



Insulin resistance and bone age advancement in girls with central precocious puberty

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Purpose: Precocious puberty has significantly increased recently. While obesity is associated with puberty timing, the relationship between obesity and central precocious puberty (CPP) remains controversial. The purpose of this study was to determine whether insulin resistance is associated with bone age (BA) advancement in girls with CPP.

Methods: We retrospectively analyzed the records of 804 girls referred for puberty evaluation. Anthropometric measurements, BA, sex hormone, sex hormone binding globulin (SHBG), and insulin levels, lipid profiles, and gonadotropin releasing hormone stimulation tests were assessed. Insulin resistance parameters were calculated using the homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) models.

Results: BA, BA advancement, free estradiol index, insulin, and HOMA-IR increased significantly in girls with high body mass index (BMI) compared with that of girls with low BMI in cases of CPP. HOMA-IR was positively correlated with BA advancement and BMI but negatively correlated with SHBG. QUICKI was negatively correlated with BA advancement and BMI and positively correlated with SHBG. When HOMA-IR increased by 1, the odds for BA advancement increased 120% after adjusting for age and BMI ($P=0.033$).

Conclusion: Insulin resistance could be associated with BA advancement in girls with CPP.

Keywords: Precocious puberty, Luteinizing hormone, Gonadotropin-releasing hormone

Introduction

Recently, a shift in pubertal timing has been reported worldwide¹. Historical data from several countries shows that the average menarcheal age has decreased remarkably². A recent study suggests similar decreases in average menarcheal age in Korean girls³. Consequently, the prevalence of precocious puberty has increased in Korea and it is becoming a social concern⁴.

Various factors appear to affect the timing of pubertal development, including the environment and nutrition. Adequate nutrition is important for normal timing of pubertal development, and poor childhood nutrition delays growth and pubertal onset⁵. The increase of precocious puberty in girls has been coincided by increases in childhood obesity⁶. Insulin resistance is associated with obesity and is a key risk factor for type 2 diabetes mellitus, cardiovascular disease, and dyslipidemia in adulthood⁷. Early pubertal timing in girls may be associated with early insulin resistance and cardiometabolic diseases in adults⁸.

However, the relationship between obesity for precocious puberty remains a controversial topic. Bordini et al.⁹ suggested that excess weight, in the absence of excess sex steroid, may subtly suppress hypothalamic-pituitary-gonadal function in premenarcheal pubertal girls. Jasik and Lustig¹⁰ reported that there is little support for an association between weight gain

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and early menarche.

Some groups have studied the relation of central precocious puberty (CPP) and obesity, particularly insulin resistance, but clinical studies are still lacking^{11,12}. The purpose of this study was to evaluate the influence of obesity in girls with CPP. We analyzed differences in pubertal characteristics according to body mass index (BMI) and the correlation between insulin resistance and biochemical characteristics in girls with CPP. Furthermore, we investigated the association between pubertal characteristics including bone age (BA) advancement and insulin resistance.

Materials and methods

1. Study population and design

We retrospectively reviewed the medical records of 804 girls referred for evaluation of puberty from 2011 to 2015. We included girls younger than 8 years with objective breast budding above Tanner stage II¹³. We reviewed gonadotropin releasing hormone (GnRH) stimulation test results and defined CPP as peak luteinizing hormone (LH) ≥ 5 IU/L and non-CPP as peak LH < 5 IU/L. We excluded patients with tests collected under nonfasting condition, incomplete sex hormone studies, and history of any other systemic diseases. Therefore, 164 girls were included in the CPP group, and 99 girls were included in the non-CPP group. The control group comprised age- and sex-matched healthy girls (n=67) who did not have objective breast budding, that is, Tanner stage I. The study design is shown in Fig. 1. This study was approved by the Institutional Review Board

of Yonsei University Severance Hospital (approval number: 3-2015-0336). Written informed consent was obtained from all patients.

2. Clinical and laboratory data

BA was evaluated by a single pediatric radiologist measured by 6 months scale with Greulich and Pyle method. BMI was calculated as weight divided by height squared. The data for height standard deviation scores (SDS), weight SDS, and BMI SDS were calculated using z-scores from the 2005 Korean National Growth Chart¹⁴.

The hypothalamic-pituitary-gonadal axis was determined using GnRH stimulation test results. Basal serum samples were obtained before GnRH injection (100- μ g Relefact; Sanofi-Aventis, Paris, France). Serum LH and follicle-stimulating hormone levels were measured using a chemiluminescence immunoassay with an analytical sensitivity of 0.2 IU/L (Beckman Coulter, Brea, CA, USA). Estradiol (E2) levels were determined using an electrochemiluminescence immunoassay with an analytical sensitivity of 5 pg/mL (Roche, Basel, Switzerland). Sex hormone binding globulin (SHBG) was determined using an electrochemiluminescence immunoassay (Roche, Basel, Switzerland). Free estradiol index (FEI) was calculated by dividing the serum E2 level (pg/mL) by the serum SHBG level (nmol/L) and multiplying by 100. The molar ratio of E2/SHBG was calculated to convert E2 to picomolar, the picogram per milliliter value is multiplied by 3.67. A peak LH of at least 5 IU/L was used as the cutoff criteria for pubertal response for the GnRH stimulation test. Insulin-like growth factor-1 (IGF-

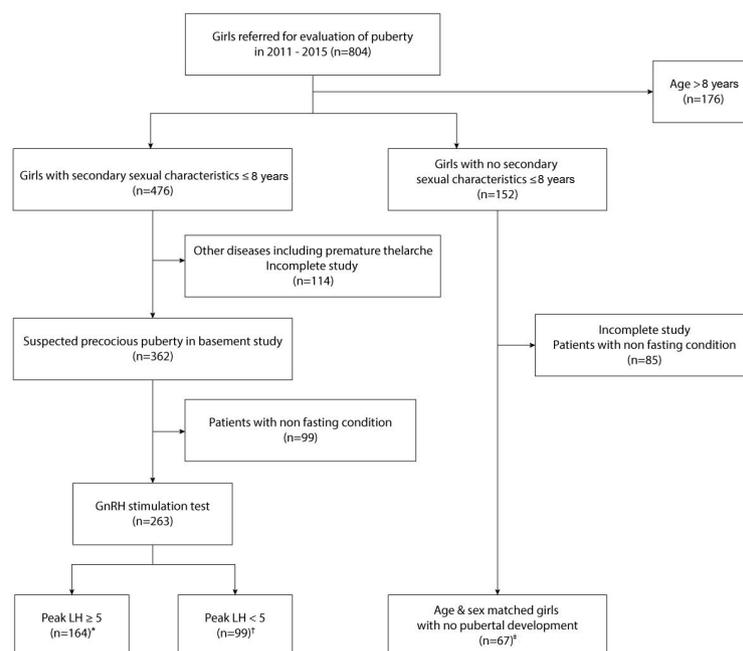


Fig. 1. Summary of patients and study design in this study. CPP*, non-CPP†, and control‡. CPP, central precocious puberty; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone.

1) was measured using a solid-phase, enzyme-labeled, 2-site chemiluminescent immunometric assay (Siemens, Munich, Germany). We reviewed medical records to obtain total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, fasting serum glucose, alanine aminotransferase, and insulin levels. These tests were performed in a fasting state over 8 hours. Insulin resistance was assessed from fasting plasma glucose (G_0 , in mg/dL) and fasting plasma insulin (I_0 , mU/L) levels using the homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) models. HOMA-IR was calculated as $I_0 \times G_0 / 405^{15}$, and QUICKI was calculated as $1/(\log G_0 + \log I_0)^{16}$.

3. Statistical analysis

We analyzed data with SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). We used independent-samples T-test and analysis of variance (ANOVA) to compare the clinical and biochemical characteristics between the CPP, the non-CPP, and the control

groups. We used ANOVA to compare the characteristics in the groups categorized according to BMI scores. We used a trend test to determine the significance of the increase or decrease in the variables as the increasing BMI. Pearson correlation analysis was used to define the correlation between each characteristic and insulin resistance. Multiple logistic regression analysis was used to determine the correlation between insulin resistance parameters and BA advancement. We suggested 2 models adjusted for associated variables such as age and BMI. *P*-values less than 0.05 were considered statistically significant. Multiple comparisons were adjusted by Bonferroni correction.

Results

1. The comparison of the baseline clinical, biochemical characteristics and insulin resistance parameters of CPP, non-CPP, and control groups

We compared the baseline characteristics of the CPP, non-CPP, and control groups (Table 1). BA and baseline serum LH,

Table 1. The comparison of the baseline clinical, biochemical characteristics and insulin resistance parameters of CPP, non-CPP, and control groups (n=330)

Characteristic	CPP (n=164)	Non-CPP (n=99)	Control (n=67)	<i>P</i> -value*	<i>P</i> -value [†]	<i>P</i> -value [‡]	Overall <i>P</i> -value [§]
CA (yr)	8.3±0.6	8.1±0.8	7.9±0.6	0.001	0.077	0.056	0.001
BA (yr)	9.7±0.9	9.2±1.0	8.2±0.9	0.001	0.001	0.003	0.001
BA-CA (yr)	1.3±0.7	1.1±0.7	0.0±1.5	0.001	0.001	0.117	0.001
Ht. SDS	0.9±1.1	0.8±1.0	0.5±0.9	0.011	0.063	0.999	0.012
Wt. SDS	0.7±1.3	0.9±1.3	0.5±0.9	0.714	0.142	0.782	0.138
BMI SDS	0.3±1.1	0.9±1.3	0.4±0.9	0.999	0.633	0.237	0.195
SHBG (nmol/L)	80.2±36.7	76.5±34.7	83.3±31.5	0.999	0.671	0.999	0.460
LH ₀ (IU/L)	1.1±1.2	0.5±0.4	0.3±0.3	0.001	0.615	0.001	0.001
Peak LH (IU/L)	12.9±9.5	3.2±1.0	-	-	-	0.003	0.001
Peak LH/LH ₀	23.3±22.7	9.3±5.8	-	-	-	0.003	0.001
E2 (pg/mL)	12.0±12.5	9.5±9.0	5.0±0.3	0.001	0.016	0.162	0.001
FEI (pmol/L)	17.8±18.3	15.3±17.1	7.0±2.7	0.001	0.004	0.675	0.001
IGF-1 (ug/L)	271.6±91.4	238.9±70.9	220.6±64.3	0.001	0.463	0.005	0.001
AST (IU/L)	27.3±8.9	28.6±10.3	27.1±5.1	0.999	0.883	0.713	0.433
ALT (IU/L)	14.8±5.7	17.5±12.1	14.8±6.7	0.999	0.112	0.037	0.028
Total cholesterol (mg/dL)	168.5±28.7	164.7±27.2	169.4±23.0	0.999	0.831	0.842	0.457
Triglycerides (mg/dL)	116.0±68.6	109.5±61.6	111.4±58.1	0.999	0.999	0.999	0.718
LDL-cholesterol (mg/dL)	94.6±27.1	93.5±26.6	95.9±21.8	0.999	0.999	0.999	0.850
HDL-cholesterol (mg/dL)	51.2±10.1	50.4±9.9	51.8±8.5	0.999	0.999	0.999	0.637
Fasting plasma glucose (mg/dL)	94.7±11.1	96.1±11.9	91.8±8.1	0.204	0.035	0.864	0.040
Insulin (μU/mL)	23.5±22.9	22.5±26.5	12.0±6.8	0.001	0.008	0.999	0.001
HOMA-IR	5.69±5.85	5.68±7.37	2.78±1.72	0.002	0.005	0.999	0.002
QUICKI	0.32±0.04	0.33±0.05	0.34±0.04	0.003	0.194	0.390	0.004

Values are presented as mean±standard deviation.

CPP, central precocious puberty; CA, chronological age; BA, bone age; SDS, standard deviation scores; Ht., height; Wt., weight; BMI, body mass index; SHBG, sex hormone binding globulin; LH, luteinizing hormone; E2, estradiol; FEI, free estradiol index; IGF-1, insulin-like growth factor-1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index

**P*-value for CPP vs. control group. [†]*P*-value for non-CPP vs. control group. [‡]*P*-value for CPP vs. non-CPP group [§]*P*-value was calculated by analysis of variance.

Multiple comparison was adjusted by Bonferroni correction.

E2, FEI, IGF-1, and insulin levels were higher in the CPP group than in the control group. The HOMA-IR was higher in the CPP group than in the control group ($P=0.002$). The QUICKI was lower in the CPP group than in the control group; therefore, this parameter indicated high insulin resistance in the CPP group ($P=0.003$).

2. Baseline clinical, biochemical characteristics and insulin resistance parameters according to BMI in CPP group

We categorized the girls with CPP into 3 groups according to BMI (BMI<50th percentile, 50th percentile≤BMI<85th percentile, and BMI≥85th percentile) and compared clinical and biochemical characteristics. BA, BA advancement, FEI, alanine aminotransferase, insulin, and HOMA-IR were significantly higher in girls with high BMI than in girls with low BMI. Each of the variables showed an increasing trend with higher BMI. SHBG and QUICKI were lower in girls with high BMI than in girls with low BMI. Each of the variables showed a decreasing trend with higher BMI (Table 2).

3. The correlation between clinical, biochemical characteristics and insulin resistance parameters in total girls

We analyzed all girls including CPP, non-CPP, and control groups. Pearson correlation analysis results for HOMA-IR and

QUICKI for all of girls showed that HOMA-IR was positively correlated with BA advancement, BMI SDS, FEI, IGF-1, and triglycerides and was negatively correlated with SHBG. QUICKI was negatively correlated with BA advancement, BMI-SDS, baseline LH, and FEI and was positively correlated with SHBG (Table 3).

4. The change of BA advancement associated with insulin resistance

We used logistic regression analysis to determine the probability of precocious puberty according to changes in the insulin resistance parameters. We also analyzed all girls to clarify the relationship between insulin resistance and BA advancement. When HOMA-IR increased by 1, the odds for BA advancement increased 119% ($P=0.033$). We analyzed the odds after adjusting for chronological age (model 1) and both chronological age and BMI (model 2) to exclude the influence of them. Similar results were achieved through models 1 and 2. When QUICKI increases by 0.01, the odds for BA advancement increased 92% ($P=0.030$). After adjusting for age and both age and BMI, the odds were similar but not significant (Table 4).

Discussion

Trends toward early pubertal timing have coincided with increased obesity prevalence¹⁷⁾. Known factors that affect timing

Table 2. Baseline clinical, biochemical characteristics and insulin resistance parameters according to BMI in CPP group (n=164)

Characteristic	BMI<50th %ile (n=87)	50th %ile≤BMI<85th %ile (n=57)	BMI≥85th %ile (n=20)	P-value*	P for trend†
CA (yr)	8.3±0.6	8.4±0.6	8.2±0.7	0.482	0.960
BA (yr)	9.6±0.9	9.6±0.9	10.2±1.0	0.018	0.018
BA-CA (yr)	1.2±0.7	1.2±0.7	2.0±0.9	0.001	0.001
SHBG (nmol/L)	98.6±34.2	66.0±27.2	40.7±17.0	0.001	0.001
LH ₀ (IU/L)	1.1±1.3	1.1±1.3	1.1±0.8	0.952	0.842
Peak LH (IU/L)	12.7±9.7	13.3±9.2	12.5±9.9	0.924	0.953
E2 (pg/mL)	13.2±14.1	10.3±10.3	11.2±9.6	0.367	0.259
FEI (pmol/L)	15.0±16.7	18.1±18.7	29.5±20.1	0.007	0.004
IGF-1 (ug/L)	278.4±94.0	251.5±87.4	298.9±83.5	0.081	0.950
AST (IU/L)	26.4±5.7	29.6±12.5	24.3±6.8	0.032	0.887
ALT (IU/L)	12.8±3.4	16.1±6.0	19.8±8.0	0.001	0.001
Total cholesterol (mg/dL)	165.6±25.7	174.0±33.2	165.2±26.2	0.198	0.457
Triglycerides (mg/dL)	108.3±72.8	122.4±66.3	130.9±53.4	0.284	0.117
LDL-cholesterol (mg/dL)	92.8±27.3	98.3±26.6	92.4±27.6	0.457	0.630
HDL-cholesterol (mg/dL)	52.0±10.5	51.2±9.6	46.9±8.7	0.139	0.081
Fasting plasma glucose (mg/dL)	94.3±11.6	94.4±11.2	96.9±8.1	0.647	0.461
Insulin (μU/mL)	17.2±13.9	23.2±22.8	51.9±32.8	0.001	0.001
HOMA-IR	4.15±3.87	5.60±5.79	12.60±8.14	0.001	0.001
QUICKI	0.33±0.04	0.32±0.04	0.28±0.02	0.001	0.001

Values are presented as mean±standard deviation.

BMI, body mass index; CPP, central precocious puberty; CA, chronological age; BA, bone age; SHBG, sex hormone binding globulin; LH, luteinizing hormone; E2, estradiol; FEI, free estradiol index; IGF-1, insulin-like growth factor-1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index.

*P-value was calculated by analysis of variance. †P for trend was calculated by trend test.

Table 3. Pearson correlation for HOMA-IR and QUICKI in total girls (n = 330)

Variable	HOMA-IR		QUICKI	
	Pearson correlation coefficient	P-value	Pearson correlation coefficient	P-value
BA-CA	0.244	0.001	-0.235	0.001
Weight SDS	0.212	0.001	-0.195	0.001
Height SDS	0.394	0.001	-0.367	0.001
BMI SDS	0.398	0.001	-0.398	0.001
SHBG	-0.215	0.001	0.254	0.001
LH	0.060	0.280	-0.111	0.044
FEI	0.109	0.048	-0.127	0.022
IGF-1	0.118	0.033	-0.174	0.002
AST	-0.048	0.382	0.310	0.001
ALT	0.335	0.001	-0.085	0.121
Total cholesterol	-0.114	0.039	0.027	0.630
Triglycerides	0.119	0.032	-0.170	0.102
LDL-cholesterol	-0.165	0.003	0.116	0.035

Insulin resistance is positively correlated with BA advancement, BMI SDS, FEI, IGF-1, and triglycerides and was negatively correlated with SHBG.

HOMA-IR, homeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index; BA, bone age; CA, chronological age; SDS, standard deviation scores; BMI, body mass index; SHBG, sex hormone binding globulin; LH, luteinizing hormone; FEI, free estradiol index; IGF-1, insulin-like growth factor-1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein.

Table 4. Multiple logistic regression results for change of bone age advancement associated with insulin resistance (n=330)

Model	HOMA-IR				QUICKI x 100			
	β coefficient	SE β	OR (95% CI)	P-value	β coefficient	SE β	OR (95% CI)	P-value
Unadjusted	0.177	0.083	1.19 (1.02–1.40)	0.033	-0.086	0.040	0.92 (0.85–0.99)	0.030
Model 1	0.174	0.081	1.19 (1.02–1.39)	0.031	-0.072	0.040	0.93 (0.86–1.01)	0.075
Model 2	0.183	0.086	1.20 (1.02–1.42)	0.033	-0.070	0.045	0.93 (0.85–1.02)	0.115

When insulin resistance increased, the odds for BA advancement increased. Model 1 is a multiple logistic regression adjusted for chronological age. Adjusted OR for chronological age and BMI represented in model 2.

HOMA-IR, homeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index; SE β , standard error of β coefficient; OR, odds ratio; CI, confidence interval; model 1, adjusted for chronological age (CA); model 2, adjusted for CA and body mass index (BMI).

of puberty include estrogen in food, cosmetics, and hair care products, endocrine disrupters in the environment, nutrition and obesity¹⁸⁻²⁰. However, these factors remain controversial. For example, while there are several studies associating weight gain and obesity with earlier thelarche, there is not much support for the association between weight gain or obesity and earlier menarche¹⁰.

In our study, we analyzed the association between characteristics of precocious puberty and insulin resistance. Baseline serum LH, E2, FEI, IGF-1, BA, insulin levels, and insulin resistance parameters were higher in the CPP group than in the control group. Although BMI SDS did not differ among the groups, insulin resistance parameters differed in the CPP and control groups. Because one of the roles of insulin is stimulating ovary and adrenal steroidogenesis, E2 and FEI levels might increase in girls with precocious puberty²¹.

Another factor that modulates maturational timing is the GH/IGF-1 axis. The GH/IGF-1 axis is affected by glucose homeostasis²². Sørensen et al.²³ showed that IGF-1 levels were significantly positively associated with insulin levels. While low IGF-1 serum concentrations are generally related to insulin

resistance²⁴, we found that insulin resistance and IGF-1 were significantly higher in the CPP group than in the control group. Due to limitation of the cross-sectional design of our study, a causal relationship between IGF-1 levels, insulin resistance, and pubertal timing could not be determined. However, we found a significant relationship between IGF-1 and insulin levels in girls with CPP.

In our study, girls with high BMI had increased BA, BA advancement, FEI, insulin levels, and HOMA-IR and lower SHBG and QUICKI than girls with low BMI. Because BA advancement and increased FEI are characteristic of sexual precocity, our data suggest that obesity is associated with sexual precocity. SHBG, a glycoprotein that binds sex hormones, also links obesity and precocious puberty²⁵. Hyperinsulinemia from obesity-related insulin resistance can reduce hepatic SHBG production and increase sex steroid bioavailability²⁶. In our study, insulin resistance was positively correlated with BA advancement and was negatively correlated with SHBG. We found that serum insulin levels were higher in girls with precocious puberty than in girls in the control group. High levels of insulin predict adverse cardiovascular risk factors

and metabolic syndrome. Insulin resistance in precocious puberty also might be associated with increased cardiovascular morbidity and mortality in adulthood⁸⁾. Obviously, it is important to prevent obesity and insulin resistance in children.

Obesity during childhood may lead to thelarche in girls¹⁰⁾. It remains unclear whether early thelarche in overweight girls is related to central activation of the GnRH-gonadotropin axis²⁷⁾. Our findings show that girls with precocious puberty had high insulin resistance. Although we did not find a direct mechanism of GnRH-gonadotropin axis activation, the association between obesity and precocious puberty is important.

One study suggested that obesity can lead to precocious puberty through leptin-induced pubertal development. Leptin serves as a signal to the hypothalamus regarding energy stores in adipose tissue and may directly stimulate GnRH and gonadotropin secretion²⁸⁾. Insulin and, paradoxically, obesity increase leptin levels²⁹⁾. Obesity-related insulin resistance with compensatory hyperinsulinemia increase serum leptin levels and may also play a role in early pubertal development. Further research is needed to identify the relationship between serum leptin levels and BA advancement.

BA studies can evaluate the rate of skeletal maturation, which can help diagnose conditions that delay or accelerate physical growth and development. Advanced BA is associated with earlier puberty³⁰⁾. We predicted the probability of precocious puberty through the quantification of insulin resistance and BA advancement. When insulin resistance increases, BA advancement occurs, which may result in precocious puberty. Our findings show that the risk of BA advancement increased 119% when HOMA-IR increased by 1. Although there are multiple factors influencing precocious puberty, our results suggest that insulin resistance may be an important factor for CPP after adjusting for age and BMI.

There was a limitation in our study to classify CPP and non-CPP with peak LH. We defined CPP as peak LH \geq 5 IU/L and non-CPP as peak LH $<$ 5 IU/L. Accordingly, non-CPP group includes peripheral precocious puberty and slowly progressive CPP. In addition, the control group comprised girls who did not have secondary sexual character among the girls visited the hospital to check their puberty status. It is attributed to a hospital based observation study.

In conclusion, our findings suggest that insulin resistance is elevated and associated with BA advancement in girls with CPP. Unlike other studies, our retrospective study included more than 100 patients with CPP from a single country. Longitudinal prospective studies that include more precise methods of evaluating body fat mass, such as triceps skin-fold thickness or waist circumference, are needed to determine the causality between obesity and precocious puberty.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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