

Cardiometabolic Risk Profile Among Young Adult Females With a History of Premature Adrenarche

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Context: Premature adrenarche (PA) is associated with childhood overweight and hyperinsulinemia; the long-term cardiometabolic outcome is unknown.

Objective: To study cardiometabolic profile in adult women with previous PA.

Design and participants: Thirty women with PA and 41 control subjects were followed from pre-puberty to young adulthood.

Main outcome measures: Prevalence of the metabolic syndrome (MetS) and clinical and biochemical cardiovascular risk factors.

Results: There were no differences in the prevalence of MetS or in any parameters indicating dyslipidemia, hypertension, hepatosteatosis, atherosclerosis, or low-grade inflammation between the study groups. However, prevalence of insulin resistance (IR; $P = 0.014$) and acanthosis nigricans ($P = 0.010$) was higher in the PA group. Neither fasting glucose nor insulin concentrations differed between the study groups, but HbA1c [adjusted for body mass index (BMI) $P = 0.011$] and Homeostatic Model Assessment of Insulin Resistance ($P = 0.044$; BMI-adjusted $P =$ nonsignificant) were higher in the PA group. Although BMI and fat percentage were comparable between the study groups, the PA group had higher central fat mass than the control group. In the whole study population, MetS and IR were associated with greater adult fat mass, but no prepubertal factors predicting later IR were found.

Conclusion: PA does not seem to be associated with MetS, dyslipidemia, hypertension, atherosclerosis, or low-grade inflammation in young adult women. However, some women with PA may be at an increased risk of unfavorable glucose metabolism, which is associated with increased central adiposity at adult age rather than determined by prepubertal factors.

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Freeform/Key Words: dehydroepiandrosterone sulfate, body composition, metabolic syndrome, insulin resistance

Abbreviations: ALT, alanine aminotransferase; AN, acanthosis nigricans; BMI, body mass index; BP, blood pressure; DHEAS, dehydroepiandrosterone sulfate; GT, glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; hsCRP, high-sensitivity C-reactive protein; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; PA, premature adrenarche; PP, premature pubarche; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Premature adrenarche (PA) refers to early maturation of the zona reticularis in the adrenal cortex, which leads to an increase in the secretion of adrenal androgen precursors, mostly dehydroepiandrosterone sulfate (DHEAS). When this is associated with clinical signs of androgen action in a girl before the age of eight years, adrenarche is defined as premature [1–3]. Androgenic signs of PA include adult-type body odor, comedones and acne, greasiness of hair and skin, and pubic or axillary hair. The most studied PA phenotype including the appearance of pubic hair is termed premature pubarche (PP) [1–3].

PA has been linked to unfavorable metabolic profile at prepubertal and early pubertal age: Children with PA tend to have an increased prepubertal body mass index (BMI) [4–6] and hyperinsulinemia [7–9]. Some studies have reported also an unfavorable lipid profile [7, 10] or slightly increased blood pressure (BP) in prepubertal girls with PP [4]. A tendency to be overweight and hyperinsulinemic seems to persist at least until early puberty [7, 11, 12], and it has been suggested that PA is a risk factor for the development of later cardiometabolic abnormalities, such as the metabolic syndrome (MetS) [13]. However, the number of studies exploring long-term cardiovascular risk profile and adult outcomes of PA is limited.

In our prospective case-control study, we have followed a cohort of girls with PA from prepuberty to young adult age [14–16]. At prepubertal age, these girls with PA had tall stature, a tendency to be overweight and hyperinsulinemic, and an increased prevalence of childhood MetS [14]. At pubertal age, BMI was higher in PA than control girls [15] and, at young adult age, girls with PA still tended to have slightly higher median BMI and waist circumference (WC) [16]. In the current study, our goal was to investigate whether these adult women with a history of PA have a more unfavorable cardiometabolic risk factor profile or body composition than healthy control subjects. Furthermore, if any cardiometabolic risk factors were detected more frequently in women with PA, the secondary objective was to analyze possible explanatory and predictive factors.

1. Subjects and Methods

A. Subjects and Design

The design of our case-control follow-up study has been described previously [16]. Altogether, 30 patients with PA and 42 healthy, age- and sex-matched control women were first examined in prepuberty (median age, 7.6 years) and re-examined at young adult age (median age, 18.1 years). We did not find any differences in prepubertal data between the groups of PA females when compared with the PA females who participated in a follow-up visit at age 18, to those who did not. There were differences between the PA and control group in prepubertal data as shown in Table 1. Women with PA had at least one clinical sign of adrenal androgen action (*i.e.*, adult-type body odor, greasiness of hair and skin, comedones/acne, and axillary or pubic hair) together with increased DHEAS secretion before the age of 8 years, and other sources of hyperandrogenism (including central puberty, congenital adrenal hyperplasia, and androgen-producing tumors) had been excluded.

All control subjects were healthy, did not use any medications, and have any premature signs of androgen action. Between the baseline and follow-up examinations, one woman in the control group had been diagnosed with familial hypercholesterolemia and her data were excluded from the analyses. None of the other women with PA or control women reported any significant health issues or use of long-term medications that could have an impact on the results. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo and informed consents were obtained in accordance with the ethical principles stated in the Declaration of Helsinki.

B. Clinical Assessment

The procedures for gathering the prepubertal and birth data have been reported [14]. Table 1 depicts birth and prepubertal data of the women participating in the current study. At the

Table 1. Birth and Prepubertal Data of the PA and Control Groups in the Study

	PA Group (n = 30)	Control Group (n = 41)	<i>P</i> ^{a,b}
Birth data			
Gestational age, wk	40.1 (29.0–42.3)	40.1 (29.1–42.1)	0.767
Birth length, cm	49.5 (38.0–56.0)	50.0 (38.5–54.0)	0.056
Birth length, SD score	−0.17 (1.06)	0.24 (0.89)	0.074
Birth weight, g	3510 (1020–5460)	3550 (1190–4590)	0.158
Birth weight, SD score	−0.31 (−2.12 to 3.85)	−0.01 (−2.08 to 1.99)	0.081
SGA, yes	2 (7)	4 (10)	0.773
Preterm, yes	1 (3)	1 (2)	0.742
Prepubertal data			
Age, y	7.6 (4.8–9.1)	7.4 (5.8–8.8)	0.780
Height, cm	130.5 (8.7)	124.8 (6.9)	0.003
Weight, kg	31.5 (16.7–50.5)	24.6 (16.5–48.4)	<0.001
BMI, kg/m ²	17.1 (14.2–25.1)	15.9 (13.2–22.5)	0.018
BMI, SD score	0.79 (1.30)	0.05 (1.07)	0.012
Fat mass, kg	7.2 (1.6–17.6)	4.2 (2.0–16.4)	0.007
Fat, %	21.8 (9.7–38.2)	17.1 (9.2–33.4)	0.017
Lean mass, kg	24.3 (4.2)	21.7 (3.0)	0.008/0.341 ^c
Muscle mass, kg	22.6 (4.1)	20.2 (2.8)	0.008/0.348 ^c
Areal BMD LS, g/m ²	0.72 (0.08)	0.67 (0.07)	0.019/0.197 ^c
Areal BMD FN, g/m ²	0.73 (0.09)	0.68 (0.10)	0.056/0.211 ^c
Areal BMD F, g/m ²	0.75 (0.10)	0.71 (0.08)	0.070/0.384 ^c

Continuous variables are expressed as mean (SD) or median (range), and categorical variables as no. (%). Boldface indicates statistical significance.

Abbreviations: BMD, bone mineral density; F, femur; FN, femoral neck; LS, lumbar spine; SGA, small for gestational age.

^aThe independent samples *t* test or the Mann-Whitney *U* test for continuous variables and Pearson χ^2 test for categorical variables.

^bStatistical significance set at $P < 0.05$.

^cLean and muscle mass and BMDs were compared also with BMI adjustment, using one-way analysis of covariance.

follow-up examination from which data were collected for this study, pubertal development was evaluated by one physician (J.L.) using Tanner staging scales [17]. Body composition was assessed in the morning after an overnight fast, and all anthropometric parameters were measured by a single trained research nurse. Height was measured with a calibrated Harpenden stadiometer (Holtain Ltd., Crymch, United Kingdom) and recorded to the nearest 0.1 cm as the mean of three repeated measurements. Weight was measured with a calibrated electronic scale and recorded to the nearest 0.1 kg. WC was measured after exhalation at mid distance between the bottom of the rib cage and the top of the iliac crest, and hip circumference was measured horizontally to the floor at the widest part of the hip at the level of the greater trochanter, both recorded to the nearest 0.1 cm. Wrist circumference was measured from the dominant arm and recorded to the nearest 0.1 cm. BP was measured by one physician (J.L.) using a standard sphygmomanometer from the left arm in sitting position after a 30-minute rest in a chair and recorded as the average of three repeated measurements. Acanthosis nigricans (AN) was evaluated by one trained physician (J.L.) and recorded as present or absent. Information about smoking habits was collected by direct interviews.

C. Body Composition

Parameters of body composition (body fat mass and percentage, android and gynoid fat mass, bone mineral content and density, and lean and muscle mass) were assessed using a dual-energy X-ray absorptiometry device (Lunar Prodigy Advance; GE Medical Systems, Madison, WI). Fat percentage was expressed as percentage of total body mass. Android and gynoid fat were expressed as percentage of total body fat, and fat distribution as android-to-gynoid ratio (android fat divided by gynoid fat). Android region was defined as the area between the ribs

and the pelvis that is totally enclosed by the trunk region. The gynoid region included the hips and upper thighs, overlapping both the leg and trunk regions.

D. Carotid Artery Measurements

Ultrasound measurements were performed by trained sonographers following the standardized protocol described previously [18]. With the woman in supine position, carotid artery imaging was performed using Sequoia 512 ultrasound scanner (Acuson, Mountain View, CA) equipped with a 14-MHz linear array transducer. The ECG signal (modified chest lead 5) was recorded and presented along with B-mode image sets. A resolution box function was used to scan the left common carotid artery to record a 25-mm \times 15-mm (width by height) image, including the beginning of the carotid bifurcation and the distal common carotid artery. For subsequent off-line analyses, a 5-second cine loop (25 frames per second) was digitally stored.

The derived parameters included intima media thickness and the inner artery diameters during diastole and systole. The ability of the arteries to expand in response to the pulse pressure caused by cardiac contraction and relaxation (*i.e.*, carotid artery distensibility) was calculated by dividing the relative change in diameter [(systolic diameter – diastolic diameter)/diastolic diameter] by pulse pressure (systolic BP – diastolic BP). Systolic and diastolic BPs used in this calculation were means of the measurements performed just before and immediately after ultrasound scanning.

E. Biochemical Analyses

All blood samples were collected between 7:00 and 8:00 AM after an overnight fast. Serum samples for high-sensitivity C-reactive protein (hsCRP) were stored at -80°C until assayed; other analyses were performed immediately after sampling. Levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) were analyzed by a colorimetric enzymatic assay; insulin by an electrochemiluminescence immunoassay [19]; glucose by the hexokinase method; HbA1c by a turbidimetric inhibition immunoassay; alanine aminotransferase (ALT) and glutamyl transferase (GT) by the kinetic method (37°C) according to the International Federation of Clinical Chemistry; and hsCRP by a particle-enhanced turbidimetric assay. The analyzers in these assays were either the Cobas 6000 c501 (to measure TC, TG, ALT, GT, glucose, HbA1c, and hsCRP levels) or Cobas 6000 e601 (to measure insulin, HDL-C, and LDL-C levels), both from Hitachi High Technology Co. (Tokyo, Japan). All reagents were from Roche Diagnostics (Mannheim, Germany).

F. Definitions and Computed Indices

The definitions of MetS and its components (Table 2) were based on the definitions by Adult Treatment Panel of the US National Cholesterol Education Project, International Diabetes Federation, and World Health Organization [20, 21]. BMI was calculated as weight in kilograms divided by the square of height in meters. Overall adiposity was classified using the World Health Organization definitions for overweight and obesity, with BMI thresholds of 25 and 30 kg/m^2 , respectively. All anthropometric SD scores were calculated using the current Finnish references [22, 23]. MetS score was derived by standardizing and then summing the following continuously distributed variables: WC, mean BP [(systolic BP + diastolic BP)/2], fasting insulin, fasting glucose, and the TG-to-HDL-C ratio [24]. Standardization of each factor was based on the values of the control group and performed by subtracting the sample mean from the individual mean and then dividing by sample SD.

Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as [fasting glucose (mg/dL) \times fasting insulin (mU/L)]/405, and fasting glucose-to-insulin ratio was calculated as fasting glucose (mg/dL) divided by fasting insulin (mU/L). According to the 97th percentile range reported from a cohort of young white women [25], HOMA-IR cutoff level for insulin resistance (IR) was defined as 2.94. Hyperglycemia was defined as fasting glucose concentration >100 mg/dL, impaired fasting glucose as fasting glucose concentration

Table 2. Definitions of the MetS Used in the Current Study, Based on Criteria of the US National Cholesterol Education Program ATP III [20], IDF[20], and WHO [21]

	Definition	Risk Factor	Defining Level
ATP III	Any three of the risk factors in column 3	Central obesity Hyperglycemia Dyslipidemia Dyslipidemia (separate criteria) Hypertension	WC \geq 88 cm Fasting glucose \geq 100 mg/dL; or Rx TG \geq 150 mg/dL; or Rx HDL-C $<$ 50 mg/dL; or Rx Systolic BP $>$ 130 mm Hg; or diastolic BP $>$ 85; or Rx
IDF	Central obesity, plus any two of the risk factors in column 3	Central obesity (required) Hyperglycemia Hypertriglyceridemia Low HDL-C Hypertension	WC \geq 80 cm ^a Fasting glucose \geq 100 mg/dL TG \geq 150 mg/dL; or Rx HDL-C $<$ 50 mg/dL; or Rx Systolic BP $>$ 130 mm Hg; or diastolic BP $>$ 85; or Rx
WHO	IR, plus any two of the risk factors in column 3	IR Obesity Hypertriglyceridemia Very low HDL-C Hypertension (Microalbuminuria) ^c	HOMA-IR $>$ 2.94 ^b Waist-to-hip ratio $>$ 0.85; or BMI $>$ 30 kg/m ² TG \geq 150 mg/dL HDL-C $<$ 39 mg/dL BP $>$ 140/90 mm Hg

Abbreviations: ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation; Rx, pharmacological treatment; WHO, World Health Organization.

^aIDF defines central obesity by WC with cutoff levels that are specific for each population, the given value is for European women.

^bIR was defined by HOMA-IR with a cutoff level of 2.94, which is the previously reported 97th percentile for 17-y-old white girls [23].

^cWHO definition for MetS includes microalbuminuria, which was not analyzed in the current study.

within the range of 110 to 126 mg/dL, and very high fasting glucose indicating diabetes mellitus as fasting glucose concentration $>$ 126 mg/dL.

Hypertriglyceridemia was defined as fasting TG levels $>$ 150 mg/dL and low or very low HDL-C as fasting HDL-C concentrations $<$ 50 or 39 mg/dL, respectively. Dyslipidemia was defined either by lipid subfractions (TG level $>$ 150 mg/dL or HDL-C level $<$ 50 mg/dL), or by calculated TC-to-HDL-C ratio ($>$ 5.0) [26, 27].

G. Statistical Analyses

All statistical analyses were performed using SPSS 24.0 software (IBM Corp., Armonk, NY), and the associations or statistical differences for which $P < 0.05$ were considered significant. All continuous variables were tested for normality with the Shapiro-Wilk test. Normally and non-normally distributed continuous variables are expressed as mean (SD) or median (range), respectively. The independent samples t test or the Mann-Whitney U test were used to compare the difference in continuous variables between the study groups (normal and non-normal distribution, respectively). Several comparisons were also reanalyzed with BMI adjustment using the one-way analysis of covariance (after logarithmic transformation in case of non-normally distributed variables). In case of categorical variables, values are expressed as no. (%) and the Pearson χ^2 or the Fisher exact test were used to analyze the differences between the study groups. To analyze prepubertal risk factors for IR or higher HOMA-IR at adult age, we used logistic or linear regression models, respectively. The covariates in these models were standardized parameters of birth size; prepubertal BMI, height, and fat percentage; and prepubertal serum DHEAS, androstenedione, IGF-1, and insulin concentrations.

2. Results

Women with PA and those in the control group had been born mostly at term and appropriate for gestational age without significant differences in the birth measures between the study

groups (Table 1). At the current follow-up examination, all women were postpubertal and at least 3 years postmenarche. Tables 3–5 depict the essential findings of the women with PA and control subjects in early adulthood.

A. MetS and Its Components

With at least one of the used definitions, three women with PA (10%) and two control subjects (5%) could be defined as having MetS, and there was no significant difference between the study groups in the prevalence of MetS by any definition (Table 3). All women with MetS were either obese or significantly overweight (BMI > 28 kg/m²). The prevalence of IR was higher in the women with PA than in control subjects ($P = 0.014$), and most of the women with PA with IR (62%) were either overweight or obese. Except for IR, we did not detect any other significant differences in the prevalence of MetS components between the study groups. However, it should be noted that despite statistical insignificance, fasting hyperglycemia and obesity were three to four times more common in the PA group than in control subjects (Table 3).

The mean MetS score (including indexes for central obesity, hyperglycemia, hyperinsulinemia, hypertension, and dyslipidemia) was higher in the PA group than in the control group ($P = 0.026$; Table 4). Each single index score defining the overall MetS score was comparable between the study groups ($P > 0.050$); the higher overall MetS score in the PA group was mostly explained by tendencies toward higher scores in the indexes of central obesity and hyperinsulinism.

Table 3. Prevalence of the MetS and Its Components in the PA and Control Groups of Women of Median Age, 18.1 Years

	PA Group (n = 30)	Control Group (n = 41)	$P^{a,b}$
MetS			
ATP III	3 (10)	1 (2)	0.190
IDF	3 (10)	1 (2)	0.190
WHO	2 (7)	2 (5)	0.828
MetS components			
Overweight or obesity (BMI > 25 kg/m ²)	12 (40)	9 (22)	0.100
Obesity (BMI > 30 kg/m ²)	6 (20)	2 (5)	0.063
WC > 80 cm	11 (37)	10 (24)	0.263
WC > 88 cm	10 (33)	5 (12)	0.027
Waist-to-hip ratio >0.85 or BMI >30 kg/m ²	10 (33)	10 (24)	0.408
Hyperglycemia (fP-glucose > 100 mg/dL)	7 (23)	3 (7)	0.090
IFG (fP-glucose, 110–126 mg/dL)	0 (0)	0 (0)	1
DM (fP-glucose \geq 126)	1 (3)	0 (0)	0.435
IR (HOMA-IR > 2.94) ^c	13 (43)	6 (15)	0.014
Hypertriglyceridemia (fP-TG > 150 mg/dL)	1 (3)	2 (5)	0.717
Low HDLc (fP-HDL-C < 50 mg/dL)	5 (17)	3 (7)	0.281
Very low HDLc (fP-HDL-C < 39 mg/dL)	1 (3)	0 (0)	0.435
Ratio of TC to HDL-C >5.0	0 (0)	0 (0)	1
Dyslipidemia ^d	6 (20)	4 (10)	0.254
Systolic BP > 130 mm Hg	6 (20)	4 (10)	0.304
Diastolic BP > 85 mm Hg	5 (17)	2 (5)	0.125
BP > 140/90 mm Hg	2 (7)	0 (0)	0.175

Values are expressed as no. (%).

Abbreviations: ATP, Adult Treatment Panel; DM, diabetes mellitus; fP, fasting plasma; fS, fasting serum; IDF, International Diabetes Federation; IFG, impaired fasting glucose; WHO, World Health Organization.

^aStatistical differences between the study groups were analyzed using either the Pearson χ^2 test or the Fisher exact test.

^bStatistical significance was set at $P < 0.05$.

^cIR was defined by HOMA-IR with a cutoff level of 2.94.

^dDefined as hypertriglyceridemia, low HDL-C, or ratio of TC to HDL-C >5.0.

B. Glucose Metabolism

Among the biochemical parameters of glucose metabolism, both fasting glucose and insulin levels (with and without BMI adjustment) were comparable between the study groups. Mean HbA1c was slightly higher in the PA group than in control subjects and the difference remained significant after adjustment for BMI (Table 4).

Among the calculated indicators of insulin sensitivity, fasting glucose-to-insulin ratio did not differ significantly between the study groups, but HOMA-IR was higher in the PA group than in control subjects ($P = 0.044$; Table 4). However, the difference in HOMA-IR between the study groups disappeared when adjusted for BMI. AN was present in five women with PA and none of the control subjects ($P = 0.010$; Table 4). Three of the women with AN were obese at prepubertal age and either overweight or obese at current examination, one had normal weight at prepubertal age but was now overweight, and one was obese at prepubertal age but had currently normal weight. Four of the five women with PA with AN manifested IR, and each of the four was either overweight or obese at current examination. In regression analyses including the whole cohort, we did not find any significant prepubertal determinants for the presence of IR or higher HOMA-IR at adult age (data not shown).

C. Lipids, BP, Inflammation, Liver Function, and Smoking

There were no significant differences in serum hsCRP concentrations; in plasma ALT, GT, TC, TG, HDL-C, and LDL-C concentrations; or in the TC-to-HDL-C ratio between the PA group and control group (Table 4). Neither did systolic, diastolic, or mean BP differ significantly between the study groups. There was no significant difference in the number of smokers between the study groups (Table 4).

D. Carotid Artery Ultrasound Measures

We did not detect any significant differences in the carotid artery ultrasound measurements between the groups; intima media thickness, systolic and diastolic artery diameters, and changes in artery diameters from diastole to systole were all similar in the women with PA and control subjects (Table 4).

E. Body Composition

When compared with the control group, the women with PA had a trend toward higher adult BMI and WC. Body fat percentages were comparable between the study groups (Table 4), but fat distribution was more central in the PA group than in control subjects—more women with PA than control subjects had WC >88 cm (Table 3) and the women with PA had higher android fat percentage and android-to-gynoid ratio of the body fat mass than the women in the control group did (Table 4). Adult lean and muscle mass, and total body bone mineral content and bone mineral density were all significantly higher in the women with PA than in the control group, also after adjustment for BMI (Table 4). Hip and wrist measures were comparable between the study groups. In contrast to what was measured at adult age, the women with PA had significantly higher prepubertal BMI SD score and fat percentage than the control group did, but BMI-adjusted prepubertal lean and muscle mass, and areal BMDs were comparable between the study groups (Table 1).

F. Comparison of the Women With PA With and Without IR

The women with PA with IR had significantly higher current BMI, WC, waist-to-height ratio, and fat percentage than those without IR. The prevalence of overweight or obesity at postpubertal examination was also nearly threefold in the women with PA with IR compared with those without IR ($P = 0.035$; Table 5). Gestational age, birth size, prepubertal height and BMI SD score, or fat percentage did not differ between the women with PA with and without IR, and PP was equally common in both subgroups (Table 5).

Table 4. Characteristics and Cardiovascular Risk Factors of the PA and Control Groups at Young Adult Age

	PA Group (n = 30)	Control Group (n = 41)	P ^{a,b}
Age, y	18.1 (16.5–23.5)	18.1 (16.9–19.8)	0.950
MetS score ^c	1.99 (4.18)	−0.04 (3.04)	0.026
Smoking, yes	4 (13)	7 (17)	0.655
Anthropometry ^d			
Height, cm	167.2 (6.8)	164.6 (5.1)	0.072
Weight, kg	63.3 (47.4–115.0)	59.8 (47.5–88.4)	0.011
BMI, kg/m ²	22.8 (18.4–42.2)	21.6 (18.5–32.5)	0.068
BMI, SD score	0.94 (−0.92–3.41)	0.35 (−0.91–2.47)	0.068
WC, cm	75.5 (64.5–108.7)	71.9 (53.0–92.0)	0.059
Hip circumference, cm	94.1 (82.5–124.0)	92.0 (80.8–108.2)	0.082
Waist-to-height ratio	0.46 (0.38–0.66)	0.44 (0.33–0.55)	0.205
Waist-to-hip ratio	0.81 (0.71–0.90)	0.79 (0.62–0.93)	0.249
Hip-to-height ratio	0.56 (0.50–0.75)	0.55 (0.50–0.68)	0.269
Wrist circumference, cm	14.5 (13.5–16.9)	14.3 (13.3–15.8)	0.059
Wrist-to-height, %	8.8 (8.2–10.1)	8.7 (8.0–10.0)	0.503
Body composition (DXA)			
Fat mass, kg	21.2 (11.7–55.5)	18.6 (5.8–42.7)	0.056
Fat, %	34.6 (23.2–53.6)	31.6 (11.4–49.3)	0.132
Android fat, %	7.7 (1.4)	6.8 (1.6)	0.015
Gynoid fat, %	21.2 (2.8)	22.3 (3.3)	0.156
Fat distribution, android-to-gynoid fat ratio	0.37 (0.11)	0.31 (0.10)	0.017
Lean mass, kg	43.8 (6.1)	40.2 (3.3)	0.004/0.031 ^e
Muscle mass, kg	41.1 (5.8)	37.7 (3.1)	0.005/0.039 ^e
BMC, total body excluding the head, kg	2.7 (0.4)	2.4 (0.3)	0.002/0.025 ^e
BMD, total body excluding the head, g/cm ²	1.18 (0.06)	1.12 (0.07)	<0.001/0.005 ^e
BMD, total body excluding the head, SD score	0.74 (0.77)	0.00 (0.97)	0.001/0.008 ^e
BP			
Systolic BP, mmHg	121 (15)	115 (11)	0.071/0.378 ^e
Diastolic BP, mmHg	74 (9)	71 (7)	0.120/0.820 ^e
Mean BP, mmHg	96 (10)	93 (7)	0.121/0.516 ^e
Heart rate, beats/min	81 (11)	78 (9)	0.269/0.279 ^e
Lipid profile			
fP-TC, mg/dL	158 (120–220)	154 (100–274)	0.937/0.538 ^e
fP-TG, mg/dL	72 (35–156)	65 (30–220)	0.590/0.634 ^e
fP-HDL-C, mg/dL	62 (38–112)	65 (44–95)	0.561/0.785 ^e
fP-LDL-C, mg/dL	81 (42–143)	85 (39–197)	0.827/0.450 ^e
Ratio of TC to HDL-C	2.5 (1.5–4.3)	2.5 (1.8–4.5)	0.561/0.867 ^e
Glucose metabolism			
fP-glucose, mg/dL	94 (85–130)	92 (81–110)	0.205/0.195 ^e
fWB-HbA1c, mmol/mol	34 (2)	32 (2)	0.004/0.011 ^e
fS-insulin, mU/L	11 (4–56)	10 (2–24)	0.060/0.191 ^e
FGIR ^f	8.8 (2.3–23.9)	9.6 (4.1–40.1)	0.059/0.223 ^e
HOMA-IR ^g	2.6 (0.9–17.9)	2.1 (0.5–6.0)	0.044/0.172 ^e
AN, yes	5 (17)	0 (0)	0.010
Carotid artery measurements ^h			
IMT, mm	0.47 (0.05)	0.48 (0.05)	0.734/0.521 ^e
Systolic diameter, mm	5.85 (0.38)	5.75 (0.31)	0.228/0.529 ^e
Diastolic diameter, mm	5.11 (0.36)	5.03 (0.32)	0.334/0.863 ^e
Distensibility, %/mmHg ⁱ	0.286 (0.07)	0.290 (0.06)	0.790/0.858 ^e

(Continued)

3. Discussion

In this study, we investigated the long-term cardiometabolic outcome of PA by following previously formed cohorts of women with PA and control subjects from prepuberty to young adulthood. The prevalence of adulthood MetS was low and similar in women with PA and

Table 4. Characteristics and Cardiovascular Risk Factors of the PA and Control Groups at Young Adult Age (Continued)

	PA Group (n = 30)	Control Group (n = 41)	P ^{a,b}
Liver function and inflammation			
fP-ALT, U/L	17 (8–50)	16 (5–91)	0.486/0.921 ^e
fP-GT, U/L	11 (7–27)	12 (4–43)	0.689/0.393 ^e
fS-hsCRP, mg/L	0.7 (0.2–8.6)	0.6 (0.2–10.4)	0.225/0.664 ^e

Continuous variables are expressed as mean (SD) or median (range), and categorical variables as no. (%).

Abbreviations: ALT, alanine aminotransferase; AN, acanthosis nigricans; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; DXA, dual-energy X-ray absorptiometry; FGIR, fasting glucose-to-insulin ratio; fWB, fasting whole blood; fP, fasting plasma; fS, fasting serum; GT, glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; hsCRP, high-sensitive c-reactive protein; IMT, intima media thickness; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome score; PA, premature adrenarche; TC, total cholesterol; TG, triglycerides.

^aThe independent samples *t* test or Mann-Whitney *U* test were for continuous variables, and the Pearson χ^2 or Fisher exact test for categorical variables.

^bStatistical significance was set at $P < 0.05$.

^cComprises the standardized and summed value of WC, levels of fasting glucose and fasting insulin, mean BP, and ratio of TG to HDL-C [23].

^dFrom other aspects than in the current study, height, weight, BMI, waist, and hip measures were reported previously in Liimatta *et al.* [16].

^eSecond *P* value is from reanalysis of data with BMI adjustment using one-way analysis of covariance (after logarithmic transformation in the case of non-normally distributed variables).

^fFasting glucose (mg/dL) divided by fasting insulin (mU/L).

^gCalculated as [fasting glucose (mg/dL) \times fasting insulin (mU/L)]/405.

^hMeasured from left carotid artery by ultrasound with subject in lying supine.

ⁱCalculated as [(systolic diameter – diastolic diameter)/diastolic diameter]/(sBP – dBP).

control subjects. We found no significant differences between the study groups in the indicators of dyslipidemia, hypertension, hepatosteatosis, atherosclerosis, or low-grade inflammation. However, the women with PA had more unfavorable fat distribution and glucose metabolism than the control subjects did, and they also had a higher calculated mean MetS score, based on their trend to higher WC and fasting insulin levels. Regarding the measures of glucose metabolism, the women with PA had higher HbA1c concentrations, HOMA-IR, and prevalence of IR than did the control group. The observed abnormalities of glucose metabolism were associated with current central adiposity.

Cardiometabolic risk can be deduced largely from the sum of the components of MetS, and the findings in our study suggest PA does not associate with MetS at young adult age. To our knowledge, there are no previous reports on the prevalence of adulthood MetS after PA. In one study of prepubertal children, the prevalence of childhood MetS was low in those with PA and did not differ from that of control subjects [28]. In our cohort, the prevalence of childhood MetS was higher in prepubertal girls with PA than control girls [14], whereas the prevalence of adulthood MetS was relatively low in women with PA and did not differ from that of the control group. In the study by Williams *et al.* [28], childhood MetS was seen only in obese children, whether they had PA or not, and body adiposity was associated with the number of MetS risk factors. Similarly, childhood MetS in our cohort was mostly explained by a higher prevalence of obesity and hyperinsulinemia in girls with PA [14], and adulthood MetS was detectable only in those women who were either overweight or obese.

Hyperinsulinemia is a common finding among prepubertal children with PA [8, 9, 14] and the risk of decreased insulin sensitivity seems to be increased in girls with PA also at adolescence [7, 12]. In a study investigating Turkish girls with PP, decreased insulin sensitivity at pubertal age could be predicted mostly by prepubertal BMI [12]. Our current study findings indicate the risk of abnormalities in glucose metabolism persists to adult age and that the risk is strongly associated with central adiposity. On the basis of their findings from oral glucose tolerance tests (OGTT),

Table 5. Pre- and Postpubertal Characteristics of Women With PA With and Without IR at Postpubertal Examination

	Women With PA With IR ^a (n = 13)	Women With PA Without IR (n = 17)	<i>P</i> ^{b,c}
At birth			
Gestational age, wk	40.0 (29.0 to 42.0)	40.1 (35.4 to 42.3)	0.760
Birth length, SD score	-0.15 (1.33)	-0.19 (0.85)	0.925
Birth weight, SD score	0.00 (1.82)	-0.30 (0.75)	0.621
At prepubertal examination (median age, 7.6 y)			
Height, SD score	0.99 (1.17)	0.86 (0.85)	0.733
BMI, SD score	1.15 (1.29)	0.51 (1.28)	0.190
Fat, %	24.2 (9.8)	23.5 (10.1)	0.862
Lean mass, kg	24.5 (4.7)	24.0 (4.0)	0.788
Pubarche, yes	7 (54)	9 (53)	0.961
At postpubertal examination (median age, 18.1 y)			
Height, cm	167.3 (7.4)	167.1 (6.4)	0.944
BMI, kg/m ²	25.1 (20.0–42.2)	22.2 (18.4–35.8)	0.039
BMI, SD score	1.46 (1.13)	0.54 (1.04)	0.028
WC, cm	88.4 (67.8–108.7)	73.8 (64.5–96.8)	0.031
Waist-to-height ratio	0.49 (0.40–0.66)	0.44 (0.38–0.61)	0.022
Waist-to-hip ratio	0.84 (0.74–0.90)	0.80 (0.71–0.89)	0.094
Fat, %	38.0 (27.0–50.1)	31.6 (23.2–53.6)	0.039
Lean mass, kg	45.1 (6.0)	42.3 (4.5)	0.165
Overweight or obesity, yes ^d	8 (62)	4 (24)	0.035

Continuous variables are expressed as mean (SD) or median (range), and categorical variables as no. (%).

^aIR was defined by HOMA-IR with a cutoff level of 2.94.

^bIndependent samples *t* test or the Mann-Whitney *U* test for continuous variables, and Pearson χ^2 test for categorical variables.

^cStatistical significance was set at *P* < 0.05.

^dBMI > 25 kg/m².

Ibáñez *et al.* [29] have reported similar findings among Catalan girls with PP. Although the girls were mostly lean, they had increased central fat mass, which was associated with hyperinsulinemia [29]. In contrast, in a study by Meas *et al.* [30] in which 17-year-old French girls with PP and control subjects whose BMI values were within the normal range completed OGTTs, glucose tolerance was normal in all subjects without significant differences in plasma glucose or serum insulin profiles between the study groups. Our results are not straightforwardly in line with the findings of Meas *et al.* [30], but discrepancies may be explained by possible differences in body fat percentage and/or fat distribution between our cohort and that in the French study.

The associations between PA and dyslipidemia or hypertension are controversial. Some studies have reported that PA is linked to abnormalities in lipid profile [4, 7, 10] or BP [4, 10], but there also are reports suggesting normal lipid profile [30, 31] and BP [7] exist. In one of these studies, Catalan girls with a history of PP had unfavorable lipid profile but normal systolic and diastolic BP throughout their pubertal development [7]. In contrast, 27 French girls with a history of PP had normal lipid profile at postpubertal age [30]. The results of our case-control follow-up study suggest PA does not lead to increased risk of adulthood dyslipidemia or hypertension.

Previous studies have suggested that children with PA may be more susceptible to low-grade inflammation and developing atherosclerosis, because they had increased circulating cytokine levels [10, 32]. As far as we know, there are no studies measuring cardiovascular changes or inflammation markers in PA at adult age. Although we previously found an association between PA and circulating TNF- α in our prepubertal cohort [33], the adult women with PA and control subjects in the current study had comparable serum hsCRP concentrations and carotid artery measurements. Thus, our findings do not support the suggestion that PA is associated with long-term, low-grade inflammation or atherosclerotic pathology. Cardiovascular risk could be evaluated

also with calculated MetS score [24] and, interestingly, the women with PA in our study had higher MetS scores than the control group did. This difference was mostly explained by the differences in the indexes of central obesity and hyperinsulinism, and agreed well with our findings that PA was associated with increased central fat mass and IR but not with dyslipidemia or hypertension.

Although BMI, waist measures, and fat percentage did not differ significantly between our study groups, the women with PA had more centrally located fat. This finding is in accordance with the findings from a Catalan cohort of girls with PP who were mostly lean but had increased central fat mass throughout their pubertal development [29]. On the other hand, our study findings suggest total body adiposity in women with PA tends to reduce and body composition alters toward nonfat mass by adulthood. This finding is supported by some previous studies. A Brazilian study following a group of girls with PP until different stages of puberty reported that BMI and the prevalence of overweight and obesity tended to decrease through time [11]. Also, in some other studies, BMI was reported to be increased in subjects with PA in early puberty but normal at late- or postpubertal age [30, 34, 35].

It is well known that childhood obesity increases the risk of adulthood obesity [36], and that obesity, especially central obesity, is associated with the development of IR [37]. Children with PA tend to be overweight at prepubertal and pubertal age [4–6], including the girls with PA in our cohort [14, 15], so it is not surprising that central fat mass and the prevalence of IR were higher in our PA group than in control subjects. We have speculated that PA could be a part of an adaptive process in which the body tries to turn energy excess in an anabolic direction by advancing the initiation and tempo of both adrenal and pubertal maturation [16]. Also, because adrenal androgens may have antiatherogenic effects [38], prolonged adrenal androgen excess in PA could be protective regarding cardiovascular risk. However, if an energy-rich diet and a lifestyle that maintains obesity continue through adolescence, this mechanism may not be enough at the individual level to prevent the metabolic disadvantages associated with adiposity. Our current results support the assumption that the metabolic risk in PA is driven by the presence of increased central adiposity, leading especially to the risk of abnormalities in glucose metabolism.

The major strength of our study is its prospective design investigating long-term metabolic outcome of PA in young women with a carefully matched control group. We used common definitions of MetS and studied a variety of known cardiovascular risk factors at defined age in young adulthood. The limitations include a high drop-out rate and a relatively small sample size at adult age, reducing the statistical power of the study. We did not perform postpubertal OGTTs, which could have given more precise information about glucose metabolism and IR. Because PA is suggested to be associated with ovarian hyperandrogenism [13], it should be noted that we did not analyze the features related to polycystic ovarian syndrome in this study.

In conclusion, our study findings suggest that some women with PA may be at risk for having decreased insulin sensitivity at young adult age. Maintaining or gaining increased central adiposity by adulthood seems to be a major independent determinant for this risk, rather than PA or other prepubertal factors related to PA. PA does not seem to be associated with MetS, dyslipidemia, hypertension, atherosclerosis, or low-grade inflammation in young adult females. Our results emphasize the importance of lifestyle interventions for childhood overweight and obesity among girls with PA.

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