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Clinical Research Article

Association between puberty timing and metabolic health at young adulthood

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Abstract

Context **Metabolic syndrome (MetS) is a cluster of abnormalities that increase the risk of type 2 diabetes and cardiovascular disease. Cross-sectional studies in adults suggest that early pubertal timing is associated with a higher risk of MetS.**

Objective **We aimed to determine whether early puberty onset in boys and girls increases the risk of developing MetS at 18 years.**

Methods **We conducted a longitudinal study within the Growth and Obesity Chilean Cohort Study. Pubertal timing was assessed by Tanner stage (breast stage 2 [B2] in girls; gonadarche stage 2 [G2; testicular volume >3 cc] in boys) and age at menarche (AAM). MetS and insulin resistance markers were evaluated at age 18 (n = 729). Logistic regression models were used to examine associations between early pubertal markers and MetS and related metabolic parameters, adjusting by body mass index at puberty and maternal education.**

Results **At age 18, boys had higher prevalence of MetS (9.8% vs 4.1%), elevated blood pressure (9.8% vs 0.3%), and elevated triglycerides (18.1% vs 8.5%). In boys, only crude models showed inverse associations between age at G2 and MetS, waist circumference, and waist to height ratio. In girls, fully adjusted models confirmed an inverse association of AAM and the risk of MetS (odds ratio [OR] 0.54, 95% CI: 0.33-0.90), high triglycerides (OR 0.57, 95% CI: 0.39-0.83), and high triglycerides/glycemia ratio (OR 0.63, 95% CI: 0.43-0.92). No associations were observed for B2.**

Conclusion **Earlier puberty is associated with adverse metabolic outcomes, but this persists after adjustment only in girls. Secular trends toward earlier pubertal timing may therefore have significant public health implications.**

Keywords puberty, gonadarche, menarche, thelarche, metabolic syndrome

Abbreviations: AAM, age at menarche; BMI, body mass index; GnRH, gonadotrophin-releasing hormone; HOMA-IR, homeostatic model assessment for insulin resistance; INTA, Institute of Nutrition and Food Technology University of Chile; MetS, metabolic syndrome; OR, odds ratio.

Causes of death can be grouped into 3 categories: communicable, noncommunicable, and injuries. At a global level, 7 of the 10 leading causes of deaths in 2021 were noncommunicable diseases, accounting for 68% of the top 10 causes, and even more so in middle to upper income level countries (1). These statistics are worrisome, because obesity is a significant risk factor for many of these noncommunicable diseases, including cardiovascular disease, diabetes, and cancer. Once considered a high-income country problem, overweight is on the rise in low- and middle-income countries.

Nevertheless, factors such as genetic background, sedentary life, and increased intake do not explain completely the high rate of increase in obesity and in noncommunicable diseases. The hypothesis of early-life programming with the existence of critical windows, that is, specific periods in which environmental exposures can induce permanent anatomical and functional changes that in turn lead to long-term health risks, appears to contribute to this rise (2). Faster weight gain during infancy is one of the main determinants of lower insulin sensitivity in adulthood (3, 4), pointing to a key important life period.

The importance of critical windows in the association with metabolic consequences was further emphasized in a recent natural experiment of exposure to sugar restrictions in the United Kingdom, where early-life rationing reduced type 2 diabetes and hypertension risk by about 35% and 20% and delayed disease onset by 4 and 2 years, respectively. Protection was evident with in utero exposure to rationing and increased with postnatal sugar restriction, especially after 6 months, when eating of solid foods likely began (5).

Puberty timing reflects the age of onset of the reactivation of the hypothalamic-pituitary-gonadal axis, secondary to a change in the balance of inhibitory and excitatory inputs to

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gonadotropin releasing hormone (GnRH) neurons leading to the cascade of sex steroid release by the gonads. This timing is mainly genetically determined but other endogenous and environmental cues have important roles in modulating the activation of the GnRH pulse generator (6). Therefore, normative local data must be reviewed periodically to avoid arbitrariness. During the past few decades, a substantial concern has been raised about children entering puberty earlier (7-11), due to increased risk for several outcomes later in life such cardiovascular/metabolic diseases, cancer, shorter adult height, more behavioral/educational/psychological problems, and increased all-cause mortality. The link between body mass index (BMI) and earlier pubertal development has been widely considered as one of the main drivers of the increasing incidence of earlier puberty over time (12). Many studies have identified the aforementioned association only in cross-sectional studies. This finding may not be entirely clear given that the pubertal transition itself is accompanied by alterations in age-specific BMI.

The metabolic syndrome (MetS) was first described as a group of risk factors for type 2 diabetes and cardiovascular disease. The factors include insulin resistance, obesity, hypertension, and dyslipidemia (13, 14). The consensus is that there is a continuum between risk for the MetS features and progression to overt type 2 diabetes mellitus and cardiovascular disease.

Using the longitudinal study of Growth and Obesity Chilean Cohort Study (GOCS) we have established that increased prepubertal adiposity is associated to earlier thelarche, pubarche, menarche in girls, and gonadarche in boys (10, 15). The aim of this study was to test the associations of pubertal timing in girls and boys from the GOCS, and metabolic outcomes at young adulthood at about 18 years of age, adjusting for potential confounders.

Methods

Subjects

All adolescents evaluated are part of the Growth and Cohort Chilean Study (GOCs) and were recruited at age from 3.0 to 4.9 years in the year 2006. The study's primary aim was to assess the association between early growth and development of adiposity and metabolic risk (16). Briefly, the inclusion criteria were as follows: all singleton children, attending the Chilean National Nursery School Council Program (JUNJI), from the southeast area of Santiago, Chile; gestational age 37 to 42 weeks; birth weight $\geq$ 2500 g and $\leq$ 4500 g (data retrieved from medical registries); and with no physical or psychological conditions that could severely affect growth. A total of 1195 child-parent subjects (85% of all screened) agreed to participate (593 boys). We did not observe significant differences in age, sex, birth, and anthropometry at enrollment between participants and nonparticipants (16). Thereafter, annual evaluations have been conducted (anthropometry, body composition, skeletal and hormonal maturation, and metabolic/inflammatory markers) and, since 2009, at age approximately 7 years, semi-annual visits were initiated to add the assessment of secondary sex characteristics. All clinical visits were performed at the Institute of Nutrition and Food Technology, University of Chile (INTA).

The Institutional Review Board of the INTA approved the study protocol. All parents or guardians of the children signed informed consent and assent from the children was obtained. In addition, at the 18- to 19-year follow-up visit, participants themselves provided informed consent to take part in the study.

Anthropometric measures

A trained dietitian performed complete anthropometric measures at each clinic visit while the participant was wearing light clothes and barefoot. Tanita 418 BC (accuracy within 0.1 kg) was used to determine the weight and a Seca 222 (accuracy within 1 mm) stadiometer to measure height. Waist circumference was measured using a measuring tape (Lufkin, Model W606PM) with 200 cm capacity and 0.1 cm precision. The waist was defined as the midpoint between the last rib and the right iliac crest in a horizontal line to the left iliac crest.

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Age- and sex-specific BMI SDS were estimated using 2000 growth charts from the Centers for Disease Control and Prevention until age 18 years (17). Waist circumference was categorized according to specific validated cutoff points for central obesity used in the definition of MetS for the Chilean adult population ($\geq$ 92.3 cm male and $\geq$87.6 cm female) (18). Waist to height ratio was calculated as waist circumference in centimeters divided by height in centimeters. The waist to height ratio is a highly sensitive and specific predictor of dual-energy x-ray absorptiometry (DXA)-measured total body fat mass and trunk (abdominal) fat mass. Waist to height ratio cut points are <0.50 (normal fat mass), 0.50 to <0.53 (high fat mass), and $\geq$0.53 (excess fat mass) in male subjects. Waist to height ratio cut points for female subjects are <0.51 (normal fat mass), 0.51 to <0.54 (high fat mass), and $\geq$0.54 (excess fat mass) (19).

Pubertal maturation assessment

Starting at approximately age 7 (year 2009), secondary sex characteristics were evaluated every 6 months by a single corresponding sex dietitian, trained especially for this purpose, with permanent supervision of a single pediatric endocrinologist (V.M.). The primary pubertal outcomes used in this analysis were age at thelarche (Tanner breast stage 2 or more [B2]) and menarche (M) in girls and age at gonadarche (G2) in boys (testicular volume > 3 cc). In girls, thelarche was assessed through inspection and palpation to distinguish true breast development from lipomastia. Transient thelarche was defined as the appearance and subsequent regression of the breast bud between visits (20). The concordance between the dietitian and the pediatric endocrinologist was a Cohen's kappa of 0.7 (21). Every 6 months, during clinic visits at INTA or via telephone follow-up, girls were asked whether they had begun menstruating and were required to complete a brief questionnaire to differentiate from other diagnoses, including vulvovaginitis. In boys, genitalia were evaluated by inspection and palpation using the Prader orchidometer (10). For girls and boys age at thelarche and gonadarche onset was defined as the midpoint of 2 consecutive visits, the last visit without signs of sexual development (increase in testicular size genital or Tanner stage B1 in girls) and the first visit

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in which one of these signs were detected. A complete detailed sexual maturation assessment can be found elsewhere (9, 10, 15).

Circulating hormone and metabolite determinations

A fasting venous sample (early morning) was collected at age about 18 years. Participants were contacted the day before to confirm the absence of fever or symptoms of acute infection in the children. Serum glucose concentrations were assessed by enzymatic colorimetric techniques (HumaStar 80, Human German, Cobas/Roche). Insulin was measured by electroimmune chemiluminescence assay (Ortho Clinical Diagnostics VITROS XT7600 system) with a detection limit of 0.077 μU/mL and intra- and interassay coefficients of variation of 1.6% and 2.2%, respectively. Serum lipid profile (triglycerides, low-density lipoprotein cholesterol, and total cholesterol) were determined by a dry analytic methodology (Autoanalizer HumaStar 80, Human, Germany; Cobas/Roche, USA) and high-density lipoprotein cholesterol by a colorimetric assay (Vitros, Johnson & Johnson, Inc.). All above analyses were conducted at the Nutrition Laboratory of the Pontificia Universidad Católica de Chile and the laboratory of the University of Chile Clinical Hospital.

Calculations

Metabolic syndrome (MetS) was defined based on the International Diabetes Federation (IDF) definition (22) which requires central obesity plus any 2 of the other 4 factors: (i) hyperglycemia, defined as fasting glucose concentration ≥ 100 mg/dL; (ii) hypertriglyceridemia as fasting levels ≥ 150 mg/dL; (iii) low HDL-C as fasting HDL-C concentrations < 50 mg/dL in women and < 40 in men; and (iv) hypertension, defined as a systolic blood pressure of ≥ 130 mmHg or diastolic ≥ 85 mmHg. The optimal cutoff for waist circumference for adults in Chile was defined using a recent assessment (≥ 92.3 cm male and ≥87.6 cm in females) (18, 22). We estimated the following risk scales for insulin resistance by calculation: triglycerides to HDL-c ratio was obtained by dividing the value of triglycerides by the value of HDL cholesterol, values over 2.4 were considered high (23); glucose to triglyceride index was obtained by the formula Ln(triglycerides [mg/dL] × glucose [mg/dL]/2) and high values were considered from 8.8 (23); and homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as (fasting glucose [mg/dL] × fasting insulin [mU/L])/405.

Statistical analysis

We conducted descriptive analyses of anthropometric measures, sexual maturation, metabolic syndrome, and its components, stratified by sex, and expressed results as means, standard deviation scores (SDS), and percentages. Differences between groups were evaluated using Student's t test or the χ^2 test, as appropriate.

Odds ratios (OR) and 95% CI were estimated using crude and multivariable logistic regression models to assess the associations between age at pubertal milestones (thelarche, gonadarche, and age at menarche [AAM], treated as continuous variables) and metabolic syndrome, its components, and other indicators of insulin resistance. Models were adjusted for BMI z-score at the time of the pubertal milestone and maternal education as a proxy for socioeconomic status.

We further explored these associations by categorizing age at gonadarche (<9 years, 9-12 years, and >12 years) and menarche (<9 years, 9-12 years, and >11 years) into tertiles. All analyses were performed using STATA version 16, and statistical significance was set at $P < .05$.

Results

Subjects

During the follow-up between 2009 and 2022 we were able to identify 426 girls at Tanner 2 of breast, 485 boys at Tanner stage 2 of testicular volume (G2 > 3 cc) and 530 girls at age at menarche (AAM). From these children, 729 participants had their visit at 18 years, and among them, 322 girls had data on age at Tanner 2 of breast, 310 boys on age at Tanner stage 2 of testicular volume (G2 > 3 cc) and 399 girls on AAM. Finally, 584 (80.1%) (266 boys and 318 girls) of the 729 young adults had complete data to estimate metabolic syndrome (MetS). Participants with complete data were slightly younger than their counterparts (18.7 ± 0.4 vs 19.1 ± 0.5 years); however, we did not observe differences in anthropometric measures, age at pubertal milestones and maternal education (data not shown).

At age 18, boys were heavier, taller, and with larger waist circumference, but lower BMI (kg/m^2) compared to girls. Metabolic syndrome (9.8% vs 4.1%), high blood pressure (9.8% vs 0.31%), and high triglycerides (18.1% vs 8.5%) were more prevalent in boys compared to girls. Furthermore, boys were more likely to have high triglycerides to HDL ratio, as well as triglycerides to glycemia ratio; however, girls had a higher waist to height ratio and were more likely to have high HOMA-IR (2.95 ± 2.0 vs 2.51 ± 2.0). Complete data on clinic and anthropometric measurements at each pubertal milestone are shown in Table 1.

Association between age at pubertal milestones and metabolic syndrome at 18 years

Girls

In the study population, the mean age of Tanner breast 2 was 8.9 ± 1.4 years and of AAM was 11.9 ± 1.0 years. In the bivariate analysis, age at thelarche onset was similar between girls with and without MetS at 18 years. However, AAM was different between these 2 groups; girls with metabolic syndrome at age 18 had an earlier mean age of menarche 11.5 ± 1.4 vs 12.0 ± 1.0 years, $P < .05$).

We next explored the association of MetS and each of its components and other proxies of insulin resistance and pubertal timing. In girls, there was no association between age at Tanner stage B2 and MetS or other indicators of insulin resistance (Table 2). However, in the fully adjusted models, we found that girls with an earlier AAM were more likely to develop MetS at

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Table 1 Clinic and anthropometric characteristics of participants at 18 years of age

	Boys (n = 266)	Girls (n = 318)	*P* value
Age, years	18.51 ± 0.36	18.93 ± 0.41	<.001
Weight, kg	74.20 ± 16.69	66.79 ± 16.00	<.001
Height, cm	172.66 ± 6.22	159.80 ± 5.88	<.001
BMI, kg/m^2	24.85 ± 5.24	26.14 ± 6.03	0.0065
Nutritional status, n (%)			
BMI < 18.5	15 (5.64%)	13 (4.10%)	.100
BMI 18.5-24.9	141 (53.01%)	141 (44.48%)	
BMI 25-29.9	68 (25.56%)	96 (30.28%)	
BMI ≥ 30	42 (15.79%)	67 (21.14%)	
Waist circumference, cm	84.48 ± 12.96	81.63 ± 13.26	.0093
BMI SDS at Tanner stage B2, girls		0.74 ± 1.10	<.001[a]
BMI SDS at Tanner stage G2, boys	1.06 ± 1.26		
BMI SDS at menarche, girls		0.90 ± 1.04	
Metabolic syndrome			
Metabolic syndrome, n (%)	26 (9.77%)	13 (4.09%)	<.01
High waist circumference IDF, n (%)[b]	66 (24.81%)	94 (29.56%)	.200
High blood pressure, n (%)	26 (9.77%)	1 (0.31%)	<.001
Low HDL cholesterol, n (%)[c]	137 (51.50%)	178 (55.97%)	.280
High glycemia ≥ 100 mg/dL, n (%)	5 (1.88%)	4 (1.26%)	.543
High triglycerides ≥ 150 mg/dL, n (%)	48 (18.05%)	27 (8.49%)	.001
Other indicators of insulin resistance			
Waist to height, cm	0.49 ± 0.07	0.51 ± 0.08	.0010
High waist to height ratio, n (%)[d]	106 (39.85%)	147 (46.23%)	.121
Triglycerides to HDL cholesterol	2.96 ± 1.87	2.01 ± 1.21	<.001
High triglycerides to HDL cholesterol ratio (> 2.4), n (%)	133 (50.00%)	81 (25.47%)	<.001
Triglycerides to glycemia ratio	8.36 ± 0.46	8.19 ± 0.42	<.001
High triglycerides to glycemia ratio (>8.8), n (%)	45 (16.92%)	25 (7.86%)	<.001
HOMA	2.51 ± 1.99	2.95 ± 2.04	.0097

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; IDF, International Diabetes Federation.
[a]Comparison between BMI SDS at G2 in male vs BMI SDS at B2 in girls.
[b]Male ≥ 92.3 cm and female ≥ 87.6 cm.
[c]Male < 40 mg/dL and female < 50 mg/dL.
[d]Male ≥ 0.5, female ≥ 0.51.

18 years (OR 0.54, 95% CI: 0.33-0.90). Furthermore, in the fully adjusted models, girls with earlier AAM were more likely to have high levels of triglycerides (≥150 mg/dL, OR = 0.57; 95% CI: 0.39-0.83) and high triglycerides to glycemia ratios (>8.8, OR 0.63, 95% CI: 0.43-0.92) (Table 2).

We further explored the association of AAM stratified in tertiles (<11 years = 48, 11-12 years = 117, and >12 years = 159 girls), instead of as a continuous variable. The prevalence of MetS within each group was 13.2%, 6.7%, and 4.6%, respectively ($P < .05$). Girls with menarche at age 11 or younger compared to those girls with menarche at age 12 or older had a higher risk of MetS (OR 3.15, 95% CI: 1.03-9.46); however, this risk was no longer statistically significant when adjusted by covariates (BMI SDS at AAM and maternal education) (OR 3.26, CI: 0.9-11.8) (Table 3).

Similarly, the girls with earliest menarche had 3.1 times higher risk of high triglycerides (CI: 1.21-7.92) even when adjusted for covariates. In crude regression analysis, they also had twice the risk of high triglycerides to HDL ratio (OR 2.1, 95% CI: 1.1-3.8) and 3 times the risk of high triglycerides to glycemia (OR 3.1, 95% CI: 1.3-7.6), although these differences did not persist after adjusting for covariates.

Boys

In the study population (included sample) the mean age at gonadarche was 11.0 ± 1.5 years. In the bivariate analysis, age at gonadarche onset was earlier in boys with MetS compared to boys without MetS at 18 years (10.4 ± 1.5 vs 11.0 ± 1.5 years, $P < .05$) (Fig. 1).

We also found an inverse association of age at gonadarche and metabolic syndrome (OR 0.8, 95% CI: 0.6-1.0, *P* value < .05), waist circumference (OR 0.8, 95% CI: 0.7-0.98) and a high waist to height ratio (OR 0.8, 95% CI: 0.7-0.96), but all these associations were lost when adjusted by BMI SDS at age at gonadarche (Table 2).

We next categorized age at gonadarche into tertiles as follows: 10 years (n = 83), 10 to 12 years (n = 92), and >12 years (n = 84). The prevalence of MetS within these groups was 19.3%, 6.5%, and 6.0% (*P* value = .006), respectively. A significant association with MetS was observed when comparing boys with gonadarche after age 12 years vs those at age 10 years or under (OR 3.8, 95% CI: 1.3-10.8). However, this trend was attenuated after adjustment for BMI SDS at age 18 years and maternal education (Table 4). Similar results were observed for waist to height ratio.

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Table 2 Association between pubertal milestones (thelarche, gonadarche, and menarche) with metabolic syndrome, its components, and other indicators of metabolic disorders (waist to height ratio, triglycerides to HDL ratio, and triglycerides to glycemia ratio)

	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Age at B2						
Metabolic syndrome	0.95	(0.66; 1.38)	0.98	(0.68; 1.42)	0.82	(0.55; 1.23)
Waist circumference IDF[a]	0.93	(0.77, 1.11)	0.97	(0.79, 1.19)	0.94	(0.76, 1.17)
High blood pressure[b]	0.54	(0.14; 2.15)	0.55	(0.14; 2.13)	0.30	(0.04; 2.4)
Low HDL[c]	1.09	(0.93, 1.29)	1.14	(0.95, 1.35)	1.14	(0.95, 1.35)
High glycemia (≥100 mg/dL)	1.52	(0.58, 3.98)	1.51	(0.57, 4.00)	1.65	(0.58, 4.68)
High triglycerides (≥150 mg/dL)	0.85	(0.66, 1.11)	0.86	(0.66, 1.12)	0.84	(0.64, 1.10)
High waist to height ratio[d]	0.97	(0.83, 1.13)	1.04	(0.86, 1.25)	1.03	(0.86, 1.24)
High triglycerides to HDL ratio (> 2.4)	0.98	(0.81, 1.18)	0.99	(0.81, 1.20)	0.99	(0.81, 1.21)
High triglycerides to glycemia ratio (> 8.8)	0.82	(0.62, 1.07)	0.82	(0.63, 1.09)	0.81	(0.61, 1.07)
Age at G2						
Metabolic syndrome	0.77	(0.59, 1.00)	0.99	(0.73, 1.35)	0.95	(0.69, 1.31)
Waist circumference IDF[a]	0.82	(0.69, 0.98)	0.98	(0.79, 1.21)	0.99	(0.80, 1.23)
High blood pressure[b]	1.03	(0.78, 1.35)	1.15	(0.86, 1.56)	1.16	(0.86, 1.58)
Low HDL[c]	0.97	(0.83, 1.14)	1.03	(0.86, 1.23)	1.02	(0.85, 1.22)
High glycemia (≥100 mg/dL)	0.79	(0.48, 1.29)	0.79	(0.46, 1.37)	0.79	(0.45, 1.39)
High triglycerides (≥150 mg/dL)	0.89	(0.73, 1.09)	1.00	(0.81, 1.24)	0.98	(0.79, 1.22)
High waist to height ratio[d]	0.82	(0.70, 0.96)	0.88	(0.72, 1.07)	0.88	(0.72, 1.08)
High triglycerides to HDL ratio (> 2.4)	0.9	(0.76, 1.06)	0.98	(0.82, 1.17)	0.96	(0.80, 1.15)
High triglycerides to glycemia ratio (> 8.8)	0.94	(0.77, 1.16)	1.06	(0.85, 1.32)	1.03	(0.83, 1.29)
Age at menarche						
Metabolic syndrome	0.58	(0.37, 0.90)	0.68	(0.43, 1.08)	0.54	(0.33, 0.90)
Waist circumference IDF[a]	0.82	(0.65, 1.02)	1.16	(0.89, 1.53)	1.16	(0.88, 1.54)
High blood pressure[b]	–		–		–	
Low HDL[c]	1.09	(0.89, 1.34)	1.23	(0.98, 1.54)	1.21	(0.96, 1.52)
High glycemia (≥100 mg/dL)	0.85	(0.35, 2.05)	0.94	(0.38, 2.34)	0.97	(0.38, 2.47)
High triglycerides (≥150 mg/dL)	0.55	(0.39, 0.79)	0.6	(0.41, 0.86)	0.57	(0.39, 0.83)
High waist to height ratio[d]	0.87	(0.71, 1.06)	1.23	(0.96, 1.56)	1.21	(0.94, 1.54)
High triglycerides to HDL ratio (> 2.4)	0.74	(0.59, 0.94)	0.9	(0.70, 1.15)	0.85	(0.65, 1.10)
High triglycerides to glycemia ratio (> 8.8)	0.57	(0.40, 0.82)	0.64	(0.44, 0.94)	0.63	(0.43, 0.92)

Model 1; crude. Model 2: adjusted by BMI z-score at pubertal milestone. Model 3: Model 2 + maternal education.
Abbreviations: HDL, high-density lipoprotein; IDF, International Diabetes Federation.
[a]Male ≥ 92.3 cm and female ≥87.6 cm.
[b]Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg/only 1 girl had high blood pressure.
[c]Male < 40 mg/dL and female < 50 mg/dL.
[d]Male ≥ 0.5, female ≥ 0.51.

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Table 3 Association between menarche onset and metabolic syndrome, its components, and other indicators of insulin resistance

Age at menarche	Crude OR (IC 95%)	Adjusted OR (IC 95%)
Metabolic syndrome		
> 12 y	ref	ref
11-12 y	1.49 (0.53-4.24)	1.51 (0.47-4.80)
< 11 y	3.15 (1.05-9.46)	3.26 (0.90-11.83)
Waist circumference IDF (≥ 87.6 cm)		
> 12 y	ref	ref
11-12 y	1.12 (0.69-1.81)	0.73 (0.41-1.31)
< 11 y	1.44 (0.78-2.63)	0.48 (0.22-1.02)
Low HDL (male < 40 mg/dL, female < 50 mg/dL)		
> 12 y	ref	ref
11-12 y	0.94 (0.60-1.49)	0.83 (0.51-1.34)
< 11 y	0.80 (0.45-1.44)	0.59 (0.31-1.12)
High glycemia (≥100 mg/dL)		
> 12 y	ref	ref
11-12 y	1.30 (0.18-9.35)	1.14 (0.16-8.27)
< 11 y	1.39 (0.12-15.55)	0.94 (0.07-11.94)
High triglycerides (≥150 mg/dL)		
> 12 y	ref	ref
11-12 y	2.12 (0.96-4.69)	1.89 (0.84-4.25)
< 11 y	3.47 (1.44-8.34)	3.10 (1.21-7.92)
High waist to height ratio (≥0.51)		
> 12 y	ref	ref
11-12 y	1.31 (0.85-2.02)	0.91 (0.54-1.52)
< 11 y	1.19 (0.68-1.12)	0.45 (0.23-0.90)
High triglycerides to HDL ratio (> 2.4)		
> 12 y	ref	ref
11-12 y	1.39 (0.83-2.34)	1.18 (0.68-2.05)
< 11 y	2.05 (1.09-3.84)	1.24 (0.62-2.50)
High triglycerides to glycemia ratio (> 8.8)		
> 12 y	ref	ref
11-12 y	1.71 (0.75-3.91)	1.47 (0.64-3.40)
< 11 y	3.12 (1.28-7.62)	2.35 (0.91-6.08)

Model adjusted by body mass index at 18 years and maternal education.
Abbreviations: HDL, high-density lipoprotein; IDF, International Diabetes Federation; OR, odds ratio.

In addition, boys whose gonadarche occurred between the ages of 10 to 12 years were less likely to have low HDL levels, only in the crude model (OR 0.5, 95% CI: 0.3-0.98). No other significant associations were found between age at gonadarche tertiles and individual components of the metabolic syndrome or markers of insulin resistance.

Discussion

In this longitudinal cohort followed until age ∼18 years, boys showed more than double the prevalence of metabolic syndrome (9.8 vs 4.1%), 10 times more frequent high blood pressure and more than double the rate of high triglycerides compared to girls, despite a lower BMI at this age. Interestingly, at the beginning of puberty, boys had significantly higher BMI SDS compared to girls ($P < .001$) (10, 15).

In addition, at age 18 years, boys were more likely to have a higher triglyceride to HDL ratio, as well as triglycerides to glycemia ratio. Nevertheless, girls had higher HOMA-IR, higher BMI (kg/m^2) and larger percentage of central adiposity. Optimal insulin resistance assessment requires the euglycemic-hyperinsulinemic clamp, which is not widely utilized because of its complexity and invasive nature of difficult application (24). Hence several insulin resistance markers have been developed (25) using single simultaneously obtained blood samples of fasting insulin and glucose or lipids. Each of these measures uses a mathematical formula that attempts to adjust for individual variability in insulin and glucose secretion and clearance. Moreover, the distribution of the HOMA-IR varies according to the demographic characteristics of the subject's age, gender, BMI status, race, alcohol use, and smoking status (25, 26), factors that may explain the higher HOMA-IR in girls. However, the lower prevalence of MetS despite higher HOMA-IR also points toward the protective role of estrogens in developing MetS (27, 28).

An earlier age at pubertal milestones was associated in both sexes with a higher prevalence of MetS already at age ∼18 years. Moreover, girls with an earlier AAM onset displayed a worse metabolic profile at 18 years with higher levels of triglycerides, higher triglycerides to glycemia ratio and higher triglycerides to HDL ratio. Similarly, a younger age at gonadarche in boys was associated with larger waist circumference and lower HDL cutoff prevalence, but these associations in boys and girls were attenuated when adjusted by BMI SDS at age 18 and maternal education level, except for the association between AAM and high triglycerides, which persisted.

The prevalence of MetS in adolescents has been widely reported to range from approximately 2% to over 30%, depending on the diagnostic definition applied and whether the sample is population-based or clinical. These differences reflect inconsistencies across differences in diagnostic criteria as well as heterogeneity related to age and ethnic characteristics (29-31). Multinational studies estimate a population prevalence of around 5% among adolescents, which are similar to our results, with a predominant male to female ratio. Sex dimorphism in developing and progressing metabolic and cardiovascular disease is a complex phenomenon. The female sex, compared to the male sex, is protected from metabolic disturbances and their resulting cardiovascular events during premenopausal years (27, 28).

The associations of earlier puberty timing with risks on several health outcomes, including obesity, type 2 diabetes, cardiovascular disease, and hormone-sensitive cancers mostly come from studies in adult women (32-35). Puberty timing in women has been estimated through age at first menstrual period (AAM) recall, which has been validated with moderate accuracy (36).

Our results in a longitudinal adolescent cohort confirm these previous reports already at this young age. Interestingly, age at breast Tanner stage 2, was not associated with any outcome. This finding has several potential explanations. One is that breast Tanner stage 2 may have been a transient phenomenon. Nevertheless, we have excluded those girls from our analysis (20). Second, earlier Tanner stage 2 has been associated with slower progression to AAM, a phenomenon consistent with a peripheral trigger of thelarche, driven by adiposity or other environmental/endocrine-disrupting chemicals more than a central activation of hypothalamic-pituitary-gonadal axis (9, 37-41).

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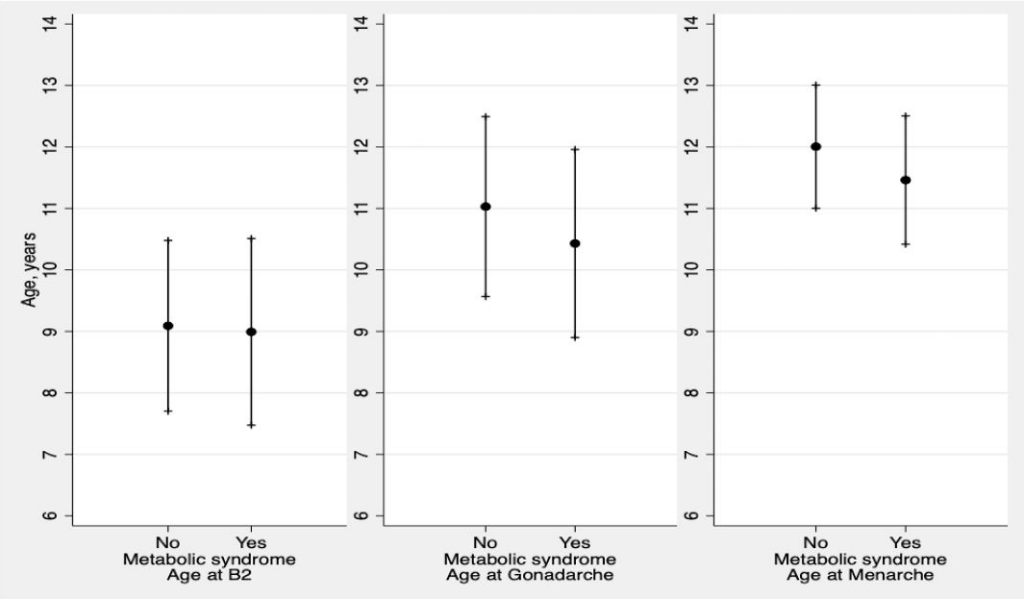

Figure 1 Mean age ±SD (years) at Tanner stage B2 and menarche in girls and Tanner stage G2 in boys according to the presence of metabolic syndrome at age 18 years.

The predictive role of pubertal timing and adverse metabolic outcome in men has not been extensively elucidated. This is partly due to the lack of easily available pubertal indicators (42, 43). In a recent study performed in 30 697 individuals with available data for BMI (from 8 to 20 years) in Sweden (44), a higher risk for type 2 diabetes among those with an earlier age at puberty onset was identified. In this cohort the assessment of pubertal timing was through the age at peak height velocity.

Progress in high-throughput sequencing and genome-wide association studies (GWAS) have transformed our understanding of common genetic risk factors for complex traits and diseases influencing reproductive lifespan and fertility. Indeed, the data emerging from GWAS demonstrates the utility of genetics to explain epidemiological observations, revealing shared biological pathways linking puberty timing, fertility, and reproductive aging and health outcomes. The UK Biobank study comprised 250 037 and 197 714 men from the United Kingdom aged between 40 and 70 years, where extensive baseline data have been recorded on a wide range of prevalent diseases. Puberty in men was estimated using recalled age at voice breaking as a pubertal marker (45). A higher risk for type 2 diabetes was found for the 4.3% who reported early voice breaking and lower risk was found for the 5.9% who reported late voice breaking compared with the approximately 90% that reported age at voice breaking "about average." The main limitation of this study was reliance on self-reported medical histories and recalled measures of the exposures. Specifically, age at voice breaking when reported by recall in adult life has not been fully validated (42). Nevertheless, the association with adverse outcomes and puberty timing was later expanded using data with a larger sample (46). In general, early genetically predicted puberty timing in men was correlated with adverse health outcomes: cardiometabolic diseases, as well as health risk behaviors, including alcohol intake frequency and smoking (46).

The question whether all these adverse metabolic profile associations with earlier age at puberty are mediated by BMI, appears in part negative. In women from the prospective European Investigation into Cancer and Nutrition (EPIC)-InterAct case-cohort study (n = 12 403 incident type 2 diabetes cases) less than half of this association appeared to be mediated by higher adult BMI (32) and studies have also confirmed that this effect appears to be partially independent of childhood BMI (33, 47).

Puberty onset is determined by a broad range of genetic factors which are tightly regulated by the metabolic and nutritional milieu to calibrate GnRH neurons (48). This control is exerted in primary order neurons, which are mostly located in the hypothalamus, where receptors of metabolic cues (ie, leptin, ghrelin, IGF1, and insulin) are found. Three distinct primary order nuclei neurons secrete proopiomelanocortin that interacts with KNDy neurons in the arcuate nuclei and kisspeptin neurons of the paraventricular nuclei, which cause kisspeptin release in a pulsatile manner, mirrored by hypothalamic GnRH and pituitary secretion of luteinizing hormone. The requirement of sufficient energy imposes a tight control over the neuropeptide kisspeptin synthesis and release and acts as a "pubertal gatekeeper."

In our cohort we have found an association of higher prepubertal BMI with earlier puberty in both girls and boys (10, 15). In addition, infancy BMI is associated with higher adulthood BMI (49). Nevertheless, earlier AAM appears to be only partially mediated by BMI (12) but the association of earlier puberty and MetS is mainly explained by adiposity. Furthermore, the biological processes underlying childhood BMI largely, but not completely, overlap with those underlying adult BMI indicating a bidirectional causal relationship between AAM and body size, with greater early weight gain leading to earlier AAM and also earlier AAM leading to higher adult BMI (50). Nevertheless we did not observe association between earlier AAM and more central obesity or larger BMI.

Interestingly, we also found that the association of earlier puberty and MetS in boys was attenuated after adjustment for BMI SDS at age 18 years. The difference in the effect of early puberty and metabolic outcome in both sexes may also be based on the genetics of puberty. Although the overall shared genetic

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Table 4 Association between gonadarche onset and metabolic syndrome, its components, and other indicators of insulin resistance

Age at gonadarche	Crude OR (IC 95%)	Adjusted OR (IC 95%)
Metabolic syndrome		
> 12 y	ref	ref
10-12 y	1.10 (0.32-3.75)	0.89 (0.22-3.56)
< 10 y	3.77 (1.31-10.84)	1.82 (0.55-6.08)
Waist circumference IDF (male ≥ 92.3 cms)		
> 12 y	ref	ref
10-12 y	0.79 (0.40-1.56)	0.91 (0.39-2.13)
< 10 y	1.82 (0.96-3.44)	1.02 (0.46-2.27)
High blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg)		
> 12 y	ref	ref
10-12 y	0.67 (0.24-1.88)	0.59 (0.17-2.00)
< 10 y	1.10 (0.42-2.84)	0.76 (0.26-2.26)
Low HDL (male < 40 mg/dL)		
> 12 y	ref	ref
10-12 y	0.55 (0.31-0.98)	0.55 (0.28-1.09)
< 10 y	1.05 (0.58-1.91)	0.84 (0.43-1.64)
High glycemia (≥100 mg/dL)		
> 12 y	ref	ref
10-12 y	2.75 (0.28-26.95)	3.06 (0.31-30.69)
< 10 y	2.97 (0.30-29.06)	2.35 (0.23-24.32)
High triglycerides (≥150 mg/dL)		
> 12 y	ref	ref
10-12 y	0.95 (0.44-2.06)	1.13 (0.47-2.73)
< 10 y	1.67 (0.80-3.45)	1.39 (0.61-3.16)
High waist to height ratio (≥0.50)		
> 12 y	ref	ref
10-12 y	0.93 (0.52-1.64)	1.03(0.47-2.25)
< 10 y	1.89 (1.07-3.32)	1.55 (0.74-3.24)
High triglycerides to HDL ratio (> 2.4)		
> 12 y	ref	ref
10-12 y	0.72 (0.40-1.29)	0.58 (0.29-1.14)
< 10 y	1.33 (0.74-2.40)	1.06 (0.55-2.04)
High triglycerides to glycemia ratio (> 8.8)		
> 12 y	ref	ref
10-12 y	0.88 (0.40-1.93)	1.15 (0.48-2.76)
< 10 y	1.39 (0.66-2.92)	1.21 (0.53-2.79)

Model adjusted by BMI at 18 years and maternal education.
Abbreviations: HDL, high-density lipoprotein; IDF, International Diabetes Federation; OR, odds ratio.

architecture for pubertal timing between sexes is high (≈ 0.68) and many genetic variants show similar effects sizes in both sexes (≈ 80%) there are a number of genetic signals that differ between sexes (46). For instance, at the SIM1/MCHR2 locus, which encodes for a transcription factor regulator of hypothalamic paraventricular nucleus development and function, the allele that promotes earlier puberty in one sex delays it in the other (51). In a recent multi-ancestry genetic analysis involving ∼800 000 women, 1080 signals were identified for AAM (50). In this study the genomic correlation in puberty timing between sexes was around ∼0.68 with 76 independent signals for male puberty timing (eg, *MC3R* that links nutrient sensing to key hypothalamic neurons and FGF8 among many others). In addition sex differences in maturation patterns of kisspeptin and NKB neurons have also been reported and may underlie sex differences in puberty onset and adult health implications (52).

Our study is not exempt from limitations inherent to the longitudinal nature of the study. We have complete data for 80.1% of our adolescents at age 18 years to estimate metabolic syndrome and these subjects were slightly younger than their counterparts. Nevertheless, there were no differences in anthropometric measures, age at pubertal milestones, and maternal education as a proxy of socioeconomic level. However, our study has several strengths: our results are based on pubertal timing determined on reliable measures of both in girls and boys (ie, breast, menarche, and gonadarche). Moreover, its prospective, long-term, longitudinal design with consistent anthropometric, metabolic, and hormonal measures throughout, and a careful statistical analysis allows for accurate results.

We conclude that early puberty is associated with adverse metabolic profile and this association was maintained only in girls when adjusted by confounders. Thus, the widespread secular trends toward earlier puberty timing may have an important impact on public health. Screening programs identifying early changes in infancy weight gain and BMI trends, restricting early sugar exposure and reinforcing exercise/activity time to increase the percentage of fat free mass can potentially lead to preventive health measures to attenuate early development of MetS. The timing of childhood growth and development has been much debated as a trait with putative selection advantages. Future evaluation of this cohort is planned to assess the persistence of the traits in later adulthood.

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Disclosures

The authors report no declarations of interest.

Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Role of funder/sponsor (if any)

None.

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