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SEX HORMONE BINDING GLOBULIN, OLIGOMENORRHEA, POLYCYSTIC OVARY SYNDROME, AND CHILDHOOD INSULIN at 14 Years of Age PREDICT METABOLIC SYNDROME AND CLASS III OBESITY AT 24 Years

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Abstract

Objective—We hypothesized that age 14 oligomenorrhea (menstrual cyclicity ≥ 42 days), hyperandrogenism-low sex hormone binding globulin (SHBG), childhood insulin, and metabolic syndrome (MetS) would predict age 24 MetS and Class III obesity (BMI ≥ 40 kg/m^2).

Study design—Prospective schoolgirl study. At age 14, girls were categorized as regularly cycling (n=375), oligomenorrheic (n=18), and oligomenorrhea plus biochemical hyperandrogenism (polycystic ovary syndrome [PCOS], n=12), altogether denoted as PCOS category.

Results—Significant explanatory variables for age 24 MetS included childhood insulin, age 14 MetS, and PCOS category (all positive), and SHBG (negative). Using categorical data, top decile childhood insulin, age 14 MetS, bottom decile SHBG, and PCOS category were significant positive predictors for age 24 MetS. Age 14 SHBG (negative), black race (positive) and oligomenorrhea (positive) were significant explanatory variables for age 24 Class III obesity. Using categorical data, black race, age 14 MetS, bottom decile SHBG, PCOS category, and top decile childhood insulin were positive explanatory variables for age 24 Class III obesity.

Conclusions—Age 14 oligomenorrhea, PCOS (a sub-cohort of oligomenorrhea), hyperandrogenism-low SHBG, MetS, and childhood insulin may represent a critical, reversible pathway for development of MetS and Class III obesity in young adulthood.

Keywords

Oligomenorrhea; Sex hormones; insulin resistance; adolescence

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Adolescent oligo-amenorrhea should point the pediatrician to investigate androgen/estrogen balance and possible underlying polycystic ovary syndrome (PCOS)[1, 2] as steps in a critical pathway for development of progressive obesity, the metabolic syndrome (MetS), and early onset type 2 diabetes mellitus (T2DM). In adolescents, low sex hormone binding globulin (SHBG) has been reported to be the only significant predictor of MetS. [3]

Most girls are menarchal at age 14 (98% of whites, 97% of blacks).[4] Chiazze et al reported that only 2.5% of 15-19 year old girls had average menstrual cycle lengths > 40 days. [5] In the NHLBI National Growth and Health Study (NGHS), a 10-year study of black and white girls from ages 9-10 to ages 18-19,[6] over 90% of girls had achieved menarche by age 14 years. Defining oligomenorrhea in 15-year-old white Dutch girls by menses ≥ 42 days, van Hooff et al reported that oligomenorrheic girls were more likely than either girls with irregular or normal menses to be hyperandrogenemic and to have polycystic ovaries. [1, 2]

In the current prospective study of black and white girls in the Cincinnati Clinic of the National Growth and Health Study (NGHS), we assessed mean age 14 pubertal, menstrual, insulin, sex hormone, and MetS data as predictors of MetS and Class III obesity (body mass index [BMI] ≥40) at mean age 24. We speculated that there was a significant role for age 14 oligomenorrhea, PCOS as a sub-cohort of oligomenorrhea, sex hormones, and insulin in the genesis of MetS syndrome and severe (Class III) obesity at age 24, facilitating a pediatric approach to primary prevention of MetS, severe obesity, type 2 diabetes, and adult cardiovascular disease.[7, 8]

METHODS

The Growth and Health Study [NGHS], initiated in 1987, investigated development of obesity in black and white girls during adolescence. [9] Participant eligibility was limited to girls and their parents who declared themselves as being either black or white and who lived in racially concordant households. Annual visits were carried out from ages 9-10 through 18-19. The follow-up rate was 89% at the 10th annual visit. Subsequently, investigator-initiated studies were done for 5 more years through ages 24-25. In Cincinnati, fasting insulin was measured at entry, age 10, and at age 16, and sex steroid hormones and SHBG were measured at ages 10, 12, and 14, in addition to lipid profiles, ApoA1, systolic and diastolic blood pressure. [10] Sexual maturation was assessed by trained registered nurses.

At each annual visit, from ages 10-19, information was obtained on menarche and on the number of days since the previous menstrual cycle. Oligomenorrhea at age 14 and ages 14 through 19 was defined as menstrual cyclicity ≥ 42 days.[1, 2,5] Separately, we also used 6-year (ages 14-19 annual visits) oligomenorrhea categories (0 [no oligomenorrhea in 6 yearly reports], 1 [1 of 6 reports], 2 [2 of 6 reports], or ≥3 [3 reports or more]) as an explanatory variable. We prospectively assessed relationships of oligomenorrhea and sex hormones at age 14 to MetS and Class III obesity at age 24.

Signed informed consent was obtained from girls' parents-guardians, assent from girls in NGHS, and signed consent from girls (now adult women) in the extension study. [10]

Laboratory and Clinical Measurements

Methods for measurement of SHBG, estradiol (E2), dehydroepiandrosterone sulfate (DHEAS), free testosterone, lipids, apolipoprotein A1, insulin, height, weight, waist circumference, and systolic and diastolic blood pressure have been previously described. [9] Blood was drawn after an overnight fast in the seated position. Blood drawing was not scheduled by menstrual status or day of menstrual period. BMI was measured annually to assess overweight, and waist circumference as an indicator of fat patterning. At age 14,

hyperandrogenism was defined by DHEAS >280 mcg/dl, or race-specific bottom decile SHBG ≤6 nmol/l for black, ≤7 for white), or race-specific top decile free testosterone (≥2.13 pg/ml for black and white). At age 14, girls were categorized as regularly cycling, oligomenorrheic, and oligomenorrheic with hyperandrogenism (PCOS, by Consensus Criteria[11]). These 3 levels were denoted as PCOS categories.

Girls having fasting blood glucose ≥ 126 mg/dl [12] at age 10, and/or type 1 diabetes (based on patient-physician records) at any time from age 10 through age 25, were excluded (n=7) from the analysis sample for this report. Diagnosis of type 1 diabetes was based on fasting glucose ≥126 mg/dl, and self-reported diabetes with treatment by a physician. [12]

Serum insulin (competitive protein-binding radioimmunoassay) was measured after an overnight fast (≥ 8 hr) using the Michigan Diabetes Research and Training Center (Ann Arbor) at ages 10 and age 16. We denoted the first insulin measure from age 10 (n=296) and age 16 (95) as 'childhood insulin'. We used fasting insulin as the indicator of insulin resistance (IR) based on reports by Huang et al [13]

Metabolic syndrome at ages 14 and 24 years

At age 14 years, we defined MetS using previously reported [14] pediatric standards, ≥ 3 of the following 5 components: triglycerides >110 mg/dl, BMI ≥age-specific 90th percentile (based of CDC 2000 growth charts), blood pressure ≥ the age and height specific 90th percentile, HDLC ≤50 mg/dl, but with glucose ≥ 100 rather than 110 mg/dl. At age 24, MetS was diagnosed by revised [15]ATP III criteria, ≥ 3 of the following 5 : waist > 88 cm, HDL cholesterol < 50 mg/dl, triglyceride ≥ 150 mg/dl, glucose ≥ 100 mg/dl, systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mm Hg.

Statistical methods

Age 14 risk factors for age 24 MetS are exhibited by race and age 24 MetS status in Table I (available at www.jpeds.com). Risk factors were categorized as race-specific top or bottom deciles vs. the other 9 deciles. Associations of MetS at age 24 with these categorized risk factors were tested by Fisher's p. Similar evaluations for age 24 class III obesity were reported in Table II (available at www.jpeds.com). The Hochberg-Benjamini [16] correction for multiple tests was used.

Wilcoxon non-parametric tests of difference were used to compare age 14 sex hormones and BMI in girls with and without oligomenorrhea at age 14. Stepwise logistic regression analysis was used to assess childhood insulin, age 14 sex hormones (free testosterone, E2, DHEAS, SHBG), along with race, age, BMI, and waist circumference as explanatory variables for oligomenorrhea (menstrual cyclicity ≥ 42 days) at age 14.

To assess age 14 correlates for age 24 MetS, stepwise logistic regression was run. Explanatory variables included race, age 14 measures (oligomenorrhea, PCOS category, MetS status, free testosterone, E2, DHEAS, SHBG), and childhood insulin (Table III). A second logistic regression model was run with the dependent variable being age 24 MetS, using race, oligomenorrhea, PCOS category and MetS at age 14, and deciles of age 14 variables (SHBG and E2 [race specific bottom decile vs. top 9 deciles], free testosterone and DHEAS [race specific top decile vs. lower 9 deciles]), and childhood insulin [race specific top decile vs. lower 9 deciles] (Table III). Separately, we used categorical summation of the number of oligomenorrhea reports at 6 annual visits from ages 14-19 (0/6, 1/6, 2/6, ≥3/6) to replace age 14 oligomenorrhea (0, 1), and then repeated the stepwise logistic regressions (data not shown).

To assess age 14 correlates for Class III obesity at age 24, stepwise logistic regression was done with explanatory variables: race, and age 14 measures: (oligomenorrhea, PCOS category, MetS status, free testosterone, E2, DHEAS, SHBG), and childhood insulin (Table IV). A second logistic regression model was run using race, oligomenorrhea, PCOS category and MetS at age 14, and categorical age 14 variables (SHBG and E2 [race specific bottom decile vs. top 9 deciles], free testosterone and DHEAS [race specific top decile vs. lower 9 deciles]), and childhood insulin [race specific top decile vs. lower 9 deciles] (Table IV). Separately, we used summation of the number of oligomenorrhea reports at annual visits from ages 14-19, categorized as 0/6, 1/6, 2/6, ≥3/6 reports, in place of age 14 oligomenorrhea (0, 1) in the stepwise logistic regression models (data not shown).

Distributions of metabolic syndrome and Class III obesity at age 24 cross categorized by PCOS category were assessed by Mantel-Haenszel X^2 analysis (Table V).

RESULTS

After exclusion for type 1 diabetes, 493 (237 white, 256 black) of 865 Cincinnati NGHS girls had measurement of sex hormones and SHBG at age 14, of whom 420 had MetS status determined at median age 24 (23.7 ±1.5) (Table I), 436 had obesity status at median age 24 (23.4±1.3) (Table II), and 427 had first childhood insulin (at age 11.4 ± 2.7 years). Complete data were available to construct regression models for MetS at age 24 in 324 girls (135 white, 189 black) (Table III) and for determinants of Class III obesity at age 24 in 333 girls (140 white, 193 black) (Table IV).

The 493 girls who had measurement of sex hormones and SHBG at age 14 did not differ (p>.09) from the 372 without sex hormones and SHBG measured for the following age 14 variables: race, BMI, waist, blood pressures, and lipids, glucose at age 10 and childhood insulin. Among the 493 girls with SHBG measurement at age 14, in constructing regression models for MetS at age 24, there was differential loss by race due to missing data, with 26% of black girls compared with 43% of whites not included in the regression models, p <.05.

Correlates of age 14 oligomenorrhea

By Wilcoxon tests of difference, comparing 14 year old girls with and without oligomenorrhea, significant differences included age 14 free testosterone (median [interquartile range-IQ], 1.41 [0.93-2.12] vs. 1.07 [0.70-1.51], p=.0059), and waist circumference (72.9 cm [64.3-87.2] vs. 68.0 [64.4-73.8], p=.026). There were no significant differences (p>0.05) in girls with and without age 14 oligomenorrhea for race, other sex hormones, SHBG, or BMI at age 14, or for childhood insulin.

By stepwise logistic regression, with age, race, BMI, waist circumference, free testosterone, E2, DHEAS, SHBG, all measured at age 14, and childhood insulin as candidate explanatory variables, free testosterone (pg/ml) was the only significant variable for oligomenorrhea at age 14, OR 1.90, 95% CI 1.22-2.95, p =.004.

Predictors of MetS and Class III obesity at age 24 years

In the 420 girls who had MetS status known at age 24, girls with MetS at age 24 were more likely to have had race-specific, top decile age 14 free testosterone and childhood insulin, age 14 MetS, and were more likely to have had race-specific bottom decile age 14 SHBG (Table I).

In the 436 girls who had class III obesity status known at age 24, class III obesity at age 24 was positively associated with black race, with high childhood insulin, and with age 14 high free testosterone, low SHBG, oligomenorrhea, and MetS (Table II).

Independent determinants at 14 years of age for metabolic syndrome at 24 years

Using continuous data, by stepwise logistic regression, significant independent determinants for MetS at age 24 included childhood insulin (positive), age 14 MetS (positive), SHBG (negative), and PCOS category (positive), AUC =0.844 (Table III).

Using categorical data, childhood insulin (race-specific top decile vs. lower 9 deciles), age 14 MetS, SHBG (race specific bottom decile vs. upper 9 deciles) and PCOS category were significant, independent, positive predictors for MetS at age 24, AUC =0.826 (Table III).

Separately, we used categorical summation of the number of oligomenorrhea reports at 6 annual visits from ages 14-19 (0,1,2, ≥3) to replace age 14 oligomenorrhea (no =0, yes= 1), and then repeated the stepwise logistic regression models. The resultant models were virtually identical to those with age 14 oligomenorrhea, data not shown.

Independent determinants at 14 years of age for Class III obesity at 24 years

Using continuous data, age 14 SHBG (negative), black race (positive) and age 14 oligomenorrhea (positive) were significantly and independently associated with Class III obesity at age 24 (Table IV). Age 14 MetS and childhood insulin, however, did not enter the model as significant explanatory variables for age 24 Class III obesity (Table IV).

Using categorical data, age 14 MetS, black race, age 14 SHBG (race-specific bottom decile vs. top 9 deciles), age 14 PCOS category, and childhood insulin (race-specific top decile vs. lower 9 deciles) were independent positive predictors for Class III obesity at age 24 (Table IV).

Separately, we used categorical summation of the number of oligomenorrhea reports at 6 annual visits from ages 14-19 (0,1,2, ≥3) to replace age 14 oligomenorrhea (no =0, yes= 1), and then repeated the stepwise logistic regression models. The models were virtually identical to those with age 14 oligomenorrhea, identifying the same factors as significant predictors, data not shown.

Sub-cohort of oligomenorrheic 14-year-old girls with defined polycystic ovary syndrome

Despite not having pelvic ultrasound data (one of the 3 Rotterdam Consensus criteria[11] for diagnosis of PCOS), of the 30 14 year old girls with oligomenorrhea, 12 (40%) also had biochemical hyperandrogenism, and thus could be defined as having PCOS, having the requisite 2 of 3 diagnostic components (oligo-amenorrhea and biochemical hyperandrogenism).[11] In 12 of 30 oligomenorrheic 14-year-old girls in whom PCOS was defined,[11] 4 (33%) had MetS, and 4 (33%) Class III obesity at age 24, versus 7.8% (26/333) (p=.014) and 8.4% (29/345) (p=.018) girls without oligomenorrhea (Table V). Age 24 MetS (33%) and Class III obesity (33%) were most common in girls with defined PCOS (Table V).

DISCUSSION

The current study indicates a significant role for adolescent (age 14) sex hormones, oligomenorrhea, PCOS (a hyperandrogenic sub-cohort of oligomenorrhea), and insulin in the genesis of young adult MetS and severe obesity. Moreover, in the current report, logistic models incorporating oligomenorrhea reported over 6 visits from ages 14-19 had virtually the same predictive nature for MetS and severe obesity at age 24 as those using oligomenorrhea data only at age 14. Oligomenorrhea has been associated with insulin, androgen, and gonadrotropin concentrations in the first years after menarche, [1, 2] The presence of adolescent oligomenorrhea should lead pediatricians to assess insulin, sex

hormones, and the diagnosis and treatment of PCOS, [17-19] which may represent critical, potentially reversible pathways for development of progressive obesity, metabolic syndrome, and type 2 diabetes in adolescence and young adulthood, and later cardiovascular disease. [7, 20]

Almost all girls are postmenarchal at age 14. [4, 6] Oligomenorrhea is not normative during the first two years after menarche. [5] In a study of 237 white 9th grade schoolgirls (mean age 15.2 years), van Hooff et al, [1] whose ≥ 42-day indicator of oligomenorrhea we used in the current study, reported oligomenorrhea in 56 (24%). They concluded that "…our oligomenorrheic group will be a mixture of girls in whom this menstrual cycle pattern is a stage in their maturation to a regular menstrual cycle pattern and girls who have or will develop PCOS, characterized by oligo-or anovulation with high LH or androgen concentrations." [1, 2] Previous longitudinal studies on oligomenorrhea or hyperandrogenemia have shown that adolescents maintain menstrual length characteristics in adulthood. [21] Van Hooff et al suggested, "about 50% of our oligomenorrheic girls will develop PCOS as adults." In a study of 58 adolescents with regular menstrual cycles, 50 with irregular menstrual cycles, and 29 with oligomenorrhea (group mean age 16.7), van Hooff et al [2] reported polycystic ovaries in 9% of girls with regular menses, 28% in girls with irregular menses, and 45% in girls with oligomenorrhea, the group with the highest androgen and LH concentrations. Avvad et al[22] reported that menstrual irregularity within the first postmenarchal years can be an early clinical sign of PCOS.

In the current study, the sub-cohort of oligomenorrheic 14 year olds with defined[11] PCOS were much more likely than girls without oligomenorrhea to have metabolic syndrome (33% vs. 8%) and Class III obesity (33% vs. 8%) at age 24. Even though we did not have pelvic ultrasound[11] data to optimize the diagnosis of PCOS, 40% of our oligomenorrheic girls could be defined as having PCOS by virtue of oligomenorrhea and biochemical hyperandrogenemia,[11] comparable with the ~50 reported by van Hooff et al. [1]

Our 10-year prospective study is congruent with cross-sectional studies in children [3, 17] that have reported that low SHBG is associated with MetS. In cross sectional studies, PCOS in adolescents, which is commonly characterized by low SHBG and hyperandrogenemia, is associated with MetS. [18] To our knowledge, however, our current report provides the first prospective cohort evidence that modifiable [23] age 14 PCOS, SHBG, insulin, and MetS predict MetS in young adulthood 10 years later.

Hepatic production of SHBG is suppressed by insulin, accounting in part for low SHBG levels in insulin resistance-hyperinsulinemia. [24] Genetic alterations that affect SHBG levels also are associated with an increased risk of insulin resistance and type 2 diabetes mellitus. [25] Within this frame of reference, childhood insulin and SHBG are probably inter-related in their prediction of young adult MetS.

Peripubertal obesity is associated with marked hyperandrogenemia. [26] In the current study, significant independent determinants for Class III obesity at age 24 included black race (positive), and age 14 SHBG (negative), oligomenorrhea (positive), oligomenorrhea with hyperandrogenism (PCOS), and top decile childhood insulin. Low SHBG, oligomenorrhea, and high free testosterone are characteristics of PCOS, which is known to be associated with obesity in adolescence and adulthood.[17-19, 23, 27, 28] These findings should provide an opportunity to initiate primary prevention of class III obesity in oligomenorrheic, hyperandrogenemic 14-year-old girls with diet, exercise, and (possibly) metformin. [29, 30] When added to lifestyle modification in obese adolescents, metformin furthers weight loss. [30] Metformin, in combination with lifestyle modification and oral contraceptives, has

been reported to reduce central adiposity, reduce total testosterone, and increase HDL in obese female adolescents. [23]

Going from the 493 girls with SHBG at age 14, to regression models for MetS and Class III obesity at age 24, there was differential loss by race, greater in white than black girls. This is a study limitation and might relatively bias the results to effects more closely linked to black race. However, black race was a significant explanatory variable only for Class III obesity at age 24. A second study limitation was that predictors of MetS and Class III obesity at age 24 were measured at different ages, insulin at ages 10 and 16, SHBG, free testosterone, estradiol, and oligomenorrhea at age 14. Nonetheless, this limitation should make it harder to reject the null hypothesis, due to increasing the size of the variance of the data. Despite these limitations, in our prospective study, the combination of childhood insulin, and age 14 SHBG and oligomenorrhea plus hyperandrogenism (PCOS), or oligomenorrhea from ages 14 through 19, predicted MetS ten years later at age 24. Moreover, age 14 metabolic syndrome, bottom decile SHBG, top decile childhood insulin, and age 14 PCOS category were associated with Class III obesity at age 24. A third study limitation was the collection of only the number of days since the previous onset of menses. Thus, a participant with periods ≥ 42 days could have been seen within 1-28 days of the onset of her previous menses frequently, resulting in an underestimate in the prevalence of oligomenorrhea. By combining data from ages 14-19, the effects of underestimation are minimized.

Age 14 oligomenorrhea, PCOS as a sub-cohort of oligomenorrhea, hyperandrogenism-low SHBG, MetS, and childhood insulin are important, potentially reversible pathways for development of MetS and severe obesity in young adulthood. Triggered by the presence of adolescent oligomenorrhea, evaluation of sex hormones, insulin, MetS, and diagnosis of PCOS could identify girls at high risk for MetS and severe obesity as young adults, at increased risk for type 2 diabetes and cardiovascular disease in later adult life, and should facilitate early, primary prevention treatment.

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Table 1

Metabolic syndrome at age 24 and potential risk factors at age 14: race, free testosterone, estradiol, dehydroepiandrosterone sulfate, sex hormone binding globulin, oligomenorrhea (menses delay ≥42 days), metabolic syndrome, and childhood insulin

Age 14 variables	n	Median, interquartile range (IQ)	Metabolic Syndrome Yes at age 24 (n=35)	Metabolic Syndrome no at age 24 (n=385)	Fisher's p
WHITE (n=194)					
FreeT (pg/ml)	194	1.16 (0.75, 1.63)	14% (2/14) in race-spec. top decile	8% (15/180) in race-spec. top decile	.35
E2 (pg/ml)	194	76.7 (50.3, 135.8)	14% (2/14) in race-spec. bottom decile	7% (13/180) in race-spec. bottom decile	.30
DHEAS (mcg/dl)	194	159.2 (109.1, 236.9)	14% (2/14) in race-spec. top decile	10% (18/180) in race-spec. top decile	.64
SHBG (nmol/l)	194	18 (12, 24)	50% (7/14) in race-spec. bottom decile	8% (14/180) in race-spec. bottom decile	.0001 *
Insulin (uU/ml)	176	8.8 (5.6, 12.9)	42% (5/12) in race-spec. top decile	7% (11/164) in race-spec. top decile	.0018 *
Oligomenorrhea at age 14	153	12 Yes (8%)	18% (2/11) had oligomenorrhea	7% (10/142) had oligomenorrhea	.21
MetS at age 14	194	11 Yes (6%)	36% (5/14) had MetS at age 14	3% (6/180) had MetS at age 14	.0003 *
BLACK (n=226)					
FreeT (pg/ml)	226	1.06 (0.65, 1.43)	29% (6/21) in race-spec. top decile	8% (17/205) in race-spec. top decile	.011 *
E2 (pg/ml)	225	90.7 (53.7, 187.5)	10% (2/21) in race-spec. bottom decile	10% (20/204) in race-spec. bottom decile	1.0
DHEAS (mcg/dl)	226	165.2 (117.1, 226)	14% (3/21) in race-spec. top decile	9% (19/205) in race-spec. top decile	.44
SHBG (nmol/l)	226	17 (11, 24)	33% (7/21) in race-spec. bottom decile	7% (14/205) in race-spec. bottom decile	.0011 *
Insulin (uU/ml)	203	12.5 (7.9, 20.8)	40% (8/20) in race-spec. top decile	7% (13/183)) in race-spec. top decile	.0002 *
Oligomenorrhea at age 14	212	18 Yes (8%)	15% (3/20) had oligomenorrhea	8% (15/192) had oligomenorrhea	.39
MetS at age 14	226	16 Yes (7%)	38% (8/21) had MetS at age 14	4% (8/205) had MetS at age 14	<.0001 *
TOTAL COHORT (n=420)					
Race	420		60% (21/35) black	53% (205/385) black	.44
FreeT (pg/ml)	420	1.07 (0.71, 1.51)	23% (8/35) in race-spec. top decile	8% (32/385) in race-spec. top decile	.011 *
E2 (pg/ml)	419	84.9 (52.3, 160.8)	11% (4/35) in race-spec. bottom decile	9% (33/384) in race-spec. bottom decile	.53
DHEAS (mcg/dl)	420	161.8 (115.3, 228.4)	14% (5/35) in race-spec. top decile	10% (37/385) in race-spec. top decile	.38
SHBG (nmol/l)	420	17 (12, 24)	40% (14/35) in race-spec. bottom decile	7% (28/385) in race-spec. bottom decile	<.0001 *
Insulin (uU/ml)	379	10.5 (6.7, 16.4)	41% (13/32) in race-spec. top decile	7% (24/347) in race-spec. top decile	<.0001 *
Oligomenorrhea at age 14	365	30 Yes (8%)	16% (5/31) had oligomenorrhea	7% (25/334) had oligomenorrhea	.16

Age 14 variables	n	Median, interquartile range (IQ)	Metabolic Syndrome Yes at age 24 (n=35)	Metabolic Syndrome no at age 24 (n=385)	Fisher's p
MetS at age 14	420	27 Yes (6%)	37% (13/35) had MetS at age 14	4% (14/385) had MetS at age 14	<.0001 *

* significant using Hochberg-Benjamini method controlling for false discovery rate (p<.05), 7 tests in each race group, 8 tests in race-pooled group

Abbreviations: Free testosterone = FreeT, estradiol = E2, dehydroepiandrosterone sulfate = DHEAS, sex hormone binding globulin = SHBG, MetS = metabolic syndrome

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Table 2

Class III obesity (BMI ≥ 40 kg/m^2) at age 24 and potential risk factors at age 14: race, free testosterone, estradiol, dehydroepiandrosterone sulfate, sex hormone binding globulin, oligomenorrhea (menses delay ≥42 days), metabolic syndrome, and childhood insulin

Age 14 variables	n	Median interquartile range (IQ)	Class III obesity at age 24	Not Class III obese at age 24	Fisher's p
WHITE (n=203)					
Free T (pg/ml)	203	1.17 (0.77, 1.67)	50% (2/4) in race-spec. top decile	8% (16/199) in race-spec. top decile	.040
E2 (pg/ml)	203	75.5 (50.3, 137.5)	0% (0/4) in race-spec. bottom decile	9% (18/199) in race-spec. bottom decile	1.0
DHEAS (mcg/dl)	203	158.7 (105.2, 228.4)	0% (0/4) in race-spec. top decile	10% (20/199) in race-spec. top decile	1.0
SHBG (nmol/l)	203	18 (12, 24)	50% (2/4) in race-spec. bottom decile	10% (20/199) in race-spec. bottom decile	.059
Insulin (uU/ml)	184	8.8 (5.6, 12.9)	50% (2/4) in race-spec. top decile	8% (15/180) in race-spec. top decile	.043
Oligomenorrhea at age 14	156	12 Yes (8%)	67% (2/3) had oligomenorrhea	7% (10/153) had oligomenorrhea	.016
MetS at age 14	203	11 Yes (5%)	25% (1/4) had MetS at age 14	5% (10/199) had MetS at age 14	.20
BLACK (n=233)					
Free T (pg/ml)	233	1.06 (0.67, 1.44)	24% (8/33) in race-spec. top decile	8% (15/200) in race-spec. top decile	.0073*
E2 (pg/ml)	232	93.7 (54.0, 194.7)	6% (2/32) in race-spec. bottom decile	11% (21/200) in race-spec. bottom decile	.75
DHEAS (mcg/dl)	233	160.6 (114.2, 224.1)	18% (6/33) in race-spec. top decile	9% (17/200) in race-spec. top decile	.11
SHBG (nmol/l)	233	17 (11, 24)	24% (8/33) in race-spec. bottom decile	7% (14/200) in race-spec. bottom decile	.0053*
Insulin (uU/ml)	207	12.4 (7.9, 20.8)	26% (8/31) in race-spec. top decile	7% (13/176)) in race-spec. top decile	.0052*
Oligomenorrhea at age 14	219	18 Yes (8%)	15% (5/33) had oligomenorrhea	7% (13/186) had oligomenorrhea	.16
MetS at age 14	233	16 Yes (7%)	24% (8/33) had MetS at age 14	4% (8/200) had MetS at age 14	.0004*
TOTAL COHORT (n=436)					
Race	436		89% (33/37) black	50% (200/399) black	<.0001*
FreeT (pg/ml)	436	1.09 (0.73, 1.52)	27% (10/37) in race-spec. top decile	8% (31/399) in race-spec. top decile	.0010*
E2 (pg/ml)	436	85.4 (52.3, 164.5)	5% (2/37) in race-spec. bottom decile	10% (39/399) in race-spec. bottom decile	.56
DHEAS (mcg/dl)	436	160.2 (112.5, 225.1)	16% (6/37) in race-spec. top decile	9% (37/399) in race-spec. top decile	.24
SHBG (nmol/l)	436	17 (12, 24)	27% (10/37) in race-spec. bottom decile	9% (34/399) in race-spec. bottom decile	.0018*
Insulin (uU/ml)	391	10.6 (6.7, 16.3)	29% (10/35) in race-spec. top decile	8% (28/356)) in race-spec. top decile	.0007*
Oligomenorrhea at age 14	375	30 Yes (8%)	19% (7/36) had oligomenorrhea	7% (23/339) had oligomenorrhea	.017*

Age 14 variables	n	Median interquartile range (IQ)	Class III obesity at age 24	Not Class III obese at age 24	Fisher's p
MetS at age 14	436	27 Yes (6%)	24% (9 /37) had MetS at age 14	5% (18/399) had MetS at age 14	.0001 *

* significant using Hochberg-Benjamini method controlling for false discover rate (p<.05), 7 tests in each race group, 8 tests in race-pooled group

Abbreviations: Free testosterone = FreeT, estradiol = E2, dehydroepiandrosterone sulfate = DHEAS, sex hormone binding globulin = SHBG, MetS = metabolic syndrome

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Table 3

Significant adolescent predictors for metabolic syndrome at age 24 by logistic regression models.

Dependent variable	Significant explanatory variables	p	Odds ratio, 95% CI
Metabolic syndrome at age 24 Yes (n=28) vs No (n=296)	Childhood insulin (uU/ml)	+, .0041	1.03, 1.01-1.05
324 observations used (135 W, 189 B) AUC=0.844	Metabolic syndrome at age 14 (Yes as 1, no as 0)	+, .0047	4.95, 1.64-15.0
	SHBG at age 14 (nmol/l)	-, .012	0.92, 0.86-0.98
	Oligomenorrhea-hyperandrogenism (PCOS category)	+, .034	2.18, 1.06-4.47
Metabolic syndrome at age 24 Yes (n=28) vs No (n=296)	Childhood insulin Race-spec. top decile as 2, Lower 9 deciles as 1	+, .0045	4.44, 1.59-12.4
324 observations used (135 W, 189 B) AUC =0.826	Metabolic syndrome at age 14 (Yes as 1, no as 0)	+, .0069	5.06, 1.56-16.4
	SHBG at age 14 Race-spec. bottom decile as 2, Upper 9 deciles as 1	+, .0062	4.38, 1.52-12.6
	Oligomenorrhea-hyperandrogenism (PCOS category)	+, .021	2.41, 1.14-5.10

Stepwise selection from race, age 14 variables (FT, E2, DHEAS, SHBG, metabolic syndrome, oligomenorrhea [yes, no], PCOS category [3 levels—no oligomenorrhea as 0, oligomenorrhea as 1, oligomenorrhea plus hyperandrogenism, i.e. PCOS as 2]), and childhood insulin.

Stepwise selection from race, age 14 categorical variables (race-specific top decile vs lower 9 deciles of FT, DHEAS, race-specific bottom decile vs upper 9 deciles of E2 and SHBG, metabolic syndrome, oligomenorrhea and PCOS category), and race-specific top decile vs lower 9 deciles of childhood insulin.

Table 4

Significant adolescent predictors for class III obesity at age 24 by logistic regression models.

Dependent variable	Significant explanatory variables	Sign, p	Odds ratio, 95% CI
Class III obesity at age 24 Yes (BMI ≥40, n=33) vs No (BMI <40,n=300)	SHBG at age 14 (nmol/l)	-, <.0001	0.82, 0.76-0.88
333 observations used (140 W, 193 B) AUC=0.881	Race (W=1, B=2)	+, .0002	11.4, 3.14-41.7
	Oligomenorrhea at age 14 (Yes as 1, No as 0)	+, .037	3.64, 1.08-12.3
Class III obesity at age 24 Yes (BMI ≥40, n=33) vs No (BMI <40,n=300)	Metabolic syndrome at age 14 (Yes as 1, no as 0)	+, .018	4.12, 1.28-13.2
	Race (W=1, B=2)	+, .0002	13.8, 3.45-55.3
333 observations used (140 W, 193 B) AUC=0.806	SHBG at age 14 Race-spec. bottom decile as 2, Upper 9 deciles as 1	+, .012	3.85, 1.35-10.9
	Oligomenorrhea-hyperandrogenism (PCOS category)	+, .016	2.41, 1.18-4.94
	Childhood insulin Race-spec. top decile as 2, Lower 9 deciles as 1	+, .048	2.93, 1.01-8.48

Stepwise selection from race, age 14 variables (FT, E2, DHEAS, SHBG, metabolic syndrome, oligomenorrhea [yes, no], PCOS category [3 levels—no oligomenorrhea as 0, oligomenorrhea as 1, oligomenorrhea plus hyperandrogenism, i.e. PCOS as 2]), and childhood insulin.

Stepwise selection from race, age 14 categorical variables (race-specific top decile vs lower 9 deciles of FT, DHEAS, race-specific bottom decile vs upper 9 deciles of E2 and SHBG, metabolic syndrome, oligomenorrhea and PCOS category), and race-specific top decile vs lower 9 deciles of childhood insulin.

Table 5

Regular menses, oligomenorrhea, and oligomenorrhea with hyperandrogenism (polycystic ovary syndrome) at age 14: Associations with metabolic syndrome and class III obesity at age 24.

	Regular menses	**Oligomenorrhea**	**Oligomenorrhea plus Hyperandrogenism (polycystic ovary syndrome)**	**All**
Metabolic syndrome at age 24	7.8% (26/333)	5.6% (1/18)	33% (4/12)	8% (31/363)
	Mantel-Haenszel χ^2=6.1, p=.013			
Class III obese at age 24	8.4% (29/345)	16.7% (3/18)	33% (4/12)	10% (36/375)
	Mantel-Haenszel χ^2=9.1, p=.0026			