smoking, current alcohol use, physical activity, sedentary behavior, LDL-C, use of any lipid-lowering medication, eGFR, BMI, CRP, fibrinogen, IL-6, NT-proBNP (ln-transformed) and GGT at baseline, the addition of ln-transformed FGF21 levels to the this

model result in a modest, non-significant increase of 0.4% in the C-statistic for incident MetS ($p = 0.088$, Supplementary Table 6). However, the increase in the C-statistic was significant in non-Hispanic White (0.4%, $p = 0.037$) and Chinese Americans (0.6%, $p < 0.001$), but not in African Americans (0.2%, $p = 0.43$) and Hispanic Americans (0.4%, $p = 0.071$, Supplementary Table 6).

3.4. Further adjustment for HOMA-IR

Since HOMA-IR is a component of MetS, it was not adjusted in all the analyses. However, in another separate analysis, the association of baseline FGF21 levels with prevalent and incident MetS remained significant after further adjustment for HOMA-IR (Supplementary Table 7). The increase in C-statistics by the addition of FGF21 levels in the adjustment model remained significant only in Chinese Americans, but not the other three racial/ethnic groups (Supplementary Table 6).

4. Discussion

In this study, baseline FGF21 levels were associated with both prevalent and incident MetS. Only a few studies in adult populations have previously investigated the relationship of circulating FGF21 levels with MetS [6–8]. In a cross-sectional study in 232 Chinese subjects, those with MetS had significantly higher serum FGF21 levels than those without MetS [6]. In a longitudinal study of 440 healthy Caucasian subjects, FGF21 levels predicted incident MetS over a follow-up period of 5.3 years [7]. In another recent study of 221 Korean adults, baseline FGF21 levels also predicted the development of incident MetS over an average 2.8-year follow-up period [8]. In a recent meta-analysis, higher FGF21 levels were found to be predictive of incident MetS as well as coronary artery disease, diabetes mellitus, and renal progression in diabetes [21]. The findings from the present study with a larger sample size and multi-ethnic study design were consistent with these previous studies. In addition, the present study showed that the association of FGF21 levels with MetS was independent of well-established biomarkers to include CRP, fibrinogen, IL-6, NT-proBNP, and GGT. Moreover, in non-Hispanic White and Chinese Americans, the addition of FGF21 levels had a modest, but significant, incremental value in discriminating between participants with and without incident MetS beyond that provided by age, sex, ethnicity, socioeconomic and lifestyle factors, cardiovascular risk factors not included in the MetS definition, and other relevant biomarkers.

Despite the beneficial effects of FGF21 administration on glucose metabolism and lipid metabolism in animal studies and human clinical trials [22,23], elevated FGF21 levels have been reported in different cardiometabolic diseases, including obesity, dyslipidemia, type 2 diabetes, and hypertension [4,24]. The association of higher FGF21 levels with all five prevalent MetS components in the present study is consistent with the literature. The elevation in FGF21 levels may be a compensatory protective response to the underlying metabolic stress in these cardiometabolic diseases. It may also be due to FGF21 resistance, in which impaired interactions of FGF21 with its receptor and down-regulation of downstream signaling pathways results in the need for supraphysiological doses of FGF21 to achieve its protective physiological function [4].

In the longitudinal analysis, baseline FGF21 levels were significantly associated only with incident hypertriglyceridemia and not other components of incident MetS. The association of FGF21 levels with plasma triglycerides has been reported extensively [25–27], including our previous study of patients with type 2 diabetes [11]. FGF21 has been suggested as a biomarker for nonalcoholic fatty liver disease and its circulating levels correlate with intrahepatic triglyceride levels [26]. In another study, FGF21 levels were found to be associated with hypertriglyceridemia, as well as hyperinsulinemia and pericardial fat accumulation, independently of obesity [27]. In a recent study in mice, FGF21 was found to reduce plasma triglycerides by lowering plasma levels of non-esterified fatty acids and hence hepatic very-low-density lipoprotein production as well as increasing disposal of triglyceride-rich lipoproteins in white and brown adipose tissue [28].

On the other hand, circulating FGF21 levels are predictive of the development of type 2 diabetes in Hong Kong Chinese [29,30]. However, in the present study, although baseline FGF21 levels did predict the development of overall MetS, they did not significantly predict the development of elevated fasting glucose levels. The discrepancy between the present study and previous studies in Hong Kong Chinese could be due to the difference in clinical characteristics of the study participants and the definition of the outcome events. However, it should be noted that in two proof-of-concept trials, treatment with FGF21 variants did not lower glucose levels in obese patients with type 2 diabetes, even though they had a favorable effect on body weight, lipid profile, fasting insulin, and adiponectin levels [22,23]. Further studies are needed to investigate the role of FGF21 in the development of hyperglycemia and type 2 diabetes.

In the present study, the association of baseline FGF21 levels with prevalent and incident MetS did not differ by gender and race/ethnicity. However, the association of baseline with FGF21 levels tended to be attenuated over time. As this study has a long-term follow-up period of 9.2 years, it is expected that the effects of competing comorbidities potentially related to FGF21 may increase with time. Therefore, our study suggests FGF21 levels could be a better biomarker for near-term, rather than long-term, incident MetS or CVD risk.

The MESA study has several strengths. It has a large well-characterized sample of participants apparently free of clinical CVD at the time of recruitment with good quality of data. The long follow-up period and the multi-ethnic design are also strengths of this study. Moreover, we have adjusted the data for several important CVD biomarkers, including CRP, fibrinogen, IL-6, NT-proBNP, and GGT. This is particularly important, given that FGF21 has already been suggested as a biomarker for CVD risk and nonalcoholic fatty liver disease. However, we cannot exclude the possibility of residual bias due to unmeasured confounders. There are also some limitations in this study. FGF21 levels were assessed at baseline only, and therefore, longitudinal analysis of the change in FGF21 levels is not possible. Moreover, FGF21 levels are highly skewed and this may impede the development of clinical useful cut-off points for FGF21 in CVD risk prediction. As participants attended up to only four additional clinic visits over a 10-year period, the occasion to detect MetS is not frequent and uneven. This may cause the misclassification of participants as MetS is an easily reversible state.

In conclusion, higher FGF21 levels were associated with both prevalent and incident MetS in an ethnically diverse population followed long-term. Given the nature of the current observational study and the multitude of analyses provided in the present study, the presented data are hypothesis-generating and should not be considered definitive. Further studies are needed to confirm the potential role of FGF21 as a biomarker for MetS in an ethnically diverse population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Elevated FGF21 levels were associated with prevalent and incident MetS.
- Elevated FGF21 levels were associated with incident hypertriglyceridemia.
- The association of FGF21 levels with incident MetS was attenuated with time.
- No significant interaction was found with age, sex, and race/ethnicity.
- FGF21 may be a potential MetS biomarker in an ethnically diverse population.

Table 1

Baseline characteristics of participants with and without prevalent or incident MetS.

Characteristics	Prevalent MetS		*p*	Incident MetS		*p*
	Without (n = 3672)	With (n = 2111)		Without (n = 2379)	With (n = 1100)	
Age (years)	61.9 (10.4)	63.9 (9.8)	< 0.001	61.7 (10.6)	61.9 (9.8)	0.48
Women, n (%)	1819 (49.5%)	1192 (56.5%)	< 0.001	1136 (47.8%)	585 (53.2%)	0.003
Race/ethnicity, n (%)			< 0.001			< 0.001
Non-Hispanie White	1456 (39.7%)	697 (33.0%)		1028 (43.2%)	382 (34.7%)	
African American	1035 (28.2%)	631 (29.9%)		652 (27.4%)	315 (28.6%)	
Hispanic American	683 (18.6%)	577 (27.3%)		365 (15.3%)	274 (24.9%)	
Chinese American	498 (13.6%)	206 (9.8%)		334 (14.0%)	129 (11.7%)	
Education, n (%)			< 0.001			< 0.001
< High school	550 (15.0%)	505 (24.0%)		281 (11.9%)	214 (19.5%)	
High school	1473 (40.3%)	940 (44.7%)		923 (38.9%)	469 (42.7%)	
> High school	1636 (44.7%)	658 (31.3%)		1167 (49.2%)	415 (37.8%)	
Total gross family income, n (%)			< 0.001			< 0.001
< $30,000	1207 (34.2%)	906 (45.2%)		695 (30.3%)	409 (38.6%)	
$30,000- $74,999	1410 (39.9%)	775 (38.6%)		922 (40.2%)	437 (41.2%)	
>$75,000	917 (25.9%)	325 (16.2%)		679 (29.6%)	214 (20.2%)	
Smoking, n (%)			0.86			0.90
Never	1835 (50.1%)	1064 (50.6%)		1187 (50.1%)	551 (50.2%)	
Former	1366 (37.3%)	770 (36.6%)		897 (37.8%)	409 (37.2%)	
Current	459 (12.5%)	269 (12.8%)		287 (12.1%)	138 (12.6%)	
Pack-years of smoking	10.7 (19.1)	12.3 (23.0)	0.005	10.1 (18.5)	11.6 (19.8)	0.041
Current alcohol use, n (%)	2139 (58.7%)	1015 (48.5%)	< 0.001	1462 (61.9%)	596 (54.5%)	< 0.001
Physical activity (MET-hours/week)	98.7 (98.6)	87.1 (92.4)	< 0.001	100.4 (96.0)	96.8 (99.7)	0.30
Sedentary behavior (hours/week)	27.5 (18.5)	30.6 (19.9)	< 0.001	27.6 (18.2)	27.6 (18.8)	0.96
BMI, kg/m^2	26.7 (4.9)	31.0 (5.3)	< 0.001	25.7 (4.3)	29.1 (5.2)	< 0.001
Waist circumference (cm)	93.6 (13.2)	106.1 (12.7)	< 0.001	90.7 (11.9)	100.1 (13.5)	< 0.001
HOMA-IR[a]	0.77 (0.59–1.08)	1.31 (0.95–1.84)	< 0.001	0.71 (0.55–0.93)	0.97 (0.72–1.36)	< 0.001
Fasting glucose (mg/dL)[a]	87 (81–93)	101 (89–117)	< 0.001	86 (81–92)	90 (84–96)	< 0.001

Characteristics	Prevalent MetS		*p*	Incident MetS		*p*
	Without (n = 3672)	With (n = 2111)		Without (n = 2379)	With (n = 1100)	
Anti-diabetic medication, n (%)	107 (2.9%)	461 (21.9%)	< 0.001	35 (1.5%)	60 (5.5%)	< 0.001
LDL-C (mg/dL)	117.7 (30.6)	116.2 (33.1)	0.094	117.2 (30.3)	118.9 (30.7)	0.11
HDL-C (mg/dL)	55.3 (15.1)	43.3 (10.8)	< 0.001	57.2 (15.5)	51.0 (13.2)	< 0.001
Triglycerides (mg/dL)[a]	93 (69–124)	164 (115–215)	< 0.001	86 (64–115)	110 (83–139)	< 0.001
Lipid-lowering medication, n (%)	506 (13.8%)	468 (22.2%)	< 0.001	299 (12.6%)	187 (17.0%)	< 0.001
Systolic BP (mmHg)	122.7 (20.4)	134.6 (21.2)	< 0.001	120.4 (20.2)	126.5 (19.7)	< 0.001
Diastolic BP (mmHg)	71.2 (10.0)	73.5 (10.5)	< 0.001	70.5 (9.9)	72.4 (10.2)	< 0.001
Anti-hypertensive medication, n (%)	961 (26.2%)	1226 (58.1%)	< 0.001	533 (22.4%)	368 (33.5%)	< 0.001
eGFR (mL/min/1.73m^2)	78.2 ()15.5	76.3 (17.7)	< 0.001	78.0 (15.0)	78.7 (16.2)	0.23
CRP (mg/L)[a]	1.43 (0.68–3.39)	2.88 (1.36–5.79)	< 0.001	1.22 (0.60–2.76)	2.06 (0.98–4.55)	< 0.001
Fibrinogen (mg/dL)	337.7 (71.5)	362.3 (75.6)	< 0.001	331.5 (68.1)	348.5 (74.3)	< 0.001
Interleukin-6 (pg/mL)[a]	1.06 (0.70–1.68)	1.52 (1.02–2.29)	< 0.001	0.96 (0.64–1.54)	1.25 (0.84–1.89)	< 0.001
NT-proBNP (pg/mL)[a]	53.1 (23.6–106.9)	54.6 (26.3–114.7)	0.010	53.1 (24.2–106.7)	50.9 (22.0–98.7)	0.32
GGT (μL)[a]	7.30 (4.40–12.42)	10.00 (6.41–16.63)	< 0.001	6.72 (4.05–11.26)	8.58 (5.24–14.50)	< 0.001
FGF21 (pg/mL)[a]	123.7 (65.9–210.3)	189.4 (114.4–302.1)	< 0.001	112.0 (57.0–194.5)	145.6 (84.9–240.8)	< 0.001

Data are shown as mean (SD), n (%), or median (interquartile range).

[a] *p* values were estimated using ln-transformed data.

Table 2

Association of baseline FGF21 levels with prevalent MetS at baseline.

FGF21	Model 1[a] OR (95% CI)	*P*	Model 2[b] OR (95% CI)	*P*	Model 3[c] OR (95% CI)	*P*	Model 4[d] OR (95% CI)	*P*
ln-transformed FGF21	1.83 (1.69–1.98)	< 0.001	1.75 (1.62–1.90)	< 0.001	1.72 (1.59–1.87)	< 0.001	1.52 (1.39–1.66)	< 0.001
FGF21 quartile								
1 (≤81.1 pg/mL)	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
2 (81.2–145.9 pg/mL)	1.84 (1.55–2.19)	< 0.001	1.90 (1.59–2.27)	< 0.001	1.90 (1.58–2.27)	< 0.001	1.73 (1.43–2.11)	< 0.001
3 (146.0–245.2 pg/mL)	2.67 (2.26–3.16)	< 0.001	2.58 (2.16–3.07)	< 0.001	2.56 (2.15–3.06)	< 0.001	2.11 (1.74–2.55)	< 0.001
4 (≥245.3 pg/mL)	3.91 (3.31–4.63)	< 0.001	3.76 (3.15–4.48)	< 0.001	3.59 (3.00–4.29)	< 0.001	2.80 (2.30–3.40)	< 0.001
Overall *p*	–	< 0.001	–	< 0.001	–	< 0.001	–	< 0.001

For continuous FGF21 levels, data are expressed as OR (95% CI) in terms of per SD (1.357) increase in ln-transformed FGF21 levels (pg/mL).

[a]Model 1: adjusted for age, sex, and race/ethnicity.

[b]Model 2: further adjusted for education, family income, smoking, pack-years of smoking, current alcohol use, physical activity and sedentary behavior.

[c]Model 3: further adjusted for LDL-C, use of any lipid-lowering medication, and eGFR.

[d]Model 4: further adjusted for other cardiovascular risk biomarkers, including BMI, CRP, fibrinogen, IL-6, NT-proBNP (ln-transformed), and GGT.

Table 3

Association of baseline FGF21 levels with incident MetS.

FGF21	Model 1[a] HR (95% CI)	*P*	Model 2[b] HR (95% CI)	*P*	Model 3[c] HR (95% CI)	*P*	Model 4[d] HR (95% CI)	*P*
ln-transformed FGF21	1.32 (1.23–1.43)	< 0.001	1.30 (1.20–1.41)	< 0.001	1.30 (1.21–1.41)	< 0.001	1.21 (1.12–1.31)	< 0.001
FGF21 quartile								
1 (≤64.8 pg/mL)	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
2 (64.9–122.5 pg/mL)	1.25 (1.04–1.50)	0.020	1.23 (1.01–1.49)	0.036	1.21 (1.00–1.47)	0.050	1.16 (0.95–1.41)	0.13
3 (122.6–208.3 pg/mL)	1.53 (1.28–1.83)	< 0.001	1.52 (1.26–1.83)	< 0.001	1.52 (1.26–1.83)	< 0.001	1.39 (1.15–1.68)	< 0.001
4 (≥208.4 pg/mL)	1.92 (1.61–2.29)	< 0.001	1.82 (1.52–2.18)	< 0.001	1.82 (1.52–2.18)	< 0.001	1.55 (1.29–1.87)	< 0.001
Overall *p*	–	< 0.001	–	< 0.001	–	< 0.001	–	< 0.001

For continuous FGF21 levels, data are expressed as HR (95% CI) in terms of per SD (1.478) increase in ln-transformed FGF21 levels (pg/mL).

[a]Model 1: adjusted for baseline age (as both time-independent and -dependent variables), sex, and race/ethnicity (as both time-independent and -dependent variables).

[b]Model 2: further adjusted for education, family income, smoking, pack-years of smoking, current alcohol use, physical activity and sedentary behavior at baseline.

[c]Model 3: further adjusted for LDL-C, use of any lipid-lowering medication, and eGFR at baseline.

[d]Model 4: further adjusted for other cardiovascular risk biomarkers, including BMI, CRP, fibrinogen, IL-6, NT-proBNP (ln-transformed), and GGT at baseline.

Table 4

Interaction of baseline FGF21 levels with time (continuous number of years after baseline exam) for incident MetS.

FGF21 levels	Main effect	*P*	Interaction with time (years)	
	HR (95% CI)		HR (95% CI)	*P*
ln-transformed FGF21	1.37 (1.19–1.57)	< 0.001	0.97 (0.94–1.00)	0.033
FGF21 quartile				
1 (≤64.8 pg/mL)	1.00 (referent)	–	1.00 (referent)	–
2 (64.9–122.5 pg/mL)	1.62 (1.14–2.31)	0.007	0.92 (0.85–0.99)	0.025
3 (122.6–208.3 pg/mL)	1.64 (1.17–2.30)	0.004	0.96 (0.90–1.03)	0.27
4 (≥208.4 pg/mL)	2.46 (1.76–3.43)	< 0.001	0.88 (0.82–0.95)	< 0.001
Overall *p*	–	< 0.001	–	0.005

For continuous FGF21 levels, data are expressed as HR (95% CI) in terms of per SD increase in ln-transformed FGF21 levels (pg/mL). All data were adjusted for age (as both time-independent and -dependent variables), sex, race/ethnicity (as both time-independent and -dependent variables), education, family income, smoking, pack-years of smoking, current alcohol use, physical activity, sedentary behavior, LDL-C, use of any lipid-lowering medication, eGFR, BMI, CRP, fibrinogen, IL-6, NT-proBNP (ln-transformed), and GGT at baseline.

Table 5

Association of baseline FGF21 levels with individual components of incident MetS over follow-up period.

FGF21 levels	n	Outcome (%)	HR (95% CI)	*P*
Abdominal obesity				
ln-transformed FGF21, per SD (1.573)	2209	26.3	1.04 (0.86–1.25)	0.68
FGF21 quartile				
1 (≤ 57.9 pg/mL)	552	24.1	1.00 (referent)	–
2 (58.0–114.7 pg/mL)	552	26.3	1.03 (0.61–1.74)	0.92
3 (114.8–198.3 pg/mL)	553	25.9	0.85 (0.49–1.48)	0.56
4 (≥198.4 pg/mL)	552	28.8	1.16 (0.68–1.97)	0.59
Overall *p*			–	0.73
Elevated triglycerides				
ln-transformed FGF21, per SD (1.504)	3071	23.6	1.26 (1.08–1.47)	0.003
FGF21 quartile				
1 (≤61.5 pg/mL)	769	17.7	1.00 (referent)	–
2 (61.6–118.6 pg/mL)	768	23.4	1.23 (0.83–1.82)	0.30
3 (118.7–203.0 pg/mL)	768	22.9	1.36 (0.92–2.02)	0.13
4 (≥203.1 pg/mL)	766	30.3	2.21 (1.52–3.21)	< 0.001
Overall *p*			–	< 0.001
Reduced HDL-C				
ln-transformed FGF21, per SD (1.486)	2886	20.7	1.08 (0.92–1.26)	0.36
FGF21 quartile				
1 (<63.7 pg/mL)	722	16.5	1.00 (referent)	–
2 (63.8–119.7 pg/mL)	7 21	21.9	1.30 (0.85–2.01)	0.23
3 (119.8–204.7 pg/mL)	721	19.8	1.12 (0.71–1.77)	0.63
4 (>204.8 pg/mL)	722	24.7	1.46 (0.94–2.28)	0.093
Overall *p*			–	0.34
Elevated BP				
ln-transformed FGF21, per SD (1.545)	1990	45.1	1.04 (0.92–1.17)	0.57
FGF21 quartile				
1 (≤57.7 pg/mL)	497	41.0	1.00 (referent)	–
2 (57.8–113.9 pg/mL)	497	44.3	1.15 (0.82–1.60)	0.41

FGF21 levels	n	Outcome (%)	HR (95% CI)	*P*
3 (114.0–195.4 pg/mL)	498	42.4	1.27 (0.91–1.77)	0.15
4 (≥195.5 pg/mL)	498	52.8	1.23 (0.89–1.71)	0.22
Overall *p*			–	0.49
Elevated blood glucose				
ln-transformed FGF21, per SD (1.483)	3120	31.0	1.13 (0.99–1.29)	0.062
FGF21 quartile				
1 (≤64.3 pg/mL)	781	25.2	1.00 (referent)	–
2 (64.4–121.2 pg/mL)	779	30.7	1.47 (1.06–2.04)	0.020
3 (121.3–207.7 pg/mL)	780	31.4	1.36 (0.96–1.90)	0.080
4 (≥207.8 pg/mL)	780	36.8	1.25 (0.88–1.78)	0.21
Overall *p*			–	0.13

Participants with the metabolic syndrome at baseline as well as those with that component at baseline were excluded from the analysis. Data were adjusted for age, sex, race/ethnicity, education, family income, smoking, pack-years of smoking, current alcohol use, physical activity, sedentary behavior, LDL-C, use of any lipid-lowering medication, eGFR, BMI, CRP, fibrinogen, IL-6, NT-proBNP (ln-transformed), and GGT at baseline.