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High levels of FSH before puberty are associated with increased risk of metabolic syndrome during pubertal transition

Banu Kucukemre Aydin[1,2] | Rasmus Stenlid[1,2] | Iris Ciba[1,2] | Sara Y. Cerenius[2] | Marie Dahlbom[1] | Peter Bergsten[1,2] | Ricard Nergårdh[1] | Anders Forslund[1]

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[2]Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden

Correspondence
Banu Kucukemre Aydin, Department of Women's and Children's Health, Uppsala University, Akademiska Sjukhuset, 751 85, Uppsala, Sweden.
Email: banu.aydin@kbh.uu.se

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Summary

Background: During perimenopause, the rise in serum follicle-stimulating hormone (FSH) is associated with increased adiposity, insulin resistance (IR), and metabolic syndrome (MetS). However, data for the pubertal period, which is characterized by increasing FSH levels and changing body composition, are limited.

Objectives: To investigate the relationships between FSH and anthropometric changes, IR markers, and development of MetS in the peripubertal period.

Methods: Uppsala Longitudinal Study of Childhood Obesity (ULSCO) is an ongoing study that aims to understand the factors contributing to childhood obesity and the development of obesity-related diseases. We analysed the subset of participants who were prepubertal at the first visit (n = 95, 77 with obesity). Mean follow-up time was 3.0 ± 1.4 years.

Results: Higher serum FSH levels at the first visit were associated with an increased likelihood of elevation in body mass index (BMI SDS) ($p = 0.025$, OR = 16.10) and having MetS ($p = 0.044$, OR = 4.67) at the follow-up. We observed nonlinear relationships between varying serum FSH levels and markers of adiposity and IR, especially in girls. At the first visit, when girls were prepubertal, FSH was negatively associated with BMI ($\beta = -0.491$, $p = 0.005$) and positively associated with sex hormone-binding globulin (SHBG) ($\beta = 0.625$, $p = 0.002$). With the progression of puberty, negative associations between BMI and SHBG disappeared while FSH became positively associated with HOMA-IR ($\beta = 0.678$, $p = 0.025$) and fasting insulin ($\beta = 0.668$, $p = 0.027$).

Abbreviations: BMI SDS, body mass index standard deviation score; BMI, body mass index; CPP, central precocious puberty; FSH, follicle-stimulating hormone; FSHR, follicle-stimulating hormone receptor; GH, growth hormone; GnRH, gonadotropin-releasing hormone; HC, hip circumference; HDL, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; IDF, International Diabetes Federation; IGF-1, insulin-like growth factor 1; IQR, interquartile range; IR, insulin resistance; LDL, low density lipoprotein cholesterol; LH, luteinizing hormone; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; RedCap, Research Electronic Data Capture tool; SFT, skinfold thickness; SHBG, sex hormone binding globulin; ULSCO, the Uppsala Longitudinal Study of Childhood Obesity; WC, waist circumference.

Ricard Nergårdh and Anders Forslund are co-last authors on this manuscript

Conclusions: Higher serum FSH levels in prepubertal children were associated with an increased risk of MetS development during pubertal transition. Along with nonlinear associations between varying serum FSH levels and IR markers, our results might imply a relationship between FSH and IR of puberty.

KEYWORDS
follicle-stimulating hormone (FSH), insulin resistance, metabolic syndrome, obesity, sex hormone binding globulin (SHBG)

1 | INTRODUCTION

Follicle-stimulating hormone (FSH) has been believed to only function as a gonadotropic hormone, responsible for sexual differentiation, puberty, and reproduction, but with recent studies especially in perimenopausal women, this view is changing.[1] Elevated serum FSH levels may play a significant role in the development of obesity, insulin resistance (IR), metabolic syndrome (MetS), and cardiovascular disease.[1–5] During perimenopause, while serum oestrogen levels are still largely unaltered, the rise in serum FSH has been reported to be associated with increased visceral adiposity.[6] Animal models have revealed that FSH directly regulates adipose tissue and blocking its action reduces body fat profoundly.[7] FSH was reported to act via a pertussis toxin–sensitive Gai-coupled FSH receptor (FSHR) on adipocytes.[7] Liu et al.[7] designed an antibody to prevent the entry of FSH into the FSHR binding pocket. Using this antibody, they found dramatically reduced body fat in all compartments, including viscera, subcutaneous tissue, and bone marrow in every mouse model they used.[7]

Thus, while there is a substantial amount of information on the association of high FSH levels and adiposity in perimenopause, the data for prepubertal and pubertal children, whose FSH levels are many times lower, are very limited. Moreover, the results of these studies are contradictory.[8,9] Like perimenopause, puberty is a time of transition that is characterized, in part, by increasing gonadotropins, although levels do not become as high as they do during perimenopause.[10] Rapid changes in body composition, shape, and size also occur during the pubertal transition.

The links between insulin sensitivity, adiposity, and puberty are well known, but despite extensive research, the exact mechanisms are not clearly understood. The association between age of menarche and critical fat mass was first proposed in early seventies,[11] and recently, the relationship between childhood obesity and earlier puberty has received particular attention.[12–15] Furthermore, conditions causing low levels of body fat, such as anorexia nervosa or extreme physical activity, are associated with low levels of gonadotropins and late pubertal timing.[16] Although an appropriate amount of adipose tissue is necessary for the development of puberty, excessive amounts may increase the risk for adult obesity, MetS, and cardiovascular disease.[17]

In this study, we aimed to investigate the relationships between FSH and anthropometric changes, IR markers, and development of MetS, during the pubertal transition.

2 | METHODS

2.1 | Subjects

The Uppsala Longitudinal Study of Childhood Obesity (ULSCO) is an ongoing study, aiming to define and understand the factors contributing to childhood obesity and development of obesity-related diseases.[18] This cohort consists primarily of patients who visit the Obesity Unit for Children and Adolescents at Uppsala University Children's Hospital. Healthy, lean controls were recruited through collaboration between Uppsala University and local schools in the Uppsala area, and through advertisement.[18–20]

This study analysed a subset of participants from the ULSCO cohort, with available data on anthropometric measurements and pubertal status. There were records of 480 children and adolescents at the time of data extraction (June 2019). In order to reduce the confounding effects of puberty on FSH levels, only prepubertal children with complete anthropometric and biochemical data at the first visit were included in the final analyses ($n = 95$, with obesity $n = 77$, Figure 1). All participants were given lifestyle advice regarding diet and physical exercise at each visit.[18] Children who were on medications which may affect their insulin or FSH levels, such as metformin, acarbose, glucagon-like peptide-1 agonists, and birth control pills, were not included in the analyses. In addition, children with syndromic obesity, serious psychiatric disorders, and severe diseases were not included in the study.[18]

Data on age, sex, pubertal stage, weight, height, body mass index (BMI), BMI standard deviation score (BMI SDS), waist circumference (WC), hip circumference (HC), skinfold thickness (SFT) measurements, systolic and diastolic blood pressures, luteinizing hormone (LH), FSH, estradiol, sex hormone binding globulin (SHBG), insulin-like growth factor 1 (IGF-1), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides, and oral glucose tolerance test (OGTT) results were retrieved using Research Electronic Data Capture tool (RedCap) of the ULSCO cohort. Detailed information can be found in the ULSCO protocol description article by Forslund et al.[18] Fasting glucose and insulin concentrations were derived from the baseline measurements of the OGTT.

Among 95 children, 56 (59%) had at least one follow-up visit. First and last visits were included in this study (Figure 1). Age ($p = 0.96$), BMI SDS ($p = 0.14$), LH ($p = 0.33$) and FSH ($p = 0.53$) values at the

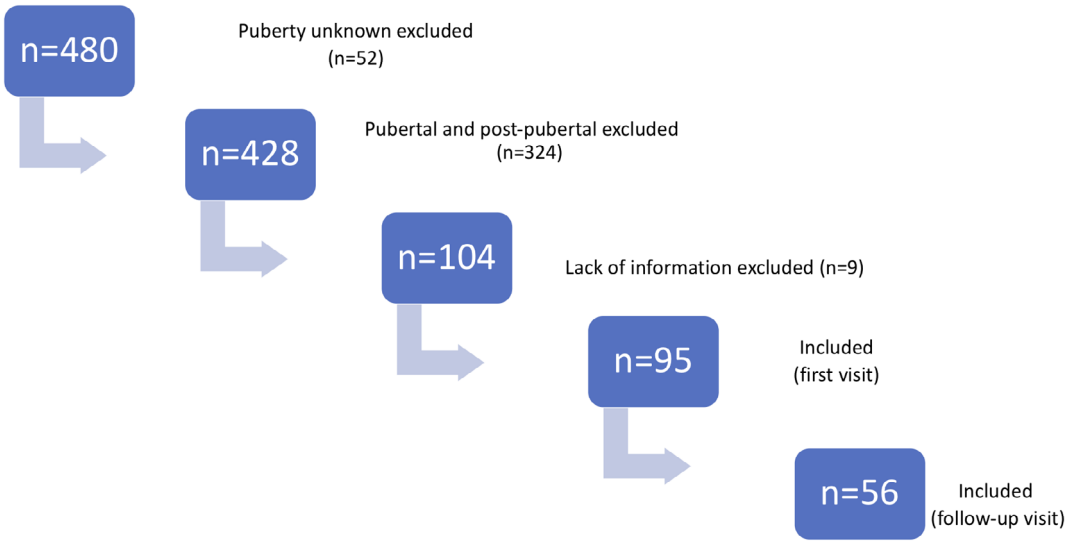

FIGURE 1 Process of case selection

first visit were not significantly different between the children with and without a follow-up visit.

2.2 | Anthropometric measurements, pubertal staging, and laboratory evaluation

All measurements were performed by trained research assistants. Height was measured to the nearest 0.1 cm using an Ulmer stadiometer (Busse, Elchingen, Germany). Measurements were taken twice and the mean value was used. Subjects were barefooted, and measured in the morning. Weight was measured to the nearest 0.1 kg using a calibrated electronic column scale Seca 704 (Seca, Hamburg, Germany). Subjects were weighed after an overnight fast, and a standard of 0.5 kg was subtracted to compensate for light clothing. WC was measured to the nearest 0.1 cm using a flexible tape in the horizontal plane, midway between the inferior costal arch and the iliac crest with the subject standing with feet together. HC was measured to the nearest 0.1 cm using the point of maximum girth around the buttocks to the nearest. SFT measurements were taken using a Harpenden skinfold calliper (Baty International, Burgess Hill, West Sussex, UK) on the right side of the body from four points: triceps, biceps, subscapular, and suprailiac. Measurements were taken twice and mean values were used. Children were evaluated for puberty according to the Tanner classification.[21,22] Because of the high refusal rate of pubertal examination, Tanner staging was supplemented with self-description and basal LH levels. A basal LH level ≥0.3 IU/L was accepted as a marker for pubertal onset, in accordance with previous research.[23,24]

All blood samples were collected in the fasting state, between 8:00 and 10:00 a.m. FSH analyses were all done at the same laboratory, using the same assays throughout the study period. FSH levels were measured by electrochemiluminescence immunoassay (ECLIA, Cobas analyser, Roche Diagnostics, Indianapolis, IN), with a detection limit between <0.10 and > 200 mIU/mL.

2.3 | Calculations and definitions

BMI was calculated by dividing the body weight in kilograms by the square of body height in meters (kg/m^2). The age- and sex-adjusted BMI (BMI SDS) was calculated according to the World Health Organization 2006–2007 growth reference (http://www.who.int/growthref/en/). Sum of skin folds was determined (triceps SFT + biceps SFT + subscapular SFT + suprailiac SFT). Waist to hip ratio (WC/HC) and waist to height ratio (WC/height) were also calculated. All of these calculations were done for the first visit and for the latest follow-up visit. In addition, we calculated ΔBMI SDS (by subtracting the first visit BMI SDS from the last visit BMI SDS) for each child with at least one follow-up visit.

Triglyceride to HDL ratio (triglyceride/HDL) was calculated. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [fasting insulin (μIU/mL) x fasting glucose (mg/dL)/405)] was calculated.

MetS is defined as a cluster of alterations related to IR, which are associated with a higher risk of cardiovascular disease. For children aged 10 years or older, the International Diabetes Federation (IDF) consensus suggests that MetS can be diagnosed with abdominal obesity and the presence of two or more additional clinical features [elevated triglycerides (≥150 mg/dL), low HDL-cholesterol (<40 mg/dL), high blood pressure (systolic blood pressure > 120 mmHg or diastolic blood pressure > 80 mmHg), increased plasma glucose (≥100 mg/dL)].[25,26] However, IDF suggests that MetS cannot be diagnosed in children younger than 10 years,[25] and since the vast majority of children in our study were younger than 10 years at the first visit, MetS evaluation was done only for the follow-up visit.

TABLE 1 Comparison of the clinical and laboratory characteristics at the first visit and at the follow-up visit in girls and boys

	Girls			Boys				
	First visit (n = 47)	Follow-up visit (n = 25)	*p* value[1]	First visit (n = 48)	Follow-up visit (n = 31)	*p* value[2]	*p* value[3]	*p* value[4]
Age (years)	8.8(7.6–9.5)	11.8(10.3–13.2)	**<0.001**	8.3(7.0–9.8)	11.0(9.8–13.3)	**<0.001**	0.53	0.39
BMI SDS	3.0(2.6–3.5)	2.9(2.5–3.3)	0.17	3.5(2.4–4.2)	3.2(2.0–3.6)	**0.002**	**0,028**	0.15
Biceps SFT (mm)	15.8(9.4–19.0)	31.7(24.4–42.9)	0.07	17.0(6.2–21.7)	21.8(10.1–31.8)	**0.045**	0.29	0.11
Triceps SFT (mm)	23.9(17.7–27.0)	38.4(35.4–46.6)	0.07	24.7(10.0–28.6)	30.2(12.9–39.4)	**0.007**	0.59	0.09
Subscapular SFT (mm)	24.6(16.5–29.5)	44.1(37.1–63.3)	0.07	26.2(6.4–32.9)	37.5(7.2–44.3)	**0.004**	0.99	0.14
Suprailiac SFT (mm)	26.1(16.7–29.0)	39.0(36.1–53.2)	0.07	25.1(5.6–31.6)	34.1(14.5–46.7)	**0.008**	0.97	0.34
Sum of SFT (mm)	88.4(68.3–103.5)	152.2(133.9–206.0)	0.07	98.4(25.4–112.5)	130.1(42.1–157.2)	**0.003**	0.53	0.20
Waist/hip circumference ratio	0.98(0.92–1.0)	0.92(0.84–0.98)	**0.035**	0.97(0.92–1.0)	0.95(0.84–0.99)	0.13	0.74	0.64
Waist/height ratio	0.63(0.54–0.65)	0.62(0.52–0.68)	0.51	0.64(0.50–0.67)	0.63(0.45–0.70)	0.85	0.63	0.98
Systolic blood pressure (mm Hg)	111(105–120)	113(104–123)	0.86	108(100–116)	109(104–121)	**0.028**	0.10	0.75
Diastolic blood pressure (mm Hg)	69(61–75)	71(64–76)	0.31	67(62–74)	64(60–76)	0.85	0.49	0.45
LH (IU/L)	0.1(0.1–0.1)	1.94(0.1–6.8)	**0.001**	0.1(0.1–0.1)	0.1(0.1–2.35)	**0.001**	0.63	**0.034**
FSH (IU/L)	1.45(0.78–2.0)	3.8(2.3–5.3)	**<0.001**	0.63(0.45–0.88)	1.18(0.62–3.2)	**<0.001**	**<0.001**	**0.002**
LH/FSH ratio	0.07(0.05–0.13)	0.51(0.10–1.35)	**0.005**	0.16(0.11–0.22)	0.28(0.14–0.74)	**0.005**	**<0.001**	0.68
Estradiol (pmol/L)	40(40–40)	93(40–164)	**0.001**	40(40–40)	40(40–46.5)	**0.018**	0.16	**0.002**
SHBG (nmol/L)	35(26.5–57.8)	29(21–45)	**0.001**	54(35.5–91.8)	35(24–55)	0.39	0.074	0.30
IGF-1 (nmol/L)	189(157–216)	349(218–469)	**<0.001**	159(134–204)	224(166–389)	**0.005**	0.10	**0.028**
Fasting glucose (mg/dL)	96(93–101)	101(95–103)	0.69	97(94–104)	106(99–110)	0.20	0.18	0.08
Fasting insulin (μIU/mL)	16.9(9.8–23.0)	25.5(16.2–45.1)	**0.008**	11.3(6.2–18.3)	12.7(8.2–40.5)	0.18	**0.006**	0.12
HOMA-IR	3.87(2.26–5.64)	5.88(4.0–11.2)	**0.019**	2.77(1.34–4.54)	2.94(2.0–12.6)	0.45	**0.018**	0.17
OGTT 2nd hour glucose (mg/dL)	130(120–148)	123(109–159)	0.45	135(115–144)	146(128–160)	0.31	0.87	0.19
OGTT 2nd hour insulin (μIU/mL)	97,2(67.1–175.9)	125.6(80.2–367.2)	0.084	89.1(46.3–136.6)	90.3(68.3–267)	0.37	0.37	0.55
Triglyceride (mg/dL)	85.0(63.9–121.0)	91.2(67.3–120.4)	0.67	66.8(46.0–87.2)	65.5(56.2–110.6)	0.17	**0.011**	0.24
HDL cholesterol (mg/dL)	42.5(38.4–50.2)	46.3(38.6–54.0)	0.055	46.3(38.6–54.0)	48.3(38.6–54.0)	0.54	**0.029**	0.81
LDL cholesterol (mg/dL)	98.4(81.1–124.5)	100.4(77.2–115.9)	0.51	100.4(84.9–118.7)	100.4(84.0–127.4)	0.44	0.96	0.57
Triglyceride/HDL ratio	2.04(1.35–2.76)	2.21(1.41–2.84)	0.55	1.43(0.80–2.33)	1.58(0.97–2.56)	0.32	**0.008**	0.34

Note: *p* value[1] belongs to the comparisons between the first visit and the follow-up visit, in girls. *p* value[2] belongs to the comparisons between the first visit and the follow-up visit, in boys. *p* value[3] belongs to the comparisons between girls and boys, at the first visit. *p* value[4] belongs to the comparisons between the girls and boys, at the follow-up visit.
Bold text indicates a statistically significant difference with a *p* value less than 0.05.

2.4 | Data analysis

The Shapiro–Wilk test was used to determine whether variables were normally distributed. Since most variables were not distributed normally, comparisons were made using Mann–Whitney U-test or Wilcoxon Signed Ranks test. The variables were reported as the median and interquartile range (IQR), and Spearman's rank correlation coefficients were used. The chi-squared test was used for categorical variables. Girls and boys were evaluated separately for comparison and correlation analyses. We created several linear regression models in which the independent associations of FSH with adiposity and IR parameters were evaluated after adjustment for potential confounders. We used logistic regression analysis to examine the predictors of MetS and BMI change at the follow-up visit. All statistical analyses were conducted using SPSS version 15.0 (SPSS Inc, Chicago, IL). Statistical significance was defined as $p < 0.05$.

2.5 | Ethics

The present study was performed in accordance with the Declaration of Helsinki. It was a part of our ongoing cohort study ULSCO, which was approved by the regional ethical review board in Uppsala (2010/036 and 2012/318). Participation was voluntary. The subjects and guardian/s received oral and written information regarding participation in the study project, and written approvals were collected from at least one guardian. Collected data was stored in the database REDCap, in which the subjects were coded. The register with which personal identification could be

TABLE 2 Comparison of the clinical and laboratory characteristics of girls at the first visit according to their follicle stimulating hormone (FSH) levels[a]

	Low FSH[b] (n = 24)	High FSH[c] (n = 23)	*p* value*
Age (years)	8.7 (7.5–9.4)	9.2 (7.6–10.3)	0.34
BMI SDS	3.2 (2.7–3.5)	2.7 (1.6–3.5)	0.10
Biceps SFT (mm)	18.3 (13.2–20.5)	10.8 (7.0–17.3)	**0.003**
Triceps SFT (mm)	25.6 (21.1–27.6)	20.5 (13.0–24.0)	**0.004**
Subscapular SFT (mm)	24.7 (21.7–29.5)	22.9 (8.9–29.5)	0.27
Suprailiac SFT (mm)	25.7 (19.9–31.0)	26.5 (8.9–28.3)	0.26
Sum of SFT (mm)	97.2 (81.7–106.2)	83.7 (37.6–98.2)	0.050
Waist/hip circumference ratio	1.0 (0.95–1.03)	0.96 (0.85–0.99)	**0.03**
Waist/height ratio	0.64 (0.60–0.67)	0.61 (0.48–0.64)	**0.047**
Systolic blood pressure (mm Hg)	112 (110–123)	108 (103–114)	0.075
Diastolic blood pressure (mm Hg)	70 (61–76)	68 (60–75)	0.69
LH (IU/L)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.07
FSH (IU/L)	0.80 (0.41–1.20)	2.0 (1.60–2.80)	**<0.001**
LH/FSH ratio	0.13 (0.08–0.25)	0.05 (0.04–0.07)	**<0.001**
Estradiol (pmol/L)	40 (40–40)	40 (40–40)	0.17
SHBG (nmol/L)	33.0 (23.5–44.5)	51.0 (31.0–107.0)	**0.036**
IGF-1 (nmol/L)	176 (126–248)	190 (176–215)	0.38
Fasting glucose (mg/dL)	97 (94–102)	95 (88–100)	0.13
Fasting insulin (μIU/mL)	19.2 (12.0–24.0)	13.4 (7.9–20.6)	0.078
HOMA-IR	4.65 (2.79–6.18)	2.94 (1.79–4.80)	**0.041**
OGTT 2nd hour glucose (mg/dL)	133 (121–157)	128 (119–134)	0.20
OGTT 2nd hour insulin (μIU/mL)	97.2 (69.5–167.8)	99.0 (50.9–182.9)	0.54
Triglyceride (mg/dL)	93.8 (73.9–130.5)	79.7 (48.7–108.0)	0.07
HDL cholesterol (mg/dL)	40.5 (34.8–49.2)	46.3 (38.6–52.1)	0.40
LDL cholesterol (mg/dL)	94.6 (82.0–120.6)	102.3 (77.2–127.4)	0.89
Triglyceride/HDL ratio	2.33 (1.88–3.29)	1.80 (1.00–2.61)	0.07

Abbreviations: BMI, Body mass index; FSH, Follicle stimulating hormone; HDL, High-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGF-1, Insulin-like growth factor 1; LDL, Low-density lipoprotein; LH, Luteinizing hormone; OGTT, Oral glucose tolerance test; SFT, Skinfold thickness; SDS, Standard deviation score; SHBG, Sex hormone binding globulin.

[a]All values are median and (Q1-Q3 interquartile ranges), except if otherwise stated.

[b]Low FSH: Girls whose FSH values were in the lower two FSH quartiles (Q1 and Q2).

[c]High FSH: Girls whose FSH values were in the upper two FSH quartiles (Q3 and Q4).

*Bold text indicates a statistically significant difference with a *p*-value less than 0.05.

made was safely stored in a safe in a locked room and accessible only to a few people within the research group.

3 | RESULTS

3.1 | Baseline characteristics (first visit)

In our final study group, there were 47 girls, of whom 40 had obesity, and 48 boys, of whom 37 had obesity. Although the obesity rate was not different between the sexes ($p = 0.32$), BMI SDS was higher in boys than in girls at the first visit (Table 1).

Age and LH levels were not different between the sexes at the first visit (Table 1), but plasma FSH levels were higher in girls than boys (Table 1). First visit fasting insulin, HOMA-IR, and triglyceride levels were also significantly higher in girls, and HDL cholesterol levels were lower. The triglyceride/HDL cholesterol ratio was higher in girls than in boys (Table 1).

Table 2 shows the comparison of the clinical and laboratory characteristics of girls at the first visit according to their FSH levels. Low FSH group ($n = 24$) consisted of girls whose FSH values were in the lower two FSH quartiles (Q1 and Q2) and high FSH group ($n = 23$) consisted of girls whose FSH values were in the upper two FSH quartiles (Q3 and Q4). Age was not different between the two groups. Although the difference between BMI SDS was not significant, biceps SFT and triceps SFT were higher in girls with lower FSH levels. WC/HC and WC/Height ratios were also higher in these girls. In addition, serum SHBG was

TABLE 3 Comparison of the clinical and laboratory characteristics of boys at the first visit according to their follicle stimulating hormone (FSH) levels[a]

	Low FSH[b] (n = 24)	High FSH[c] (n = 24)	*p* value*
Age (years)	8.0 (7.0–9.1)	8.5 (7.0–10.6)	0.23
BMI SDS	3.6 (2.95–4.2)	3.3 (0.8–3.9)	0.24
Biceps SFT (mm)	18.9 (9.6–21.1)	17 (5.9–23.6)	0.99
Triceps SFT (mm)	23.4 (13.5–28.0)	26.1 (9.2–29.7)	0.83
Subscapular SFT (mm)	27.0 (10.6–34.0)	24.8 (5.8–31.5)	0.58
Suprailiac SFT (mm)	26.0 (12.6–34.9)	22.6 (5.2–30.6)	0.31
Sum of SFT (mm)	99.0 (45.6–114.5)	90.6 (24.3–113.1)	0.73
Waist/hip circumference ratio	0.96 (0.93–0.96)	0.97 (0.91–1.0)	0.67
Waist/height ratio	0.65 (0.54–0.68)	0.63 (0.46–0.66)	0.19
Systolic blood pressure (mm Hg)	106 (101–117)	109 (100–114)	0.65
Diastolic blood pressure (mm Hg)	66 (62–73)	67 (64–76)	0.40
LH (IU/L)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.15
FSH (IU/L)	0.46 (0.30–0.56)	0.88 (0.76–1.07)	**<0.001**
LH/FSH ratio	0.22 (0.18–0.33)	0.11 (0.095–0.13)	**<0.001**
Estradiol (pmol/L)	40 (40–40)	40 (40–40)	1.0
SHBG (nmol/L)	58.0 (36.5–81.5)	50.0 (30.0–106.0)	0.83
IGF-1 (nmol/L)	147 (132–191)	185 (144–210)	0.38
Fasting glucose (mg/dL)	97 (91–103)	100 (94–105)	0.21
Fasting insulin (μIU/mL)	11.5 (4.8–18.2)	11.1 (6.8–19.9)	0.66
HOMA-IR	2.83 (1.07–4.49)	2.65 (1.56–4.60)	0.83
OGTT 2nd hour glucose (mg/dL)	132 (115–148)	135 (116–143)	0.88
OGTT 2nd hour insulin (μIU/mL)	89.1 (70.6–122.7)	85.7 (40.2–169.3)	0.95
Triglyceride (mg/dL)	66.8 (46.5–80.1)	69.9 (44.0–108.6)	0.80
HDL cholesterol (mg/dL)	46.3 (42.5–54.0)	46.3 (38.6–57.9)	0.63
LDL cholesterol (mg/dL)	106.2 (84.9–111.9)	98.4 (79.1–125.5)	0.74
Triglyceride/HDL ratio	1.40 (0.89–1.97)	1.50 (0.78–3.42)	0.62

Abbreviations: BMI, Body mass index; FSH, Follicle stimulating hormone; HDL, High-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGF-1, Insulin-like growth factor 1; LDL, Low-density lipoprotein; LH, Luteinizing hormone; OGTT, Oral glucose tolerance test; SFT, Skinfold thickness; SDS, Standard deviation score; SHBG, Sex hormone binding globulin.

[a]All values are median and (Q1-Q3 interquartile ranges), except if otherwise stated.

[b]Low FSH: Boys whose FSH values were in the lower two FSH quartiles (Q1 and Q2).

[c]High FSH: Boys whose FSH values were in the upper two FSH quartiles (Q3 and Q4).

*Bold text indicates a statistically significant difference with a *p*-value less than 0.05.

lower and HOMA-IR was higher in girls with lower FSH levels (Table 2).

Boys were also evaluated by dividing into two groups according to their first visit FSH levels (Table 3). Low FSH group ($n = 24$) consisted of boys whose FSH values were in the lower two FSH quartiles (Q1 and Q2) and high FSH group ($n = 24$) consisted of boys whose FSH values were in the upper two FSH quartiles (Q3 and Q4). Unlike the girls, the boys showed no significant difference in clinical and laboratory characteristics at the first visit when divided into higher and lower FSH groups (Table 3).

First visit FSH was positively correlated with age both in girls ($r = 0.289$, $p = 0.049$) and boys ($r = 0.323$, $p = 0.025$). FSH was also positively correlated with LH levels in both sexes [girls ($r = 0.357$, $p = 0.014$), boys ($r = 0.346$, $p = 0.016$)].

We observed negative correlations between first visit FSH levels and BMI SDS both in girls ($r = -0.355$, $p = 0.014$) (Figure 2A) and in boys ($r = -0.333$, $p = 0.021$) (Figure 2B). FSH levels remained significantly associated with BMI SDS after adjusting for age and LH in girls ($\beta = -0.491$, $p = 0.005$, $R^2 = 0.23$), but not in boys ($\beta = -0.191$, $p = 0.28$, $R^2 = 0.16$).

First visit FSH was negatively correlated with biceps SFT ($r = -0.428$, $p = 0.007$) and triceps SFT ($r = -0.414$, $p = 0.010$) in girls. In girls, serum FSH was also positively correlated with serum SHBG levels ($r = 0.407$, $p = 0.009$) (Figure 3A). SHBG and FSH remained significantly associated after adjusting for LH and estradiol levels ($\beta = 0.625$, $p = 0.002$, $R^2 = 0.27$).

No significant correlation was observed between the serum LH levels and any of the anthropometric or laboratory measurements, except FSH (Data not shown). No significant correlation was observed between the serum estradiol levels and any of the anthropometric or laboratory measurements (Data not shown).

3.2 | Follow-up visit characteristics

Of the 56 children who had at least one follow-up visit, 25 were girls (23 with obesity) and 31 were boys (24 with obesity), and the obesity rate was not different between the sexes ($p = 0.14$). Additionally, BMI SDS at the follow-up visit was not significantly different between the girls and boys (Table 1).

Mean follow-up time was 3.0 ± 1.4 years and was not different between the sexes ($p = 0.93$).

In addition, age at follow-up visit was not significantly different between the girls and boys (Table 1).

Pubertal status was not significantly different between the sexes [girls: Pubertal $n = 14$ (6 with menarche), prepubertal $n = 9$, unknown $n = 2$; boys: Pubertal $n = 14$, prepubertal $n = 15$, unknown $n = 2$, ($p = 0.65$)].

Although serum FSH levels increased during the follow up both in girls (Table 1) and boys (Table 1), levels were still higher in girls (Table 1).

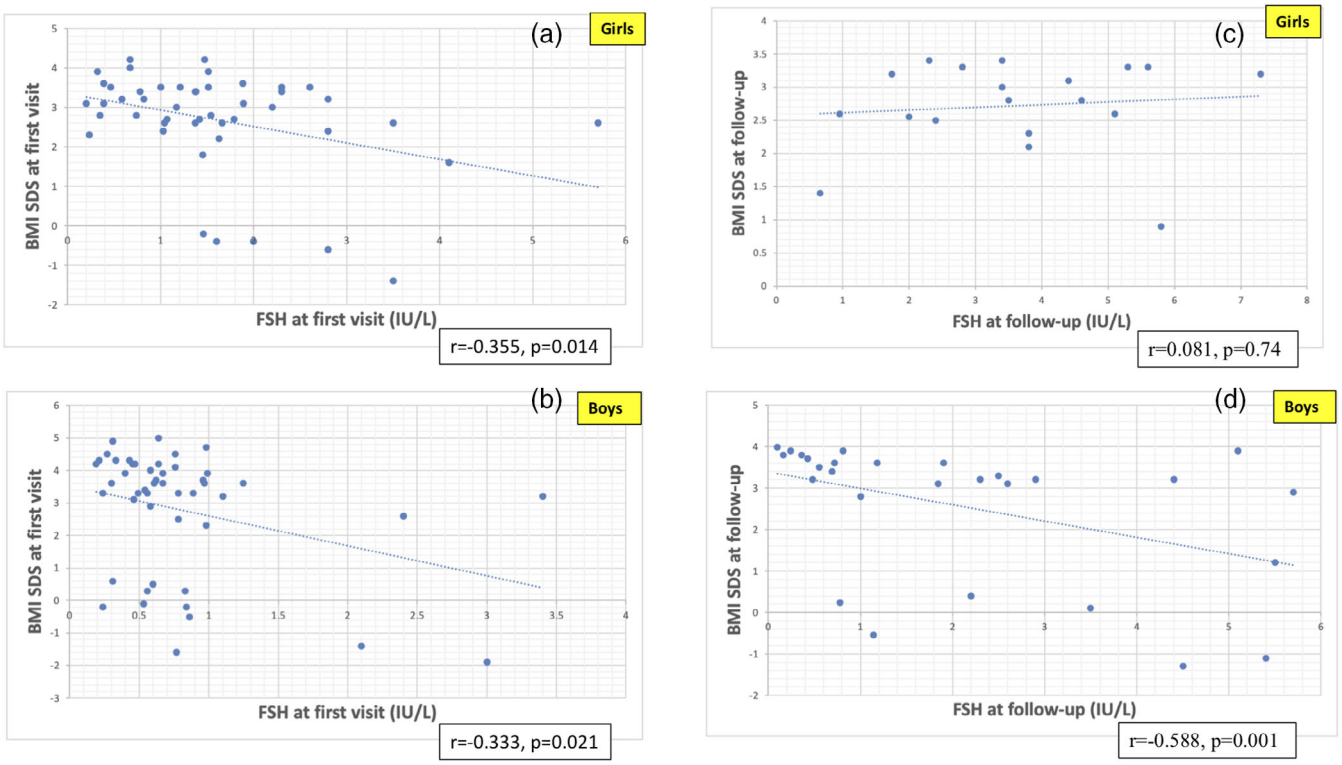

FIGURE 2 Correlations between follicle-stimulating hormone (FSH) levels and body mass index standard deviation scores (BMI SDS) in girls (A) and in boys (B) at the first visit and at the follow-up visit (C and D)

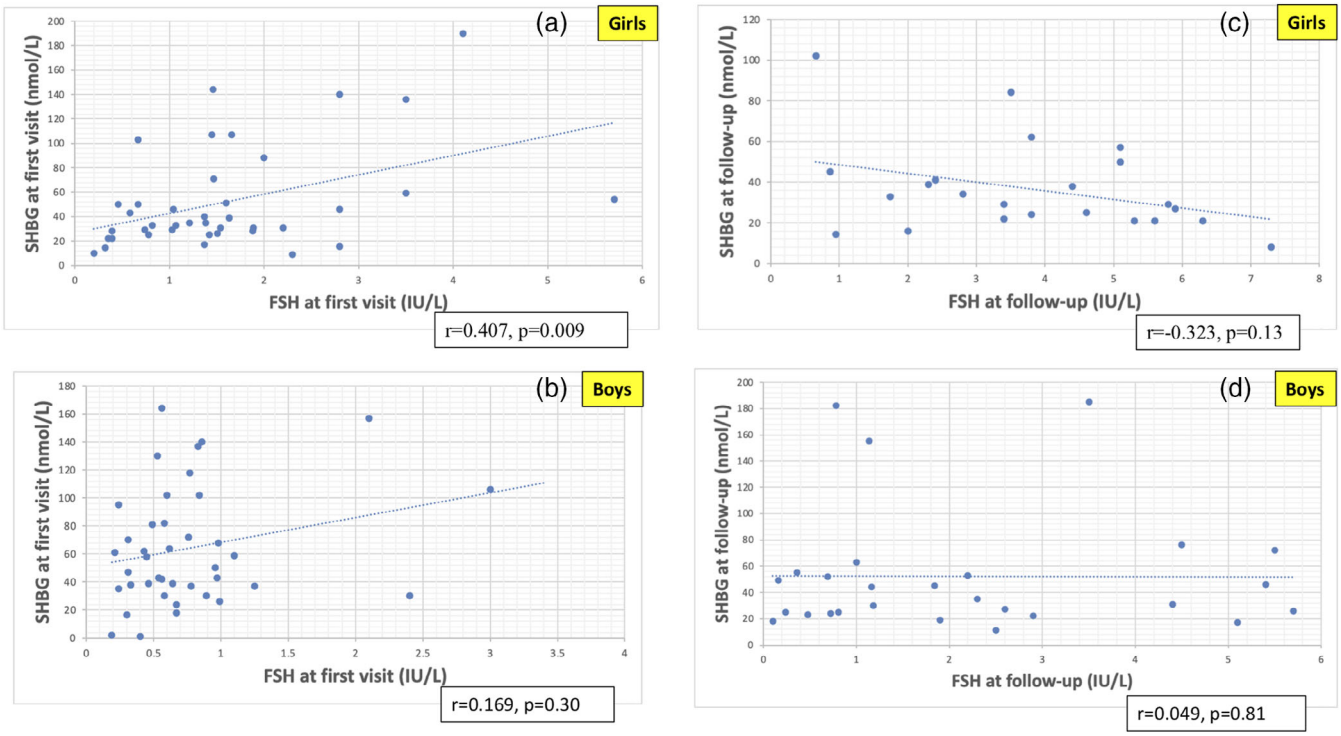

FIGURE 3 Correlations between follicle-stimulating hormone (FSH) and sex hormone binding globulin (SHBG) levels in girls (A) and in boys (B) at the first visit and at the follow-up visit (C and D)

TABLE 4 Prediction of metabolic syndrome at the follow-up based on the clinical and laboratory findings at the first visit

					95.0% CI for OR	
Variable	**B**	**SE**	***p* value**	**OR**	**Lower**	**Upper**
FSH	1.541	0.764	**0.044**	4.67	**1.045**	**20.87**
SHBG	−0.059	0.031	0.053	0.942	0.887	1.001
Sex	−2.213	2.856	0.44	0.109	0.000	29.52
Sum of SFT	0.027	0.030	0.36	1.027	0.969	1.089
BMI SDS tertiles	−3.170	2.897	0.27	0.042	0.000	12.27

Abbreviations: B, Logistic regression coefficient; BMI SDS,: Body mass index standard deviation score; CI, Confidence interval; FSH, Follicle stimulating hormone; OR, Odds ratio; SE, Standard error; SFT, Skin fold thickness; SHBG, Sex hormone binding globulin.
Bold text indicates a statistically significant difference with a *p* value less than 0.05.

BMI SDS decreased both in girls and boys during the follow-up, but the difference was only significant for the boys (Table 1), not for the girls (Table 1).

In girls, SHBG levels significantly decreased, while fasting insulin and HOMA-IR increased during the follow-up (Table 1), but the differences were not significant in boys (Table 1).

Similar to the baseline results, FSH was positively correlated with age in both sexes at the follow-up visit [girls ($r = 0.578$, $p = 0.004$), boys ($r = 0.744$, $p < 0.001$)], as well as plasma LH [girls ($r = 0.782$ $p < 0.001$), boys ($r = 0.857$, $p < 0.001$)].

In girls, the negative correlation between BMI SDS and FSH disappeared during the follow-up ($r = 0.081$, $p = 0.74$) (Figure 2C). In boys however, FSH was still negatively correlated with BMI SDS at the follow-up visit ($r = -0.588$, $p = 0.001$) (Figure 2D).

Furthermore, in girls, FSH was positively correlated with fasting insulin ($r = 0.636$, $p = 0.01$) and HOMA-IR ($r = 0.652$, $p = 0.008$), while negatively correlated with plasma HDL ($r = -0.459$, $p = 0.028$) at the follow-up visit. With the aim of investigating relationships between serum FSH and IR markers independent of growth hormone (GH) effect, we adjusted our results for serum IGF-1 levels. FSH remained significantly associated with fasting insulin ($R^2 = 0.36$, $\beta = 0.668$, $p = 0.027$), and with HOMA-IR ($R^2 = 0.36$, $\beta = 0.678$, $p = 0.025$) after adjusting for IGF-1 levels.

Lastly, in girls, the association between FSH and SHBG turned into negative direction at the follow-up visit, but did not reach significance level ($r = -0.323$, $p = 0.13$) (Figure 3C).

TABLE 5 Prediction of increment in BMI SDS at the follow-up based on the clinical and laboratory findings at the first visit

Variable	B	SE	*p* value	OR	95.0% CI for OR	
					Lower	Upper
FSH	2.776	1.239	**0.025**	16.06	**1.417**	**181.928**
SHBG	−0.030	0.028	0.28	0.970	0.918	1.025
Sex	−19.65	11816.6	0.99	0.000	0.000	0.000
Sum of SFT	0.010	0.030	0.74	1.010	0.952	1.071
BMI SDS tertiles	3.048	2.845	0.28	21.07	0.080	5562.3

Abbreviations: B, Logistic regression coefficient; BMI SDS, Body mass index standard deviation score; CI, Confidence interval; FSH, Follicle stimulating hormone; OR, Odds ratio; SE, Standard error; SFT, Skin fold thickness; SHBG, Sex hormone binding globulin.

3.3 | Relationships of baseline FSH and IR markers at the follow-up visit

Baseline FSH levels were positively correlated with follow-up fasting insulin ($r = 0.676$, $p = 0.006$) and follow-up HOMA-IR ($r = 0.683$, $p = 0.005$), in girls. Baseline FSH remained significantly associated with follow-up fasting insulin ($R^2 = 0.48$, $\beta = 0.599$, $p = 0.021$), and follow-up HOMA-IR ($R^2 = 0.48$, $\beta = 0.591$, $p = 0.024$) after adjusting for IGF-1 levels and age. No significant correlation was found between baseline FSH levels and follow-up metabolic parameters in boys (Data not shown).

3.4 | Prediction of MetS and BMI change

Thirteen children (6 girls and 7 boys) fulfilled the MetS criteria at the follow-up visit. We used logistic regression analysis to understand whether MetS can be predicted based on the clinical and laboratory findings at the first visit. Our model was statistically significant ($p = 0.018$) and explained 49% (Nagelkerke R^2) of the variance. In addition, it correctly classified 82.1% of cases.

Higher FSH levels at the first visit were associated with an increased likelihood of having MetS at follow-up (Table 4). Moreover, higher SHBG levels at the first visit were associated with a reduced likelihood of having MetS at the follow-up visit, but the p value did not reach significance (Table 4). Sex, sum of skin folds, and BMI SDS at the first visit did not add significantly to this model (Table 4).

We also used logistic regression for prediction of BMI SDS change during the follow-up. This model was also statistically significant ($p < 0.001$), explained 69% of the variance, and correctly classified 85.3% of cases.

Higher FSH levels at the first visit were associated with a greater likelihood of increase in BMI SDS at the follow-up (Table 5). Sex, sum of skin folds, BMI SDS and SHBG at the first visit did not add significantly to this model (Table 5).

4 | DISCUSSION

In the current study, we found that higher serum FSH levels in prepubertal children with obesity were associated with an increased risk of MetS development during the pubertal transition. Additionally, we showed that an increase in serum FSH at prepubertal ages was associated with an increased likelihood of elevation in BMI SDS during follow-up.

Previous studies in perimenopausal women have shown results similar to ours.[2,3] Cardiovascular disease risk significantly increases in postmenopausal women.[27] The underlying mechanisms were long attributed to oestrogen decline following menopause, but there are now many studies suggesting that increased FSH levels contribute to this phenomenon.[4,5] Studies of postmenopausal women have revealed that serum FSH predicts MetS similarly to adiponectin and better than serum SHBG, C-reactive protein, or leptin.[2,3] Munir et al.[4] showed that FSH was directly associated with the number of aortic plaques, and El Khoudary et al.[5] found that women with low FSH levels had lower carotid intima-media-thickness than women with medium or high levels of FSH.[5] Recently, it has also been suggested that suppressed FSH levels may contribute to longevity, with a 50% reduction in serum FSH resulting in a 20%–60% increase in longevity.[28]

Despite extensive research, there is still need for a better understanding of the physiological basis of puberty and the pathophysiological mechanisms of its alterations.[29] Little is known about the underlying mechanisms of pubertal IR and how its alterations may contribute to increased disease risk later in life.[30] Puberty is a complex process marked by rapid growth, accumulation of both lean and fat mass, development of secondary sexual characteristics, and reproductive competence. Disturbances in these physiological changes of puberty can be considered putative risk factors for cardiovascular disease and a number of other pathologies in adulthood.[29] Although a certain amount of weight gain is physiological during the pubertal transition, naturally occurring metabolic changes during this period may put adolescents at increased risk for excess weight gain.[17] Reduction of insulin sensitivity and compensatory hyperinsulinemia are physiological during puberty, as well.[31] It is believed that IR is necessary to promote rapid weight gain and growth in puberty, perhaps in part by contributing to leptin resistance.[17,32] Approximately 50% of adult body weight is gained during adolescence.[33] Boys gain greater amounts of fat free mass and skeletal mass, whereas girls acquire significantly more fat mass.[34,35] Furthermore, it is well known that girls have higher serum FSH levels than boys during the prepubertal

years.[36,37] It has also been reported that girls are more insulin resistant than boys at all Tanner stages, and that peak IR occurs at Tanner stage 2 to 3–4 both in boys and girls.[31,34] Similarly, BMI increases throughout puberty, with the greatest increment in Tanner stage 2 to 3–4 in both sexes.[34] There is also evidence that puberty is an important risk factor for the transition from metabolically healthy to unhealthy obesity.[30,38] Moreover, especially in youth with obesity, IR may continue to decline into late puberty.[39,40] Numerous studies have shown that measures of adiposity do not completely explain the physiological IR of puberty.[30,31,41–43] Although there is substantial evidence that the rise in GH/IGF-1 levels is an important contributor to pubertal IR,[30,43] a large portion of the variation seen is still unexplained.[30,42]

In agreement with previous studies, our study showed that even though boys were heavier than girls at the first visit, girls were more insulin resistant than boys, and IR increased with pubertal progression. Plasma FSH levels were also higher in girls than in boys at all time points. Interestingly, during the pubertal transition, we observed nonlinear relationships between varying serum FSH levels and markers of adiposity and IR, especially in girls. At the first visit, while girls were prepubertal and the FSH levels were relatively low, FSH was negatively associated with BMI and positively associated with serum SHBG. In addition, at the first visit, in girls with lower FSH levels, along with higher WC and higher SFT measurements, HOMA-IR was higher and SHBG was lower. With the progression of puberty however, serum FSH levels increased and the negative associations with BMI disappeared. More importantly, even after adjusting for IGF-1 levels, FSH was positively associated with HOMA-IR and fasting insulin, and the association with SHBG turned from positive to negative. Although the girls' BMI SDS decreased, or at least did not increase in most, HOMA-IR increased and SHBG decreased significantly during follow-up. Finally, baseline FSH was positively associated with follow-up HOMA-IR and fasting insulin, in girls.

In boys, similar to the girls, FSH was negatively correlated with BMI SDS at the first visit. During the follow-up however, this correlation remained significant and did not change direction. Moreover, the associations between adiposity parameters and FSH were weaker in boys than girls, both at baseline and follow-up, along with lower FSH levels in boys. Since puberty generally starts earlier in girls than boys, the differences between the sexes seen in our study could be due, in part, to the similar ages of these two groups.

The exact mechanisms behind the negative associations between BMI and serum FSH levels in prepubertal girls and boys are not fully known, but some hypotheses have been proposed for this phenomenon. High leptin levels in adolescents with obesity were shown to decrease gonadotropin-releasing hormone (GnRH) release.[44] Additionally, obesity may cause an increase in insulin levels,[19,20] and insulin suppresses SHBG through suppression of the transcription factor HNF4α,[45] a master regulator of hepatic gene expression. Obesity also causes increased adrenal steroids, increased aromatase activity, and eventually increased sex steroid bioavailability in the prepubertal years, and sex steroids can suppress the gonadotropic axis.[9,46,47] Supporting these hypotheses, we showed that SHBG was lower and HOMA-IR was higher in girls with lower FSH levels at the first visit.

Few studies have examined the relationship between adiposity and FSH in children and adolescents and the results are inconsistent.[44] The kisspeptin/GPR54 system is essential for gonadotropin secretion during puberty,[48] and Zhu et al.[8] reported that prepubertal girls with overweight and obesity had higher kisspeptin levels than their peers. In addition, kisspeptin was positively correlated with FSH, LH, and obesity-related parameters in all girls and boys, in this study.[8] In another study with 90 pubertal boys with obesity and 90 age matched controls, Vandewalle et al.[9] found that while median SHBG and testosterone concentrations were significantly lower in subjects with obesity during mid- and late puberty, median LH and FSH levels were comparable to those of controls. In a study in girls with central precocious puberty (CPP), Fu et al.[49] showed that although baseline LH levels were not different between the groups, baseline FSH levels were significantly higher in girls with normal weight than girls with overweight and obesity. In addition, in boys with CPP, Lee et al.[50] showed that boys with overweight and obesity had lower baseline FSH levels than their peers with normal weight. In a more recent study by Nokoff et al.[51] while girls with obesity had lower urinary FSH levels than normal weight girls, FSH levels were not significantly different between the boys with and without obesity. Contradictory results among the published studies may be arising from the differences between ages, sexes, pubertal stages, and obesity severity of the studied subjects.[44]

We suggest that the contradictory results may also be due to nonlinear associations between the adiposity parameters and the varying FSH levels. In line with our results, there are some animal studies supporting this hypothesis.[52,53] In a study with female canines, Renauld et al.[53] showed that high dose injection of LH and FSH combination increased the serum insulin response to glucose load, and produced a moderate resistance to the hypoglycemic, lipogenic, and antilipolytic actions of the insulin. More importantly, Chu et al.[52] showed that the rat pancreas could express the FSH receptor on islet cells, and that FSH has a bidirectional regulatory effect on insulin secretion from these cells in vitro. They reported that, when the concentration of FSH was below 1×10^{-5} IU/mL, the secretion of insulin gradually decreased as the concentration of FSH gradually increased, but when the concentration of FSH was above 1×10^{-5} IU/mL, the secretion of insulin gradually increased as the concentration of FSH gradually increased. If this observation is also true for human pancreas, since there is a physiological increase in FSH levels through puberty, after reaching a critical point, FSH might start to stimulate insulin secretion and contribute to the physiological IR of puberty.

A nonlinear relationship between FSH and IR might play a role in other physiological changes of puberty as well. Increased gonadotropins increase sex steroids during puberty. However, if serum FSH has a direct effect on insulin production and can increase IR in pubertal children, this can contribute to the development of secondary sexual characteristics via decreasing SHBG and increasing free sex hormone levels,[46] and thus help pubertal progression.

5 | LIMITATIONS

Most of our subjects had obesity, and this may limit generalizability of our results. Furthermore, FSH was negatively correlated with BMI SDS at the first visit, and BMI SDS decreased in children with obesity during the follow-up. Although anthropometric measurements were also included in the regression model, the analysis on BMI change still might have been affected. Thirdly, because of the high refusal rate of pubertal examination, self-description and basal LH levels were also used in addition to the Tanner staging. Especially in girls with obesity, the assessment of pubertal development would be difficult. While the use of LH values was helpful to address this issue, we could only differentiate the subjects as being pubertal, prepubertal, or of unknown pubertal status at the follow-up visit. In addition, there were six girls with menarche at the follow-up examination and the samples were not collected during a specific time of the cycle. Finally, since our sample size was relatively small, these results should be considered preliminary.

6 | CONCLUSIONS

We observed that higher serum FSH levels in prepubertal children were associated with an increased risk of MetS development during the pubertal transition. Increase in serum FSH at prepubertal ages was also associated with an elevated risk of increase in BMI SDS. In addition, we observed nonlinear associations between varying serum FSH levels and markers of adiposity and IR, especially in girls. Our results imply that FSH might play a role in physiological and/or pathological IR of puberty. Future studies, with larger samples of children with or without obesity, and more frequent follow-ups would be helpful to better understand these associations. Furthermore, in vitro studies and animal models would give additional opportunities to better comprehend the underlying mechanisms.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Anders Forslund, Ricard Nergårdh, Peter Bergsten and Banu Kucukemre Aydin conceived the study. Rasmus Stenlid and Iris Ciba contributed to acquisition of data. Marie Dahlbom coordinated and supervised data collection. Banu Kucukemre Aydin analysed the data and wrote the first draft. Sara Y. Cerenius analysed the data and helped writing the manuscript. All authors reviewed and improved the manuscript. All authors approved the final version of the manuscript.

ORCID

Banu Kucukemre Aydin https://orcid.org/0000-0003-0859-1565
Rasmus Stenlid https://orcid.org/0000-0002-1586-9310
Iris Ciba https://orcid.org/0000-0002-5062-8192
Sara Y. Cerenius https://orcid.org/0000-0002-3131-2096
Peter Bergsten https://orcid.org/0000-0002-4937-8464
Ricard Nergårdh https://orcid.org/0000-0001-9984-7866
Anders Forslund https://orcid.org/0000-0001-9109-4556

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