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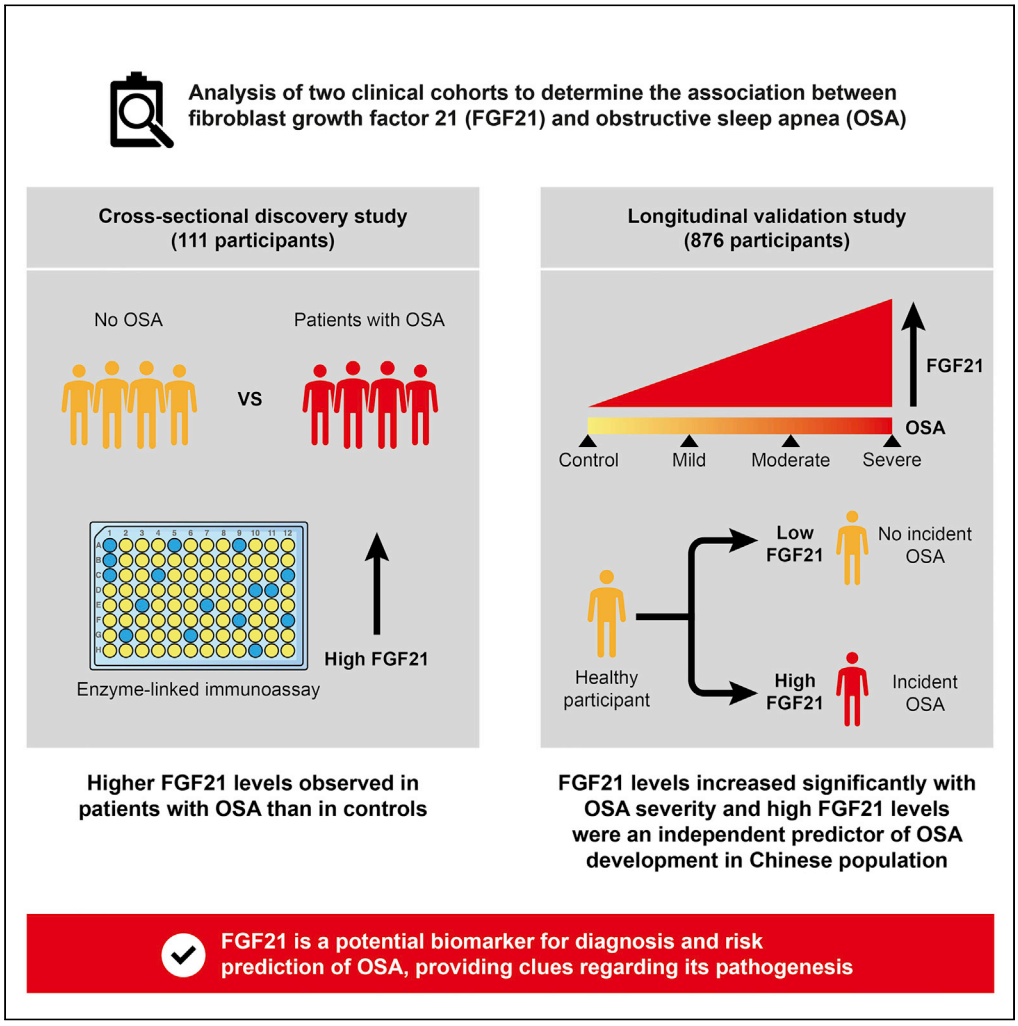

Weijun Huang, Jingyu Zhang, Jianyin Zou, ..., Hongliang Yi, Suru Liu, Shankai Yin

yihongl@126.com (H.Y.)
suruliu2011@163.com (S.L.)

Highlights

FGF21 levels are cross-sectionally and longitudinally associated with OSA

FGF21 levels increased significantly with increasing OSA severity

Higher FGF21 levels were an independent predictor of OSA development

FGF21 may be used as a biomarker for the diagnosis and risk prediction of OSA

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Fibroblast growth factor 21 is an independent predictor of prevalent and incident obstructive sleep apnea

Weijun Huang,[1,2,3,4] Jingyu Zhang,[1,2,3,4] Jianyin Zou,[1,2,3] Xiaoting Wang,[1,2,3] Huajun Xu,[1,2,3] Jian Guan,[1,2,3] Hongliang Yi,[1,2,3,*] Suru Liu,[1,2,3,5,*] and Shankai Yin[1,2,3]

SUMMARY

Fibroblast growth factor 21 (FGF21) is a metabolic regulator and a potential biomarker of metabolic diseases. Limited data are available on the association between FGF21 and obstructive sleep apnea (OSA), which is considered as a manifestation of metabolic syndrome. In the present cross-sectional and longitudinal analyses, the FGF21 level was associated with OSA. This analysis of two clinical cohorts is the first to show that the FGF21 level increased significantly with OSA severity and was an independent predictor of incident OSA in Chinese adults. The circulating FGF21 level could serve as a potential serum biomarker of OSA and its comorbidities and thus aid risk evaluation and early intervention.

INTRODUCTION

As a common and serious chronic sleep disorder, there are about 176 million patients with obstructive sleep apnea (OSA) in China, of whom about 66 million have moderate to severe OSA.[1] OSA significantly increases the risk of diabetes,[2] hypertension,[3] coronary heart disease,[4] stroke,[5] cognitive impairment,[6] and all-cause mortality,[7] and thus imposes a heavy social and economic burdens.[8] OSA is generally considered as a component of metabolic syndrome. Many pathophysiology mechanisms, such as metabolic dysregulation, oxidative stress, sympathetic activity, and so on, are considered involved due to chronic intermittent hypoxia and sleep fragmentation happened at night which may directly or indirectly mediate the expression of various cytokines.[9] These cytokines, assessed in blood or urine, serve as biomarkers and provide the pathophysiological basis for the increased risk of OSA and its comorbidities. However, unique biomarkers for early diagnosis and treatment of OSA are lacking.[10]

Fibroblast growth factor 21 (FGF21) is a recently described regulatory factor expressed in liver, adipose tissue, muscle, and pancreatic β cells.[11,12] Because it lacks a heparin-binding domain, FGF21 is secreted into the circulation to exert an endocrine-like function.[13] FGF21 regulates various metabolic processes, such as glucose, lipid, and vitamin D metabolism, as well as cholesterol and bile acid synthesis.[14,15] It also improves insulin sensitivity and triglyceride concentrations, causes weight loss, and alleviates obesity-related hyperglycemia and hyperlipidemia.[16] However, as a potential biomarker of metabolic diseases, an elevated serum FGF21 level was found in overweight individuals,[17] and in subjects with type 2 diabetes,[18,19] dyslipidemia,[20] nonalcoholic fatty liver disease,[21,22] or coronary heart disease.[23] And these characteristics above are generally considered as comorbidities of OSA, indicating the potential link between FGF21 and OSA. Since both OSA and FGF21 are closely related to metabolism, their interaction may underlie the association between metabolism and OSA. Studies regarding to the effects of OSA on serum FGF21 levels have reported conflicting results.[24,25] Additionally, no population-based, prospective study has examined the effect of the FGF21 level on future OSA risk. Therefore, we aimed to explore the association between FGF21 and OSA, cross-sectionally and longitudinally, to evaluate the usefulness of FGF21 as a potential biomarker of OSA. Our results provide a basis for further exploration of metabolic regulation of OSA, which may in turn yield insights into the early diagnosis and intervention of OSA and its related complications.

[1]Department of Otorhinolaryngology Head and Neck Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 600 Yishan Road, Shanghai, China

[2]Shanghai Key Laboratory of Sleep Disordered Breathing, 600 Yishan Road, Shanghai, China

[3]Otolaryngology Institute of Shanghai Jiao Tong University, 600 Yishan Road, Shanghai, China

[4]These authors contributed equally

[5]Lead contact

*Correspondence: yihongl@126.com (H.Y.), suruliu2011@163.com (S.L.)

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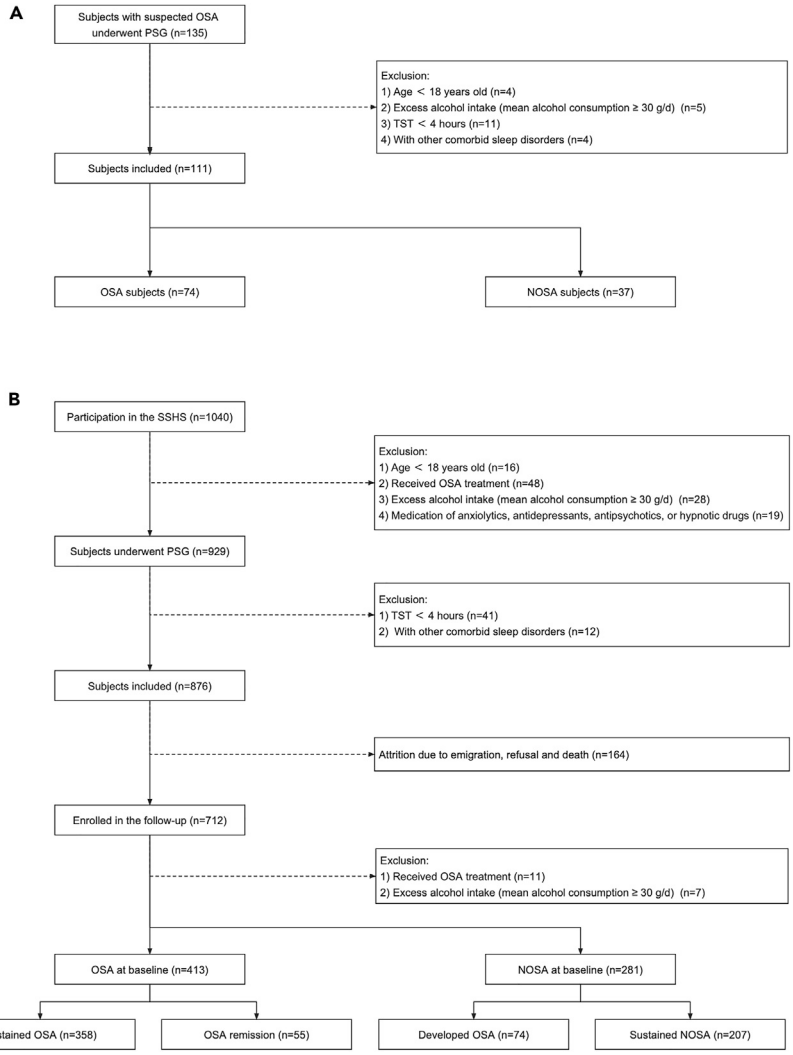

Figure 1. Flow chart of the recruitment process

(A) Flow chart of the recruitment process for the discovery study.

(B) Flow chart of the recruitment process for the validation study. OSA, obstructive sleep apnea; PSG, polysomnography; TST, total sleep time; NOSA, non-obstructive sleep apnea; SSHS, Shanghai Sleep Health Study.

RESULTS

Participant characteristics

A total of 111 and 876 Chinese adults were enrolled in discovery (Figure 1A) and validation (Figure 1B) cohorts, respectively. In the validation cohort, the attrition rate was 18.72%; 712 participants completed the follow-up, while 164 dropped out because of emigration, refusal to continue, or death (Figure 1B). The median duration of participation was 4.8 (4.1–5.5) years in the validation cohort. Among the 373 non-OSA (NOSA) participants, 281 completed the reassessment after 4.8 years. The clinical characteristics of the participants in the discovery cohort are presented in Table 1. OSA subjects were older, predominantly male, and more likely to be obese (higher BMI, neck circumference [NC], waist circumference [WC], hip circumference [HC], and waist hip ratio [WHR]); they also had deteriorated sleep-related parameters (higher apnea-hypopnea index [AHI], oxygen desaturation index, cumulative time of oxygen saturation <90% in total sleep time [CT90], microarousal index, and Epworth Sleepiness Scale [ESS] scores and lower mean oxygen saturation and lowest oxygen saturation) (all $p < 0.05$). Fasting blood glucose, fasting insulin, homeostasis model assessment insulin resistance (HOMA-IR), total cholesterol, triglyceride (TG), low-density lipoprotein, and apolipoprotein (Apo) B concentrations were significantly higher, whereas serum ApoA-I/ApoB was significantly lower, in the OSA compared with NOSA group ($p < 0.05$). As

Table 1. Characteristics of subjects in discovery study

Variables	NOSA (n = 37)	OSA (n = 74)	P
Demographic and clinical characteristics			
Age, years	41(26.50–50.50)	47(37–58)	0.010
Male, n (%)	24(64.86)	62(83.78)	0.031
BMI, kg/m2	24.02(21.84–25.49)	27.08(24.69–29.77)	<0.001
NC, cm	37(34–38)	40(37–42)	<0.001
WC, cm	88(78.50–92.50)	98(91.50–104)	<0.001
HC, cm	95(93.50–99)	100(96–108)	<0.001
WHR	0.89(0.83–0.96)	0.96(0.92–1.01)	<0.001
SBP, mmHg	120(113–124.50)	128(120–140)	0.001
DBP, mmHg	80(74–83.50)	82(76–90.50)	0.036
Smoker, n (%)	6(16.22)	23(31.08)	0.112
Drinker, n (%)	3(8.11)	21(28.38)	0.015
Hypertension, n (%)	4(10.81)	28(37.84)	0.003
Diabetes, n (%)	2(5.41)	6(8.11)	0.717
CVD, n (%)	1(2.70)	6(8.11)	0.421
Hyperlipidemia, n (%)	2(5.41)	17(22.97)	0.030
MS, n (%)	1(2.70)	21(28.38)	0.001
ESS, scores	0(0–3.50)	8(3–11)	<0.001
EDS, n (%)	2(5.41)	28(37.84)	<0.001
PSG parameters			
AHI, events/h	0.80(0.30–2.80)	46.95(23.55–60.20)	<0.001
ODI, events/h	1.20(0.50–3.70)	45.90(21.30–61.95)	<0.001
$MSaO_2$, (%)	96(95–97.50)	93(89–94)	<0.001
$LSaO_2$, (%)	94(91–96)	72(61–80)	<0.001
CT90, (%)	0(0–0.03)	10.11(2.43–30.84)	<0.001
MAI, events/h	10.30(7.05–17)	25.91(14.68–36.85)	<0.001
TST, minutes	344.50(296–408.25)	416.90(346.95–423.75)	0.005
Biochemical indicators			
FBG, mmol/L	4.87(4.50–5.31)	5.19(4.94–5.72)	0.004
Fasting insulin, μU/ml	7.83(4.84–10.82)	13.26(6.85–19.42)	0.001
HOMA-IR	1.58(1.01–2.32)	3.02(1.40–4.51)	0.002
TC, mmol/L	4.30(3.73–5.09)	4.93(4.15–5.30)	0.010
TG, mmol/L	1.132(0.76–1.65)	1.72(1.05–2.53)	0.005
HDL, mmol/L	1.02(0.92–1.27)	0.99(0.87–1.12)	0.071
LDL, mmol/L	2.44(2.07–3.06)	2.94(2.40–3.55)	0.010
ApoA-I, g/L	1.07(0.95–1.32)	1.11(1–1.25)	0.606
ApoB, g/L	0.68(0.63–0.83)	0.82(0.71–0.96)	<0.001
ApoE, mg/dL	4.31(3.14–4.97)	4.68(3.71–5.61)	0.052
Lp(a), mg/dL	7.10(2.60–19.60)	7.30(3.50–13.85)	0.793

(*Continued on next page*)

Table 1. *Continued*

Variables	NOSA (n = 37)	OSA (n = 74)	P
ApoA-I/ApoB	1.55(1.28–2)	1.33(1.15–1.58)	0.005
FGF21, pg/ml	234.18(143.37–332.43)	380.58(261.39–507.95)	<0.001

See also Figure 2.

Abbreviations: NOSA, non-obstructive sleep apnea; OSA, obstructive sleep apnea; BMI, body mass index; NC, neck circumference; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular diseases; MS, metabolic syndrome; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; PSG, polysomnography; AHI, apnea hypopnea index; ODI, oxygen desaturation index; $MSaO_2$, mean oxygen saturation; $LSaO_2$, lowest oxygen saturation; CT90, the cumulative time of oxygen saturation below 90% in total sleep time; MAI, microarousal index; TST, total sleep time; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Apo, apolipoprotein; Lp(a), lipoprotein (a); FGF21, fibroblast growth factor 21.

expected, similar results were obtained from the validation study. OSA severity was associated with male sex, higher obesity indices, worse sleep-related parameters, and glucolipid metabolism deterioration (all $p < 0.05$; Table 2).

FGF21 levels in discovery and validation study

In the discovery study, significantly higher FGF21 level was observed in OSA subjects than in the NOSA controls (380.58 [261.39–507.95] vs. 234.18 [143.37–332.43] pg/mL; $p < 0.001$) (Table 1 and Figure 2). To further validate the role of FGF21, we performed a validation study in 503 OSA subjects and 373 NOSA controls. As showed in Table 2, serum FGF21 concentrations were significantly higher in the OSA group (362.17 [226.39–479.52] pg/mL) compared with the NOSA group (213.35 [150.57–283.34] pg/mL; $p < 0.001$). Cross-sectional analysis at baseline indicated that participants with more severe OSA had higher FGF21 levels (Table 2 and Figure 3). To determine significant correlations between clinical parameters and serum FGF21, Spearman correlation analysis was used (Figure S1). Age, obesity indices, blood pressure, sleep-related parameters, and glucolipid metabolism were associated with the serum FGF21 level ($p < 0.01$). Fully adjusted logistic regression models demonstrated a significant relationship between FGF21 and prevalent OSA, with higher odds in the highest quartile (Q4; FGF21 > 424 pg/mL) of the FGF21 level (odds ratio [OR]: 3.332; 95% confidence interval [CI]: 1.474–7.533; $p = 0.004$) when using the lowest quartile (Q1; FGF21 < 175.40 pg/mL) as the reference (P trend <0.001) (Table 3 and Figures S2A–S2C). Similar results were found when using the quartile ranges from the discovery cohort at this stage (Table S1).

After 4.8 years of follow-up, 74 incident OSA cases occurred (41 males and 33 females) among 281 NOSA participants at baseline, and none of them received OSA treatment before the follow-up study. In the longitudinal cohort, subjects enrolled in the follow-up study were more likely to be male and to have higher obesity indices (NC, WC, HC, and WHR), HOMA-IR, TG, and serum FGF21 levels compared with those lost to follow-up. No differences were observed in polysomnography (PSG) indices between the groups at baseline (Table S2). At follow-up, the OSA incidence rate was 26.33% (74/281; 95% CI: 21.36%–31.96%), and the annual incidence was 5.49%. The baseline characteristics were described in Table 4. Subjects who developed OSA had higher BMI and a higher likelihood of hypertension ($p < 0.05$). Baseline FGF21 concentrations were significantly higher in subjects who developed OSA (284.13 [220.12–379.39] pg/mL) compared with those who did not (204.21 [146.28–270.02] pg/mL; $p < 0.001$) (Table 4 and Figure 4A). In the analysis stratified by baseline FGF21 quartile from validation study (Q1–Q4), Q1 subjects (FGF21 < 160.50 pg/mL) had an incidence rate of 11.43%. The rate rose to 18.57%, 27.14%, and 47.89% in Q2 (FGF21: 160.50–227 pg/mL), Q3 (FGF21: 228–289.50 pg/mL), and Q4 (FGF21 > 289.50 pg/mL) subjects, respectively (P trend <0.001) (Figure 4B). The Kaplan-Meier survival curves for the sample stratified by FGF21 are presented in Figure 4C. Higher baseline FGF21 levels were associated with a higher crude incidence rate for OSA ($p = 0.003$ by log-rank test). Cox proportional hazards models revealed that higher FGF21 quartiles were associated with a greater risk of incident OSA compared with the lowest quartile (Q1) after adjusting for potential confounding factors (Figures 5A–5C). The fully adjusted hazard ratios (95% CI) for Q2–Q4 were 1.753 (0.716–4.290), 2.489 (1.020–6.076), and 3.555 (1.547–8.168), respectively (P trend <0.001) (Table 5). Similar results on association of FGF21 levels and incident OSA were also found when using the quartile ranges from the discovery cohort at this stage (Table S3).

Table 2. Characteristics of subjects with different OSA severity in validation study

Variables	NOSA (n = 373)	OSA (n = 503)	P[a]	Mild OSA (n = 128)	Moderate OSA (n = 105)	Severe OSA (n = 270)	P[b]
Demographic and clinical characteristics							
Age, years	42(30–50)	45(35-56)	<0.001	46(37–57)	48(36.50–56.50)	44(35–55)	<0.001
Male, n (%)	209(56.03)	431(85.69)	<0.001	99(77.34)	84(80)	248(91.85)	<0.001
BMI, kg/m2	23.50(21.61–25.38)	26.97(24.57–29.14)	<0.001	26.20(23.51–28.20)	25.40(23.56–27.89)	27.68(25.89–30.16)	<0.001
NC, cm	36(33–38)	40(37–42)	<0.001	38(36–41)	39(36–41)	41(38.50–42)	<0.001
WC, cm	85(77–91)	97(91–103)	<0.001	93(86.50–100)	94(87–100)	100(94–106)	<0.001
HC, cm	95(90–99)	101(96–105.50)	<0.001	98(94.50—103)	99(95–105)	102(99–107)	<0.001
WHR	0.89(0.84–0.94)	0.96(0.92–0.99)	<0.001	0.93(0.90–0.98)	0.95(0.90–0.99)	0.96(0.93–1.01)	<0.001
SBP, mmHg	120(114–127)	126(117–137)	<0.001	121(117–132)	125(115–137)	128(119–139)	0.027
DBP, mmHg	78(71–82)	80(74–87)	<0.001	79(72–84)	78(70–87)	80(75–89)	0.003
Smoker, n (%)	86(23.06)	156(31.01)	0.009	42(32.81)	25(23.81)	89(32.96)	0.200
Drinker, n (%)	39(10.46)	125(24.85)	<0.001	23(17.97)	21(20)	81(30)	0.015
Hypertension, n (%)	34(9.12)	166(33)	<0.001	34(26.56)	33(31.43)	99(36.67)	0.125
Diabetes, n (%)	27(7.24)	53(10.54)	0.098	12(9.38)	11(10.48)	30(11.11)	0.870
CVD, n (%)	8(2.14)	38(7.55)	<0.001	8(6.25)	12(11.43)	18(6.67)	0.238
Hyperlipidemia, n (%)	13(3.49)	110(21.87)	<0.001	19(14.84)	24(22.86)	67(24.81)	0.077
MS, n (%)	15(4.02)	128(25.45)	<0.001	26(20.31)	18(17.14)	84(31.11)	0.006
ESS, scores	0(0–3)	7(3–11)	<0.001	5(1–7)	6(3-9)	10(5–12)	<0.001
EDS, n (%)	21(5.63)	139(27.63)	<0.001	10(7.81)	23(21.90)	112(41.48)	<0.001
PSG parameters							
AHI, events/h	1(0.30–2.40)	34.40(14.30–54.80)	<0.001	9.40(6.75–11.10)	21.20(18.75–24.85)	53.50(44.08–63.70)	<0.001
ODI, events/h	1.30(0.50–3.23)	29.60(13.68–53.88)	<0.001	9.90(6.80–12.60)	21.10(16.70–26.70)	50.50(38.40–66.80)	<0.001
$MSaO_2$, (%)	96(95–97)	93(91–95)	<0.001	94(93–96)	94(92–96)	92(89–94)	<0.001
$LSaO_2$, (%)	93(90–96)	78(68–84)	<0.001	85(81–89)	80(75–85)	71(63–78)	<0.001
CT90, (%)	0(0–0.05)	4.31(0.90–18.07)	<0.001	0.63(0.20–2.04)	2.14(0.63–5.32)	12.88(3.97–33.28)	<0.001
MAI, events/h	12(7.90–17.75)	23.81(14.50–34.70)	<0.001	18.65(12–28.89)	23.80(14.05–33.20)	26.29(16.45–39)	<0.001
TST, minutes	370(310–417.15)	410.70(350.50–422)	<0.001	403.15(331.63–419.50)	393(332–419.50)	419(362.38–425.63)	0.009
Biochemical indicators							
FBG, mmol/L	4.97(4.54–5.30)	5.25(4.89–5.69)	<0.001	5.14(4.80–5.57)	5.22(4.97–5.59)	5.33(4.94–5.84)	0.021
Fasting insulin, μU/ml	6.69(4.33–9.63)	11.19(6.87–16.55)	<0.001	8.60(5.76–14)	10.79(6.77–14.07)	12.85(7.95–18.64)	<0.001
HOMA-IR	1.41(0.84–2.12)	2.36(1.33–4.02)	<0.001	1.84(1.05–3.38)	2.28(1.37–3.40)	2.78(1.49–4.47)	0.004
TC, mmol/L	4.22(3.62–4.80)	4.75(4.19–5.44)	<0.001	4.55(3.91–5.24)	4.72(4.15–5.44)	4.89(4.33–5.49)	0.008
TG, mmol/L	1.02(0.68–1.51)	1.50(1.03–2.24)	<0.001	1.24(0.87–1.82)	1.45(1.04–2.38)	1.66(1.15–2.38)	<0.001
HDL, mmol/L	1.09(0.94–1.27)	0.99(0.86–1.13)	<0.001	1.05(0.89–1.25)	0.99(0.88–1.10)	0.95(0.84–1.11)	0.001

(*Continued on next page*)

Table 2. *Continued*

Variables	NOSA (n = 373)	OSA (n = 503)	P[a]	Mild OSA (n = 128)	Moderate OSA (n = 105)	Severe OSA (n = 270)	P[b]
LDL, mmol/L	2.42(2.04–2.93)	2.89(2.43–3.40)	<0.001	2.78(2.28–3.37)	2.81(2.32–3.25)	2.98(2.52–3.52)	0.012
ApoA-I, g/L	1.11(0.98–1.27)	1.09(0.97–1.20)	0.123	1.12(1–1.26)	1.09(0.97–1.21)	1.07(0.97–1.19)	0.028
ApoB, g/L	0.69(0.59–0.79)	0.82(0.73–0.92)	<0.001	0.80(0.66–0.88)	0.80(0.72–0.88)	0.85(0.75–0.95)	<0.001
ApoE, mg/dL	3.77(3.22–4.67)	4.46(3.61–5.49)	<0.001	4.10(3.43–5.07)	4.37(3.61–5.33)	4.70(3.78–5.66)	0.003
Lp(a), mg/dL	7(3.70–14.88)	8.20(4.30–16.33)	0.084	8.75(4.25–17.33)	9.60(4.70–17.73)	7.50(4–15.45)	0.403
ApoA-I/ApoB	1.63(1.33–1.97)	1.34(1.15–1.54)	<0.001	1.44(1.23–1.73)	1.38(1.19–1.59)	1.30(1.10–1.47)	<0.001
FGF21, pg/ml	213.35(150.57–283.34)	362.17(226.39–479.52)	<0.001	247.49(153.70–400.51)	299.79(194.67–460.52)	408.06(300.80–520.59)	<0.001

Abbreviations: OSA, obstructive sleep apnea; NOSA, non-obstructive sleep apnea; BMI, body mass index; NC, neck circumference; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular diseases; MS, metabolic syndrome; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; PSG, polysomnography; AHI, apnea hypopnea index; ODI, oxygen desaturation index; $MSaO_2$, mean oxygen saturation; $LSaO_2$, lowest oxygen saturation; CT90, the cumulative time of oxygen saturation below 90% in total sleep time; MAI, microarousal index; TST, total sleep time; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Apo, apolipoprotein; Lp(a), lipoprotein (a); FGF21, fibroblast growth factor 21.

[a]indicated p values between OSA and NOSA groups.

[b]indicated p values among mild OSA, moderate OSA and severe OSA groups. See also Figure 3.

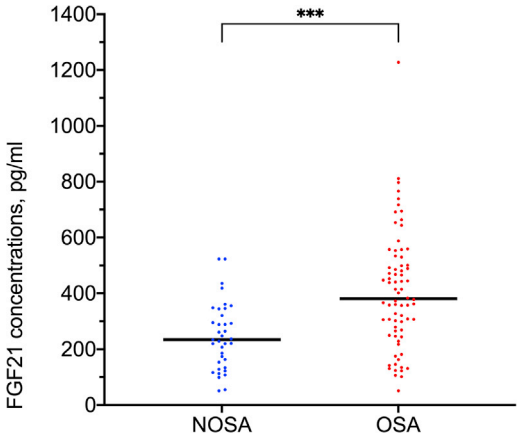

Figure 2. FGF21 levels in the OSA and NOSA groups in the discovery study

All data are represented as dots and the black line indicates the median of each group. *** indicated the significance between OSA and NOSA with a p value < 0.001. Comparison was performed by Mann–Whitney U test. See also Table 1. OSA, obstructive sleep apnea; NOSA, non-obstructive sleep apnea; FGF21, fibroblast growth factor 21.

Predictive accuracy of the FGF21 model

The conventional model for OSA prediction included the risk factors of age, sex, BMI, NC, and ESS.[3,26,27] The conventional model to which the FGF21 was added was named the FGF21 model. The value of the models for predicting OSA development was assessed using receiver operating characteristic analyses. The areas under the curve (AUCs) (95% CI) were 0.616 (0.540–0.692) and 0.742 (0.676–0.809) for the conventional and FGF21 models, respectively (Figure 6). The addition of FGF21 significantly improved the accuracy of incident OSA predictions, as reflected in the improved AUC ($p < 0.001$) with a sensitivity of 70% and a specificity of 73% (Youden index). The ability of serum FGF21 measurements to improve OSA discrimination and reclassification was shown in Table S4. FGF21 modestly but significantly improved the net reclassification index (NRI) and integrated discrimination improvement (IDI) of the conventional model in terms of incident OSA prediction (+0.187 and +0.017; $p = 0.032$ and 0.047 for NRI and IDI, respectively). The decision curve analysis showed that the FGF21 and conventional models were both superior to the intervene-all and intervene-none schemes (Figure S3). At a threshold probability of 0.1–0.2, the FGF21 model was superior to the conventional model, and may thus be useful for early OSA evaluation and intervention. The FGF21 model equation was as follows,

$$\ln\frac{P}{1-P} = \exp(-1.060 + 0.574 * \lg FGF21 - 0.004 * Age + 0.060 * Sex + 0.025 * BMI - 0.013 * NC - 0.001 * ESS)$$

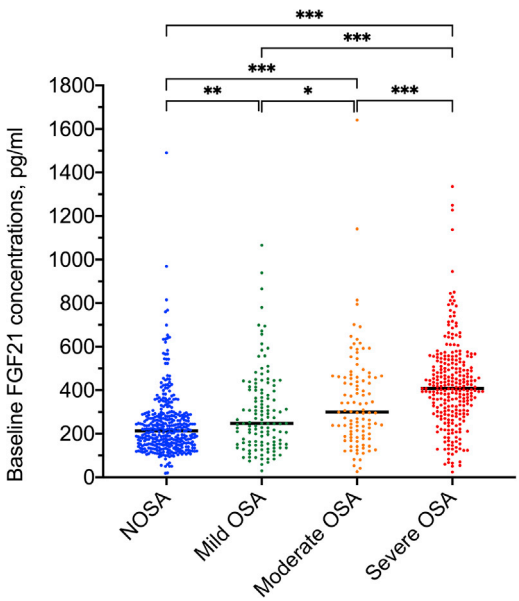

Figure 3. FGF21 levels according to OSA severity in the validation study

All data are represented as dots and the black line indicates the median of each group. * indicated the significance between each two group. Comparison was performed by Mann–Whitney U test. Single symbol indicated a p value < 0.05. Double symbols indicated a p value < 0.01. Triple symbols indicated a p value < 0.001.See also Table 2. OSA, obstructive sleep apnea; FGF21, fibroblast growth factor 21; NOSA, non-obstructive sleep apnea.

Table 3. Association of FGF21 quartiles and prevalent OSA

Predictors	Number of subjects	Number of OSA	Adjusted OR (95% CI) for cross-sectional analysis					
			Model 1	P	Model 2	P	Model 3	P
FGF21, pg/ml	876	503	/	/	/	/	/	/
Q1, <175.40	219	86	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
Q2, 175.40–272.50	219	85	0.711(0.451–1.122)	0.143	0.695(0.431–1.120)	0.135	0.555(0.281–1.096)	0.090
Q3, 272.55–424	219	144	2(1.261–3.174)	0.003	1.965(1.212–3.187)	0.006	1.252(0.619–2.536)	0.532
Q4, >424	219	188	5.528(3.206–9.532)	<0.001	5.298(3.004–9.345)	<0.001	3.332(1.474–7.533)	0.004
P trend	/	/	/	<0.001	/	<0.001	/	<0.001

Model 1 was adjusted for age, sex, BMI, and NC. Model 2 was adjusted for variables included in Model 1 and smoker, drinker, hypertension, diabetes, CVD, hyperlipidemia, MS. Model 3 was adjusted for variables included in Model 2 and ESS, $LSaO_2$, MAI. See also Figure S2.
Abbreviations: FGF21, fibroblast growth factor 21; OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval; BMI, body mass index; NC, neck circumference; CVD, cardiovascular diseases; MS, metabolic syndrome; ESS, Epworth Sleepiness Scale; $LSaO_2$, lowest oxygen saturation; MAI, microarousal index.

where P was the probability of developing OSA (male sex = 1 and female = 0). Subjects with higher FGF21 levels were more likely to develop OSA.

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate that the serum FGF21 level increased with the severity of OSA and to reveal an independent association between an elevated circulating FGF21 level and the risk of incident OSA. A significant relationship was observed, in that, individuals in the highest quartile of baseline FGF21 levels had an approximately 3-fold greater relative risk of incident OSA compared with those in the lowest quartile. FGF21 is a predictor of OSA independent of age, sex, BMI, NC, and day time sleepiness symptoms, which are generally considered OSA risk factors.[26–32] FGF21 assay can be used as a potential biomarker for simple population-based OSA screening and for identifying individuals at high risk of developing this condition. These unique findings suggest a direct pathophysiological effect of FGF21 on OSA development. Elevated circulating FGF21 occurs in the early stages of metabolic disorder, well before OSA diagnosis by PSG.

FGF21 is a recently identified putative regulator of metabolism. In the present study, significant positive associations were found between FGF21 levels and obesity indices, including BMI, WC, and WHR.[16,20,21] Individuals with type 2 diabetes, hyperlipidemia, nonalcoholic fatty liver, and coronary heart disease show FGF21 elevation to varying degrees.[17,18,20,21,23,33] A rapid increase in the FGF21 concentration in metabolic disorders via compensatory secretion has been reported.[34] However, elevated FGF21 levels in obese patients do not increase glucose tolerance or reduce serum triglycerides.[35] In mice with diet-induced obesity, endogenous FGF21 levels were significantly increased, but FGF receptor 1 levels and β-klotho expression in white adipose tissue were significantly downregulated.[35] Mice with diet-induced obesity are also less sensitive to exogenous FGF21. Taken together, these findings indicate that elevated FGF21 levels in OSA might reflect a state of FGF21 insensitivity. Other studies have shown that weight reduction in obese children can reduce FGF21 levels,[36] and that exogenous FGF21 treatment can relieve obesity and obesity-related complications in adults,[37] including hyperglycemia, insulin resistance, and dyslipidemia. The latter phenomenon may suggest the involvement of FGF21 in the onset and progression of OSA and its metabolic complications. However, at present, FGF21 can only be considered a biomarker of metabolic stress.

Several possible mechanisms to explain the relationship between FGF21 and OSA have been proposed. Hypoxia was shown to increase FGF21 expression. Circulating free fatty acids (FFAs), produced by lipolysis in adipose tissue, increase under hypoxic conditions.[38] The liver is the main organ responsible for circulating FGF21 production in humans and rodents, wherein peroxisome proliferator-activated receptor alpha and FGF21 expression are triggered by FFAs.[39] Meanwhile, lipolysis induced by oxidative stress increases the catecholamine response, and the hypoxia-mediated increase in hormone-sensitive lipase phosphorylation requires FGF21.[25] Two studies suggested that FGF21 primarily depends on the adipokine adiponectin to exert its effects on energy metabolism and insulin sensitivity in mice.[40,41] Adiponectin is secreted by adipocytes with both anti-atherogenic and anti-inflammatory properties.[42] Studies have shown that

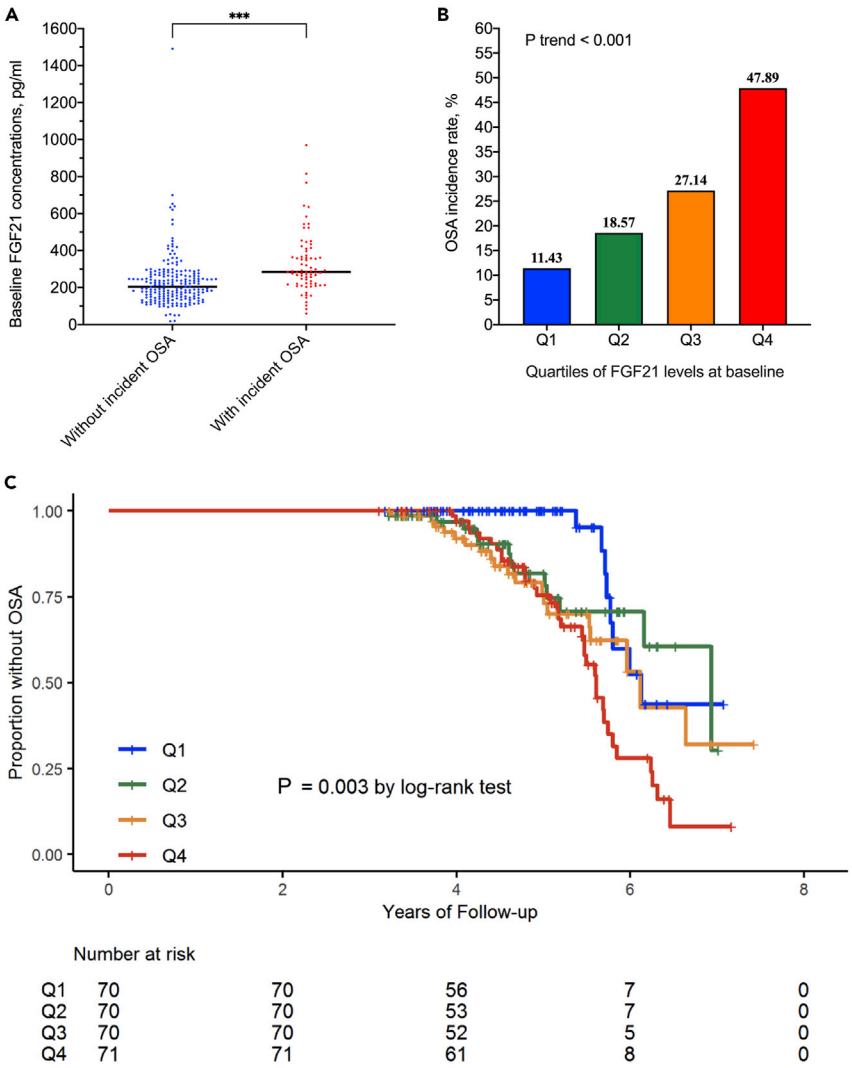

Figure 4. Association between the baseline FGF21 level and OSA incidence

(A) FGF21 levels in subjects with versus without incident OSA in the follow-up. All data are represented as dots and the black line indicates the median of each group. *** indicated the significance between the two group with a p value < 0.001. Comparison was performed by Mann–Whitney U test. See also Table 4.

(B) Incidence rate of OSA at follow-up according to the FGF21 level quartile at baseline (Q1–Q4; for 281 NOSA subjects at baseline with follow-up data): <160.50 pg/mL, 160.50–227 pg/mL, 228–289.50 pg/mL, and >289.50 pg/mL.

(C) Kaplan–Meier survival curves for incident OSA across the FGF21 level quartiles at baseline (Q1–Q4; for 281 NOSA subjects at baseline with follow-up data): <160.50 pg/mL, 160.50–227 pg/mL, 228–289.50 pg/mL, and >289.50 pg/mL.

FGF21, fibroblast growth factor 21; OSA, obstructive sleep apnea.

intermittent hypoxemia downregulates adiponectin expression at the levels of secretion and transcription.[43,44] Severe OSA subjects had lower adiponectin levels than NOSA controls, with significant improvements in adiponectin levels seen after continuous positive airway pressure.[45] Increased FGF21 levels in OSA suggest a mechanism involving a compensatory response to the decreased adiponectin induced by OSA. The paradoxical elevation of serum FGF21 might counteract the metabolic stress precipitated by OSA as a defensive response. This scenario is reminiscent of the hyperinsulinemia and hyperleptinemia seen in OSA, as compensatory responses to insulin and leptin resistance.

A high-serum FGF21 level was an independent predictor of OSA in adults, and may play a role in the multiple organ dysfunction associated with the body's attempts to alleviate its effects. These findings further support the notion that elevated circulating FGF21 occurs in the very early stages of deterioration

Table 4. Baseline characteristics of NOSA subjects with versus without incident OSA at follow-up in validation study

Baseline variables	OSA state at follow-up: Without incident OSA (n = 207)	OSA state at follow-up: With incident OSA (n = 74)	P
Demographic and clinical characteristics			
Age, years	43(30–50)	42(29–49)	0.720
Male, n (%)	137(66.18)	41(55.41)	0.122
BMI, kg/m2	23.60(21.63–24.98)	24.30(22.16–26.44)	0.035
Neck circumference, cm	36(33–38)	36(33–39)	0.526
Waist circumference, cm	86(80–92)	86(77–91)	0.441
Hip circumference, cm	96(92–99)	95.50(91–98)	0.542
Waist hip ratio	0.90(0.85–0.94)	0.89(0.83–0.94)	0.314
SBP, mmHg	120(114–128)	120(117.50–127)	0.981
DBP, mmHg	80(72–82)	77.50(72–80)	0.440
Smoker, n (%)	42(20.29)	20(27.03)	0.254
Drinker, n (%)	25(12.08)	3(4.05)	0.068
Hypertension, n (%)	12(5.80)	10(13.51)	0.044
Type 2 diabetes, n (%)	10(4.83)	7(9.46)	0.162
CVD, n (%)	2(0.97)	2(2.70)	0.284
Hyperlipidemia, n (%)	6(2.90)	2(2.70)	0.646
MS, n (%)	5(2.42)	3(4.05)	0.438
ESS, scores	0(0–3)	0(0–3)	0.926
EDS, n (%)	11(5.31)	5(6.76)	0.770
PSG parameters			
AHI, events/h	0.90(0.30–2.20)	1.05(0.38–2.73)	0.288
ODI, events/h	1.20(0.50–2.95)	1.70(0.70–4.05)	0.078
$MSaO_2$, (%)	96(95–97)	97(95–98)	0.079
$LSaO_2$, (%)	94(90–96)	93(90–95)	0.085
CT90, (%)	0(0–0.07)	0(0–0.02)	0.548
MAI, events/h	12(7.80–17.70)	12.30(9.08–18.75)	0.595
TST, minutes	371(307–415.50)	364.25(321.63–414.38)	0.773
Biochemical indicators			
FBG, mmol/L	4.99(4.62–5.32)	4.87(4.50–5.36)	0.733
Fasting insulin, μU/ml	6.90(4.33–9.74)	6.39(4.63–9.69)	0.954
HOMA-IR	1.49(0.87–2.18)	1.42(0.95–2.15)	0.926
TC, mmol/L	4.19(3.62–4.76)	4.27(3.50–4.87)	0.609
TG, mmol/L	1.05(0.70–1.53)	1.15(0.70–1.56)	0.601
HDL, mmol/L	1.07(0.93–1.24)	1.07(0.94–1.32)	0.764
LDL, mmol/L	2.42(2.07–2.87)	2.40(1.86–2.92)	0.856
ApoA-I, g/L	1.10(0.98–1.23)	1.10(0.96–1.28)	0.982
ApoB, g/L	0.69(0.60–0.79)	0.67(0.59–0.81)	0.742
ApoE, mg/dL	3.76(3.23–4.61)	4.02(3.17–5.06)	0.263
Lp(a), mg/dL	6.70(3.25–15.20)	7.20(4.13–17.65)	0.636

(*Continued on next page*)

Table 4. *Continued*

Baseline variables	OSA state at follow-up: Without incident OSA (n = 207)	With incident OSA (n = 74)	P
ApoA-I/ApoB	1.61(1.33–1.91)	1.58(1.31–2.16)	0.843
FGF21, pg/ml	204.21(146.28–270.02)	284.13(220.12–379.39)	<0.001

See also Figure 4A.

Abbreviations: NOSA, non-obstructive sleep apnea; OSA, obstructive sleep apnea; BMI, body mass index; NC, neck circumference; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular diseases; MS, metabolic syndrome; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; PSG, polysomnography; AHI, apnea hypopnea index; ODI, oxygen desaturation index; $MSaO_2$, mean oxygen saturation; $LSaO_2$, lowest oxygen saturation; CT90, the cumulative time of oxygen saturation below 90% in total sleep time; MAI, microarousal index; TST, total sleep time; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Apo, apolipoprotein; Lp(a), lipoprotein (a); FGF21, fibroblast growth factor 21.

of metabolic homeostasis,[19] well before evident sleep apnea. This phenomenon mirrors FGF21 resistance and, like insulin resistance, may be associated with the pathogenesis of OSA in humans. Further studies are needed to elucidate the pathophysiological mechanisms underlying these relationships.

The strengths of this study included the cross-sectional and longitudinal collection of detailed data on OSA risk factors and covariates over a broad spectrum of OSA severity (AHI: 0–114.2 events/hour) by standard PSG in the discovery and validation studies. Since FGF21 can be easily assayed for population-based screening and identification of high-risk individuals, we established a simple model that may be useful for early diagnosis and intervention in OSA.

Limitations of the study

However, several limitations must also be acknowledged. Although the sample size in the present study fulfilled the statistical requirements, it is difficult to enroll additional patients from a single center. Our cohort of Chinese subjects had a lower mean BMI compared with Western cohorts. The cohort also had a higher proportion of males, higher obesity indices, higher TG, and serum FGF21 levels, and a higher HOMA-IR compared with those who were lost to follow-up. Thus, the incidence of OSA might have been slightly overestimated. Therefore, the FGF21 model should be interpreted with caution as the results may not represent the general Chinese population. Furthermore, BMI might not adequately represent

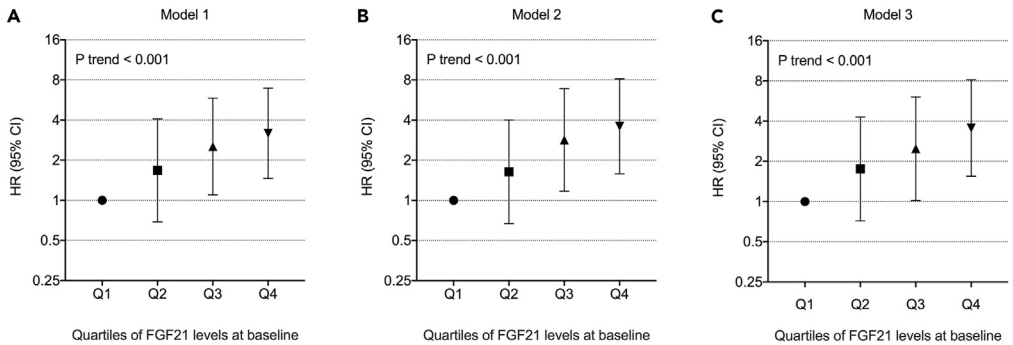

Figure 5. HRs and 95% CIs for FGF21 quartiles and incident OSA

(A–C) Cox proportional hazards regression models fitted to examine the longitudinal associations between the FGF21 level and incident OSA in (A) model 1 (adjusted for age, sex, BMI, and NC), (B) model 2 (adjusted for the variables included in Model 1 as well as smoking, alcohol consumption, hypertension, diabetes, CVD, hyperlipidemia, and MS), and (C) model 3 (adjusted for the variables included in Model 2 as well as ESS, $LSaO_2$, and MAI). See also Table 5. HR, hazard ratio; CI, confidence interval; FGF21, fibroblast growth factor 21; OSA, obstructive sleep apnea; BMI, body mass index; NC, neck circumference; CVD, cardiovascular diseases; MS, metabolic syndrome; ESS, Epworth Sleepiness Scale; $LSaO_2$, lowest oxygen saturation; MAI, microarousal index.

Table 5. Association of FGF21 quartiles and incident OSA

Predictors	Number of subjects	Number of OSA	Adjusted HR (95% CI) for longitudinal analysis					
			Model 1	P	Model 2	P	Model 3	P
FGF21 (pg/mL)	281	74	/	/	/	/	/	/
Q1, <160.50	70	8	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
Q2, 160.50–227	70	13	1.676(0.688–4.081)	0.255	1.638(0.670–4.005)	0.279	1.753(0.716–4.290)	0.219
Q3, 228-289.50	70	19	2.533(1.098–5.841)	0.029	2.837(1.172–6.867)	0.021	2.489(1.020–6.076)	0.045
Q4, >289.50	71	34	3.177(1.455–6.938)	0.004	3.590(1.580–8.158)	0.002	3.555(1.547–8.168)	0.003
P trend	/	/	/	<0.001	/	<0.001	/	<0.001

Model 1 was adjusted for age, sex, BMI, and NC. Model 2 was adjusted for variables included in Model 1 and smoker, drinker, hypertension, diabetes, CVD, hyperlipidemia, MS. Model 3 was adjusted for variables included in Model 2 and ESS, $LSaO_2$, MAI. See also Figure 5.
Abbreviations: FGF21, fibroblast growth factor 21; OSA, obstructive sleep apnea; HR, hazards ratio; CI, confidence interval; BMI, body mass index; NC, neck circumference; CVD, cardiovascular diseases; MS, metabolic syndrome; ESS, Epworth Sleepiness Scale; $LSaO_2$, lowest oxygen saturation; MAI, microarousal index.

visceral adiposity, which is considered more important than FGF21 levels. Therefore, adiposity may have confounded the results to some extent, despite adjustment for BMI. Additionally, factors that were not controlled for in this study, including diet and exercise habits, might have had a confounding effect. The results of this study thus require validation in larger multicenter or multiethnic studies of the general population.

Conclusions

Our findings indicate that FGF21 levels are cross-sectionally and longitudinally associated with OSA. FGF21 levels increased significantly with increasing OSA severity, and higher FGF21 levels were an independent predictor of OSA development in adulthood. Thus, FGF21 measurements may be useful for early diagnosis and intervention of OSA, to prevent deterioration of comorbidities. Further studies are needed to elucidate the pathophysiological mechanisms underlying this relationship.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- EXPERIMENTAL MODEL AND SUBJECT DETAILS
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  - Anthropometric and biochemical assessments
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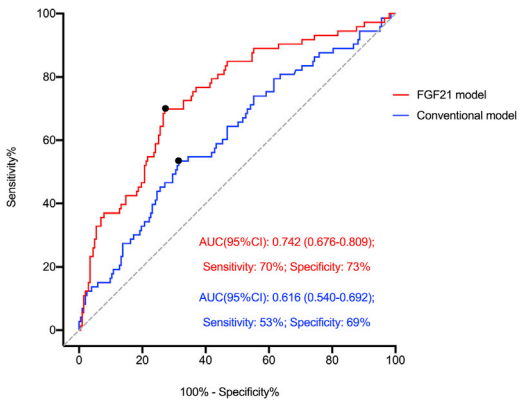

Figure 6. ROC curves and AUC values of FGF21 and conventional models for the prediction of incident OSA

ROC, receiver operating characteristic; AUC, area under the curve; FGF21, fibroblast growth factor 21; OSA, obstructive sleep apnea.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.105985.

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AUTHOR CONTRIBUTIONS

The corresponding authors, H.Y. and S.L. are responsible for the authenticity of the data. All authors made a significant contribution to the work reported, i.e., in the conception design or execution of the study, acquisition, analysis or interpretation of the data, or in all of these areas. Conceptualization, W.H., H.Y., and S.L.; Methodology, W.H., J.Z., and S.L.; Formal Analysis, W.H., J.Z., X.W., and H.X.; Data Curation W.H. and S.L.; Writing – Original Draft, W.H., J.Z., H.Y., and S.L.; Writing – Review & Editing, J.G., S.L., and S.Y.; Supervision, H.Y. and S.L.; Funding Acquisition, H.Y., S.L., and S.Y. All authors have agreed to be accountable for all aspects of the work. All authors approved the final version of the manuscript to be published, and agreed regarding the journal to which it has been submitted.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Critical commercial assays		
Human FGF-21 ELISA kit	BioVendor	Cat#RD191108200R
Software and algorithms		
Statistical Product Service Solutions, SPSS, version 22.0	IBM Corp., Armonk, NY, USA	https://www.ibm.com/support/pages/spss-statistics-220-available-download
R project, version 4.0	R Foundation, Vienna, Austria	https://www.r-project.org

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Suru Liu (suruliu2011@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

This two-stage study included two cohorts. Chinese individuals who underwent overnight PSG at our sleep center were enrolled between May and December 2018 into the discovery set of the cross-sectional study or were consecutively recruited between June 2013 and December 2015 into the validation set of the longitudinal study, as part of the Shanghai Sleep Health Study (SSHS) which is a dynamic cohort specifically designed to evaluate the relationship between OSA and metabolic disorders.[46] Subjects from the SSHS were invited to attend follow-up assessments. This study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval no. 2018-KY-021[K], 2019-KY-050[K]). The study was registered at the Chinese Clinical Trial Registry (no. ChiCTR1800016082, ChiCTR1900025714). Written informed consent was obtained from all participants. We estimated that a power of 90% could be achieved at a significance level of 5% with 48 subjects in the discovery phase and 656 subjects in the validation phase. The participants with or without OSA underwent comprehensive physical examinations, routine biochemical blood analyses, and PSG. A comprehensive questionnaire about present and past illnesses, and medical therapy, was completed by all participants. The exclusion criteria were as follows: age <18 years; use of anxiolytics, antidepressants, antipsychotics, or hypnotic drugs; excess alcohol intake (mean alcohol consumption $\geq$30 g/d); acute disease in the previous 4 weeks; previous treatment for OSA with CPAP, upper airway surgery, or oral appliance; other sleep disorders, such as central sleep apnea, restless leg syndrome, upper airway resistance syndrome, or narcolepsy; and less than 4 h of total sleep time (TST). The discovery study comprised 111 individuals (77.48% male and 22.52% female adults) with age of 44(35-55) years old. And 876 individuals (73.06% male and 26.94% female adults) with age of 43(34-53) years old were included in the validation study. The age and sex were also considered as confounding factors and were adjusted in the logistic regression and cox proportional hazards regression.

METHOD DETAILS

Anthropometric and biochemical assessments

Anthropometric parameters, including height (m), weight (kg), NC (cm), WC (cm), HC (cm), WHR, systolic blood pressure (SBP; mmHg), and diastolic blood pressure (DBP; mmHg), were recorded as the mean of two consecutive measurements before PSG. BMI was defined as weight divided by height squared (kg/m^2). Following full-night PSG, a fasting blood sample was acquired from the participants in the morning for measurement of serum glucose, insulin, and lipid levels. Serum was obtained by centrifugation and stored at −80°C until the FGF21 assay. Glycolipid metabolism indices, including FBG (mmol/L), fasting insulin (μU/mL), TC (mmol/L), TG (mmol/L), high-density lipoprotein (HDL; mmol/L), LDL (mmol/L), ApoA-I (g/L), ApoB (g/L), ApoE (mg/dL), ApoA/ApoB, and lipoprotein(a) (mg/dL) levels, were measured in our laboratory. The following formula was used to calculate the indicator of HOMA-IR: fasting insulin (μU/mL) × FBG (mmol/L)/22.5.[47]

Standardized evaluations, performed by trained physicians on the night of the in-laboratory PSG, were used to obtain the medical history of hypertension,[3] diabetes,[48] hyperlipidemia,[49] cardiovascular disease (CVD),[50] and metabolic syndrome (MS).[51] Hypertension was defined by one of two methods: clinically assessed auscultatory blood pressure equal to or above 140/90 (mmHg) or use of antihypertensive medications.[3] The diagnoses of diabetes[48] and hyperlipidemia[49] relied on past history and the biochemical index. Prevalent CVD was determined as the occurrence of events, including myocardial infarction, coronary atherosclerotic heart disease with or without coronary artery revascularization, congestive heart failure, arrhythmia and stroke.[50] MS was defined according to the definition of Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults as having ≥3 of the following metabolic risk factors: 1) central obesity (waist circumference >90 cm for men and >85 cm for women); 2) TG ≥1.70 mmol/L; 3) fasting HDL <1.04 mmol/L; 4) hypertension (sitting blood pressure ≥ 130/85 mmHg or on regular antihypertensive medications); 5) hyperglycemia defined as FBG ≥6.1 mmol/L and/or 2-h plasma glucose concentration ≥7.8 mmol/L or on hypoglycemic therapy for treatment of diabetes.[51]

OSA treatment, medication use, smoking, alcohol consumption, and subjective sleepiness symptoms (ESS score >10 was considered to indicate excessive daytime sleepiness [EDS])[52] were also recorded.

Serum FGF21 measurements

The serum FGF21 (pg/mL) level was measured using an enzyme-linked immunosorbent assay kit (BioVendor Laboratory Medicine, Brno, Czech Republic), as described previously.[16] For the measurement of FGF21, serum samples were diluted 1:1 before the assay and then 100 μl diluted sera, calibrators, and quality controls were added to 96-well microtiter plates coated with an affinity-purified polyclonal anti-human FGF21 antibody. The assay was conducted according to the manufacturer's protocol. A calibration curve was constructed by plotting the absorbance values at 450 nm versus the FGF21 concentrations of the calibrators, and concentrations of study samples were determined by using this calibration curve. Intra- and inter-assay variations were 9.07% and 9.11%, respectively. In the validation set, the FGF21 level was categorized into quartiles for analysis (Q1–Q4: <175.40, 175.40–272.50, 272.55–424, and >424 pg/mL, respectively, for the 876 subjects enrolled at baseline; Q1–Q4: <160.50, 160.50–227, 228–289.50, and >289.50 pg/mL, respectively, for the 281 NOSA subjects enrolled at baseline). Data analyses were performed with the participant identity and OSA status masked.

PSG recordings

Subjects underwent full-night PSG (Alice 4/5/6 Diagnostics System; Philips Respironics, Murrysville, PA, USA) with electroencephalography, electrooculography, electromyography, and electrocardiography. Measurements were also made using a nasal pressure transducer, thoracic and abdominal impedance belts, a thermistor (for nasal airflow), pulse oximetry, a tracheal microphone (to monitor snoring), and sensors (to determine leg and sleep positions). All PSG recordings were conducted in our sleep center and manually scored by two skilled technicians blinded to the study, in accordance with the American Academy of Sleep Medicine 2007 guidelines.[53] Apnea was defined as the absence of airflow for at least 10 s, and hypopnea as a decrease in airflow >50% accompanied by oxygen desaturation >4% or arousal from sleep. The AHI was calculated as the number of apneas and hypopneas per hour. The ODI (3% oxygen desaturation) was calculated as the number of events per hour of recording. We also recorded the

TST, MAI, $MSaO_2$, $LSaO_2$, and CT90. Participants were divided into 4 groups according to AHI by using common clinical cutoff points: <5.0 events/h (normal), 5.0–14.9 events/h (mild), 15.0–29.9 events/h (moderate), and ≥30.0 events/h (severe).[54]

Confidentiality measures

The results of research through this project may be published in medical journals, but we will keep patient information confidential in accordance with legal requirements, and patients' personal information will not be disclosed unless required by relevant laws. When necessary, the government management department, the hospital ethics committee and its relevant personnel may consult the patient's information as required.

QUANTIFICATION AND STATISTICAL ANALYSIS

Descriptive statistics were used to summarize all parameters. The Kolmogorov-Smirnov test was used to test normality. Normally distributed continuous variables are presented as means ± standard deviations; those with a nonnormal distribution are presented as medians (interquartile ranges), and were logarithmically transformed before analysis. Categorical variables are presented as percentages. Comparison of non-normally distributed data between the two groups was performed by Mann–Whitney U test, similar to the analysis of normally distributed data using t-tests. Comparisons among three groups were performed using one-way ANOVA for normally distributed data and the Kruskal-Wallis H test for non-normally distributed data. The chi-square test was used for analyzing categorical variables. Correlations between FGF21 and anthropometric or biochemical variables were analyzed with Spearman correlation. The relationships between FGF21 and prevalent OSA were analyzed by logistic regression, with ORs and 95% CIs showing the relative effect sizes of the relationships. p values for trends across groups were calculated using the polynomial linear trend test. To determine whether FGF21 was independently associated with incident OSA, the Kaplan–Meier method was used, and differences in OSA development were evaluated using the log rank test. Multivariate analyses (Cox proportional hazards regression) were used to determine adjusted relative HRs for OSA development. Age, sex, BMI, smoking, alcohol drinking, hypertension, diabetes, CVD, MS, hyperlipidemia, ESS, ODI, $LSaO_2$, and MAI were evaluated in multivariable logistic regression and Cox proportional hazards regression as covariates. The accuracy of the models was evaluated using ROC analysis and DCA. DCA was used to incorporate the clinical consequences of a decision into evaluations of diagnostic tests and determine the clinical usefulness of the model.[55] The method is based on the principle that the relative harms of true-positive (TP) and false-positive (FP) classifications can be expressed in terms of a probability threshold (PT).[55–59] The net benefit (NB) is obtained by subtracting the proportion of patients who showed false-positive results from the proportion who showed true positive results. Then the relative harm of unnecessary intervention versus the benefit of intervention was weighed by PT in order to define at-risk subjects who needed intervention. The NB of making a decision based on the model can be calculated by using the following formula,

$$NB = \frac{TPs}{n} - \frac{PT}{1 - PT} * \frac{FPs}{n}$$

where n is the total number of subjects in the study. A decision curve shows the NB of using a model at different thresholds. The NB of FGF21 model, conventional model and two reference strategies, intervene none or intervene all, was calculated. Sensitivity and specificity were calculated according to the best diagnostic cut-off points (Youden index, calculated as sensitivity + specificity−1).[60] The discrimination and reclassification performance of the models were determined by NRI and IDI.[61,62] Two-sided $p < 0.05$ was considered statistically significant. SPSS Statistics (version 22.0; IBM Corp., Armonk, NY, USA) and R (version 4.0; R Foundation, Vienna, Austria) software were used for the statistical analyses.

ADDITIONAL RESOURCES

Trial Registration: Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=27334; http://www.chictr.org.cn/showproj.aspx?proj=43057; no.: ChiCTR1800016082, ChiCTR1900025714 [retrospectively registered]; dates: 2018/05/09, 2019/09/06).