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Clinical Research Article

Cardiorespiratory Fitness in Young Adult Women With a History of Premature Adrenarche

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Abstract

Context: Premature adrenarche (PA) may predispose to some adverse long-term health outcomes. Cardiorespiratory fitness (CRF) is one of the strongest factors known to predict overall health, but no data exist on the CRF of women with a history of PA.

Objective: To study if hyperandrogenism in childhood resulting from PA leads to a measurable difference in CRF between young adult PA and control women.

Methods: A total of 25 women with PA and 36 age-matched controls were followed from prepubertal age until adulthood. Anthropometric measurements, body composition, biochemical, and lifestyle factors were assessed. The main outcome measure was maximal cycle ergometer test result at the mean age of 18.5 years. We also assessed prepubertal predicting factors for CRF with different linear regression models.

Results: Though prepubertal children with PA were taller and heavier than their non-PA peers, there were no significant differences in height, body mass index, body composition, or physical activity in young adulthood. We observed no significant differences in any of the parameters of the maximal cycle ergometer test, including maximal load ($P = .194$) or peak oxygen consumption ($P = .340$). Hemodynamic responses of the groups were similar. None of the examined models or prepubertal factors significantly predicted CRF at adult age.

Conclusion: This study suggests that hyperandrogenism in childhood/adolescence resulting from PA does not have a significant impact on adulthood CRF.

Key Words: premature adrenarche, cardiorespiratory fitness, ergometer, performance

Abbreviations: BMI, body mass index; CAH, congenital adrenal hyperplasia; CRF, cardiorespiratory fitness; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; HR, hazard ratio; PA, premature adrenarche; PCOS, polycystic ovary syndrome; sBP, systolic blood pressure; W_{max}, maximal workload.

Premature adrenarche (PA) is a hyperandrogenic state associated with increased childhood body mass index (BMI), taller stature, more advanced bone age, and earlier menarcheal age when compared with peers with normal timing of adrenarche [1, 2]. These anthropometric differences tend to attenuate by adult age [2]. Adults with prior PA have, however, been suggested to be at an increased risk for metabolic and hormonal changes, including mild persisting insulin resistance and hyperandrogenism, that might lead to unfavorable consequences [3]. One of these possible long-term consequences is the polycystic ovary syndrome (PCOS) [4].

Androgens are the drivers of sex differences in athletic performance [5], and females with hyperandrogenism (eg, PCOS or some disorders of sexual differentiation) are overrepresented among female elite athletes [6, 7]. However, although elite female athletes benefit from increased androgen levels, women with PCOS and a more sedentary lifestyle do not [8]. Cardiorespiratory fitness (CRF), the ability to transit oxygen to muscles under exercise for prolonged periods, was lower in women with PCOS in most of the studies reviewed by Dona et al [8], and correlated negatively with insulin resistance [8], commonly found in both women with PCOS [9] and PA [10]. Other factors negatively associated with CRF include central adiposity (waist circumference), BMI, weight, fat mass, and C-reactive protein, whereas socioeconomical status and physical activity have positive correlations with CRF [11].

CRF is an important predictor of long-term health outcomes. It is inversely associated with the risk for all-cause mortality and cardiovascular disease [12], metabolic syndrome [13], depression [14], and cancer mortality [15]. Moreover, poor CRF at a young age is associated with later development of cardiovascular disease risk factors [16] and even an increased risk for early death from cardiovascular diseases [17]. Although some findings in women with PA overlap

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with factors associated also with CRF, there are no previous studies investigating CRF in women with a history of PA.

We have already studied the cardiometabolic risk factors [10] and androgen profiles [18] in our cohort of adult females with a history of PA. First, we found increased prevalence of insulin resistance (associated with central adiposity) in the PA group at young adult age [10]. Later, we found comparable androgen profiles but decreased SHBG concentrations leading to increased free androgen index (FAI) in a subgroup of our cohort that did not use hormonal contraceptives [18]. In the current study, we continued to examine these groups and evaluated whether the history of PA has an impact on CRF and, in addition, whether we could find predicting factors for adulthood CRF.

Subjects and Methods

Subjects and Design

This study is part of our longitudinal case-control study on PA [2, 10, 18-22]. Altogether, 30 women with a history of PA and 42 age-matched controls performed maximal cycle ergometer test at the mean age of 18.5 years. Five women with PA and 6 control women were excluded from the analyses: 1 woman with PA had exaggerated hypertensive reaction with dizziness leading to interruption of the exercise test, and for 4 women with PA and 6 control women, ergometer test results indicated submaximal exertion. Thus, the total number of subjects in the present study was 25 women with PA and 36 control women. Originally, the women with PA were recruited solely by clinical signs, and they had presented at least 1 clinical sign of androgen action (adult-type body odor, greasiness of the hair and skin, comedones and acne, and the development of pubic or axillary hair) before the age of 8 years [21]. Of the 25 women with PA, 22 (88%) had a dehydroepiandrosterone sulfate (DHEAS) concentration higher than 1 µmol/L at the time of recruitment and 14/25 (56%) had pubarche. Other sources of hyperandrogenism (precocious puberty, congenital adrenal hyperplasia, androgen producing tumor, and external androgen exposure) had been excluded. At the present evaluation, all women were postpubertal according to the Tanner staging as evaluated by a trained physician (J.L.). Information about smoking, underlying illnesses, exercise, hormonal contraceptive use, indication for contraceptive use, and socioeconomical status were acquired via a questionnaire form. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, and informed consent was obtained in accordance with the ethical principles stated in the Declaration of Helsinki.

Clinical Assessments

Body composition was assessed, as previously described [10], in the morning after an overnight fast. Height was measured with a calibrated Harpenden stadiometer (Holtain Ltd., Crymych, UK) and recorded to the nearest 0.1 cm as the mean of 3 repeated measurements. Weight was measured with a calibrated electronic scale and recorded to the nearest 0.1 kg. BMI was calculated as the weight in kilograms divided by the square of height in meters. Lean and body fat masses were assessed using the dual-energy X-ray absorptiometry device (Lunar Prodigy Advance; GE Medical Systems, Madison, WI).

Biochemical Analyses

All blood samples were collected after an overnight fast between 9:00 and 10:00 AM (prepubertal baseline examination) or 7:00 and 8:00 AM (follow-up visit at young adulthood). All serum samples were stored at −80°C until analyzed. Hemoglobin was measured using photometric method and Sysmex K-4500 Hematology analyser (Toa Medical, Kobe, Japan). Radioimmunoassays were used to determine serum DHEAS (catalog #1950, RRID:AB_2819763) and testosterone (Siemens catalog #TKTT5, RRID: AB_2905660) concentrations in prepuberty. Specific time-resolved fluoroimmunoassays were used to measure serum insulin (Roche catalog #12017547, RRID: AB_2756877) and SHBG (Roche catalog #03052001190, RRID: AB_2891222) concentrations. FAI was calculated with the following formula: (total testosterone/SHBG) × 100). Glucose was analyzed by the hexokinase method with the Cobas 6000 c501 analyzer (Hitachi High Technology Co., Tokyo, Japan). To calculate the homeostasis model assessment for insulin resistance, the following formula was used: (fasting glucose [mg/dL] × fasting insulin [mU/L])/405).

Assessment of Cardiorespiratory Fitness and Hemodynamic Responses

Maximal cycle ergometer tests were performed between 09:00 AM and 12:00 PM using the Ergoselect 200K electromagnetic cycle ergometer (Ergoline, Bitz, Germany) in the control of the Cardiosoft electrocardiography software (version 6.5, GE-Healthcare Medical Systems, Freiburg, Germany). The saddle was targeted to the height where subjects' knee angle in the extended leg on the pedal was 160 degrees. The test protocol included pretest rest, anticipatory, test, and posttest recovery phases. In the pretest phase, subjects were lying in bed for 5 minutes. In the anticipatory phase, subjects were sitting in the ergometer for approximately 2 to 3 minutes. In the test phase, the starting workload was 20 W increasing by the steps of 20 W in every 1 minute. Subjects were asked to keep the cadence within 70 to 80 rounds per minute and cycle until exhaustion. Exhaustion was defined as the inability to maintain the cadence above 65 rounds per minute regardless of vigorous verbal abetment. The test was considered maximal if the reason for termination indicated maximal effort and cardiovascular capacity. The effort was considered maximal if the Borg rating of perceived exertion was above 17 on a scale of 6 to 20 [23], and the maximal cardiovascular capacity was defined as maximal heart rate (HR) at the end of the test above 90% of the calculated predicted maximal HR. Predicted maximal HR was calculated using the following formula [24]: (220 – age). Maximal workload (W_{max}) was defined as the workload at the end of the test to the accuracy of 1 W and calculated as: W_{max} = (last finished stage [W] + (time on the last stage [s] × 20 W/60 seconds). This study did not include respiratory gas analyses. Instead, peak oxygen consumption was calculated with the following formula [25]: (2.0 × [6.12×W_{max}/mass (kg)] + 3.5). In the posttest recovery phase, the subjects were lying in supine position for 5 minutes.

Systolic blood pressure (sBP) was measured using an aneroid sphygmomanometer (Heine Gamma G7, Herrsching, Germany) at the end of the pretest phase, in the anticipatory phase, in 2-minute intervals during the exercise test (starting from the first increase in workload [ie, 1 minute after the start of the test]), as close as possible to exhaustion, and at 2 and

4 minutes after exhaustion in the recovery phase. Expected sBP during stress depends on achieved load [26] and was calculated with the following formula: 120 + (0.333 × achieved load). The difference to expected sBP was calculated as sBP at each stage – expected sBP at stage specific workload. When calculating the expected sBP for 1 to 2 minutes before cessation phase, the following formula was used to calculate the workload at that phase: W_{max} – 90 seconds × (20 W/60 seconds). HR was recorded continuously using a 12-lead electrocardiography from the beginning of the pretest until the end of the posttest recovery phase.

Statistical Analyses

All statistical analyses were performed with the SPSS 25.0 software (IBM Corp., Armonk, NY). Normally distributed variables are expressed as mean (SD), and nonnormally distributed variables as median (interquartile range). Normally distributed variables were analyzed with the independent samples *t* test, and nonnormally distributed variables with the Mann-Whitney *U* test. All categorical variables are expressed as n (%) and analyzed with the Fisher exact test. When BMI adjustment was performed for comparison of the variables between the study groups, the 1-way analyses of covariance was used. Correlations were analyzed with the Pearson or Spearman correlation test depending on the skewness of distribution. For assessing predicting factors for CRF (maximal load per lean mass as a dependent variable), linear regression models were used, and the models were tested to meet assumptions of normality, linearity, homoscedasticity, and absence of multicollinearity. When needed, logarithmic transformation was used for nonnormally distributed variables. A mixed linear model was used to compare group differences in blood pressure during different phases of the ergometer test. A P value < .05 was considered significant.

Results

Characteristics at Prepubertal Age

Table 1 depicts the characteristics of the 25 PA and 36 control females at prepubertal (mean age, 7.5 years) and young adult age (mean age, 18.5 years); a part of these background data has been reported previously in another context [2, 10, 18-20]. At the prepubertal phase of the study, the PA women were taller, had higher weight and DHEAS concentrations, and lower SHBG concentrations leading to increased FAI when compared with control women at prepubertal age (Table 1).

Anthropometric Measurements, Body Composition, and Biochemical Analyses at Young Adult Age

At young adult age, former statistically significant differences in stature and weight between the groups had vanished and adult height and BMI were comparable between the study groups (Table 1). Overall, the PA group had higher lean and muscle mass compared with controls, but the difference vanished after BMI adjustment. Fat masses were similar. There were no statistically significant differences in fat, lean, or muscle mass percentages (Table 1). The PA group had higher sBP compared with controls. We did not find any significant differences between the PA and control women in waist circumference, resting heart rate, hemoglobin, homeostasis model assessment for insulin resistance, amount of exercise per week, smoking, or prevalence of asthma. The use of contraceptives was similar between the groups. Results about the indications for contraceptive use in these groups have been published before [18] and there were no differences between the groups. Cholesterol, creatinine, blood counts, alanine transaminase, glutamyl transferase, TSH, insulin, fasting glucose and C-reactive protein were also measured (results not shown). None of these correlated significantly with maximum load per lean mass, and none significantly predicted it in the linear regression models.

Results of the Cycle Ergometer Test

Table 2 depicts the results of the cycle ergometer test for the 25 women with PA and 36 control women. There were no differences between the study groups in W_{max}, even after taking into account their weight, BMI, and lean mass. Peak oxygen consumption and heart rate were also similar between the groups. Figure 1 depicts the changes in heart rate and Fig. 2 depicts the changes in sBP, differences to expected sBP in stress, and the rate of descend of sBP during the recovery as a function of different phases of the ergometer test. Although the absolute sBP during different phases of the test was similar, the PA group had a larger difference to workload specific expected sBP after 1 minute and after 3 minutes of stress compared with the controls. After those phases, the differences were similar between the groups. At the recovery phase, the groups had similar rates of descend in sBP. A mixed linear model was used to compare the sBP of the groups at the following phases of the experiment: anticipatory phase, after 1 minute of stress, after 3 minutes of stress, after 2 minutes of recovery, and after 4 minutes of recovery. The model detected no significant difference between the groups (P = .206). At the following phases, the individual workloads were not identical, and the mixed linear model was thus not used: 1 to 2 minutes before cessation and highest. We did not detect any significant differences in heart rate responses between the study groups.

Analyses of Predictive Factors of CRF

In addition, we performed multiple linear regression models to search for prepubertal factors that would predict adulthood CRF. Maximal load per lean mass was used as a dependent variable in these models, and independent variables included prepubertal BMI SD score, manifestation of pubarche, serum DHEAS, insulin-like growth factor-1, and insulin concentrations. The models were adjusted also with age at prepubertal examination. The models failed to significantly predict the dependent variable and none of the independent variables reached significance (data not shown).

Discussion

PA is a state in which children are exposed to endogenous hyperandrogenism for a prolonged period along with possible metabolic disturbances. The aim of this study was to assess whether such an exposure leads to measurable changes in adulthood CRF. When compared with control women, we observed no difference in CRF between young adult women with a history of PA and controls. This suggests that PA does not have an influence on adulthood CRF.

In our previous study with mostly these same PA women [18], we found that they tend to have more often hirsutism, lower circulating SHBG levels, and higher calculated FAI at

Table 1. Characteristics of the premature adrenarche (PA) and control women at prepubertal and young adult age

	PA (n = 25)	Control (n = 36)	*P*
At prepuberty			
Age, y	7.5 (1.1)	7.4 (0.7)	.682
Height, cm	131.0 (9.2)	125.1 (5.9)	**.009**
Height, SDS	0.84 (0.98)	−0.18 (0.82)	**<.001**
Weight, kg	31.8 (26.7-36.4)	25.3 (22.5-29.2)	**.001**
BMI, SDS	0.75 (1.31)	0.17 (1.13)	.072
Lean mass, kg	24.4 (4.4)	21.8 (2.9)	**.012**
Fat mass, kg	8.2 (4.6-13.1)	4.4 (2.7-6.5)	**.017**
DHEAS, µmol/L	2.05 (1.20-2.90)	0.90 (0.60-1.40)	**<.001**
Testosterone, nmol/L	0.45 (0.35-0.57)	0.36 (0.35-0.47)	.100
SHBG, nmol/L	81.4 (37.8)	104.7 (29.9)	**.018**
FAI[a]	0.68 (0.40-1.03)	0.37 (0.31-0.52)	**.009**
At young adult age			
Age, y	18.1 (17.8-20.4)	18.1 (17.9-18.4)	.676
Height, cm	167.1 (7.4)	164.7 (5.0)	.133
Weight, kg	62.6 (58.9-83.1)	60.7 (54.3-67.5)	.065
BMI	22.8 (21.1-29.0)	21.6 (19.7-25.6)	.151
Lean mass, kg	43.1 (5.2)	40.5 (3.3)	**.021**/.104[b]
Lean mass percentage, %	64.1 (9.2)	67.6 (9.1)	.150
Muscle mass, kg	40.4 (4.9)	38.1 (3.1)	**.026**/.119[b]
Muscle mass percentage, %	62.7 (9.4)	66.3 (9.3)	.144
Fat mass, kg	19.5 (16.6-36.6)	18.9 (14.5-26.7)	.127/.513[b]
Fat percentage, %	35.9 (9.2)	32.4 (9.1)	.151
Sitting height-to-height ratio, %	53.9 (1.2)	53.7 (1.3)	.504
Waist circumference, cm	75.0 (69.8-88.6)	72.7 (68.5-84.0)	.137
Heart rate, beats/min	81 (12)	80 (9)	.515
sBP, mm Hg	122 (15)	115 (11)	**.023**
Hemoglobin, g/L	131 (9)	131 (9)	.879
HOMA-IR[c]	2.43 (1.61-3.64)	1.96 (1.35-2.74)	.091
Exercise, hours/week	5.0 (3.0-7.0)	4.5 (2.0-6.0)	.314
Hormonal contraceptive use, n (%)			
Yes	13 (52.0)	17 (47.2)	.797
No	12 (48.0)	19 (52.8)	
Smoking, n (%)			
Yes	3 (12)	6 (17)	.709
No	22 (88)	30 (83)	
Asthma, n (%)			
Yes	3 (12)	2 (6)	.392
No	22 (88)	34 (94)	

Normally distributed variables are expressed as mean (SD) and analyzed with the independent samples *t* test. Nonnormally distributed variables are expressed as median (interquartile range) and analyzed with the Mann-Whitney *U* test. Categorical variables are expressed as n (%) and analyzed with the Fisher exact test. Significant *P* values (<.05) are highlighted in bold.
Abbreviations: BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; HOMA-IR, homeostasis model assessment for insulin resistance; sBP, systolic blood pressure; SDS, SD score.
[a]FAI calculated as ((testosterone × 100)/SHBG).
[b]After BMI adjustment.
[c]HOMA-IR, calculated as ((fasting glucose [mg/dL] × fasting insulin [mU/L])/405).

young adult age when compared with those women with normal timing of adrenarche. The extent to which androgens contribute to CRF seems to depend on multiple factors. Elite athletes benefit from exogenous [27] and endogenous androgen excess [6, 7]. In females with a sedentary lifestyle and no known endocrinological disorder, exogenous testosterone exposure improves CRF [28], but the effect of endogenous androgens seems only modest at best. For example, a study that investigated the relationship between androgens and CRF among 488 individuals found that only FAI had significant association with maximal oxygen consumption in women but accounted for only 3% of the outcome [29]. In another cross-sectional study, neither SHBG nor testosterone predicted CRF among 624 healthy adult males [30]. Thus, among

Table 2. Performance results and hemodynamic responses during the maximal cycle ergometer test in young adult women with a history of PA and controls

	PA (n = 25)	Control (n = 36)	*P*
W_{max}, W	178 (158-195)	161 (154-190)	.194
Max load per weight, W/kg	2.7 (0.6)	2.8 (0.6)	.280
Max load per BMI, W/(kg/m^2)	7.4 (1.6)	7.7 (1.7)	.542
Max load per lean mass, W/kg	4.2 (0.5)	4.2 (0.5)	.731
$VO2_{peak}$, mL/kg[a]	37.7 (7.5)	39.6 (7.6)	.340
Max heart rate, beats/min	195 (7)	192 (6)	.205
Max heart rate, %[b]	96.8 (3.6)	95.3 (3.0)	.103
ΔHeart rate during stress phase, beats/min[c]	113 (12)	113 (10)	.880
ΔHeart rate during recovery phase, beats/min[d]	−17 (7)	−17 (6)	.878
Max sBP, mm Hg	178 (16)	169 (21)	.076
Max dBP, mm Hg	71 (15)	66 (10)	.132
Max sBP difference to expected highest sBP, mm Hg[e]	−1.1 (13.1)	−7.8 (19.6)	.144
ΔsBP during stress phase, mm Hg[f]	56 (18)	54 (19)	.744
ΔdBP during stress phase, mm Hg[g]	−3 (11)	−6 (10)	.482

Normally distributed variables are expressed as mean (SD) and analyzed with the independent samples *t* test. Nonnormally distributed variables are expressed as median (interquartile range) and analyzed with the Mann-Whitney *U* test.
Abbreviations: BMI, body mass index; dBP, diastolic blood pressure; PA, premature adrenarche; sBP, systolic blood pressure; $VO2_{peak}$, peak oxygen consumption; W, watt; W_{max}, maximal workload.
[a]Calculated as $(2.0 \times (6.12 \times W_{max}/\text{weight (kg)} + 3.5)$.
[b]Calculated as maximum heart rate/(220 – age).
[c]Calculated as maximal heart rate – heart rate at anticipatory phase.
[d]Calculated as heart rate 1 minute after cessation – maximal heart rate.
[e]Maximum sBP – expected highest sBP (expected sBP calculated as $120 + 0.333 \times W_{max}$).
[f]Calculated as maximal systolic blood pressure – systolic blood pressure at anticipatory phase.
[g]Calculated as maximal diastolic blood pressure – diastolic blood pressure at anticipatory phase.

individuals with average physical activity and mostly normal androgen levels, which criteria most women with PA meet, endogenous androgens seem to be minor contributors to CRF. Our results are consistent with this argument. Some studies, however, have found adult women with PA to be hyperandrogenic [4], and endogenous hyperandrogenism among nonathlete adults might contribute to CRF of affected individuals to a greater degree.

PCOS is a condition characterized by hyperandrogenism and metabolic disturbance including insulin resistance, and similar findings have also been reported in some women with PA [3]. A review investigating CRF in nonathlete women with PCOS found only 6 such studies, of which 5 concerned PCOS women with overweight. Three of those [31-33] showed lower CRF among women with PCOS, and 2 found no difference when compared with controls [34, 35]. One study [36] found that CRF is significantly lower in nonobese PCOS women than in controls. In some of these studies, insulin insensitivity was found to be negatively associated with CRF [32, 35], whereas in 1 study only free testosterone, but not glucose disposal rate, predicted CRF [36]. Previously, we have reported similar androgen profiles but elevated FAI (because of decreased SHBG) and increased prevalence of insulin resistance, in a subgroup of these adult PA females who did not use hormonal contraceptives [10, 18]. If such a difference (in FAI) is obtained between the particular groups in the current study, our findings suggests that it is not enough to cause significant changes in CRF.

Another question concerns the long-term CRF outcome of increased and premature exposure to androgens or overweight during childhood. Information about CRF of adolescent PA individuals is lacking and comparable studies are few. Premature and excessive androgen exposure, similarly to PA, is also experienced by children with congenital adrenal hyperplasia (CAH). CAH is a genetic condition characterized by enzymatic defects in steroid biosynthesis pathways since childhood, leading to many clinical and biochemical findings that overlap with those sometimes found among women with PA [37]. Of note, regardless of the similarity in timing of excessive androgen exposure, PA and CAH differ in important ways—hyperandrogenism in CAH lasts longer and CAH patients are normally treated with glucocorticoids, which might independently impact CRF. Marra et al [38] studied hyperandrogenic adolescents with CAH (mean age, 13.6 years) and found the peak workload to be reduced compared with a group of controls with juvenile idiopathic arthritis, who were also treated with glucocorticoids. Nevertheless, results of our study suggest that excessive androgen exposure during childhood is insufficient to impact adulthood CRF.

Regarding the impact of overweight in childhood, in 1 longitudinal study, BMI at childhood was shown to negatively correlate with CRF at young adult age [39]. This study, however, also showed that if the high prepubertal BMI decreases by adolescence, subjects have similar CRF at young adult age compared with those with normal BMI at preschool age. Our studies are in line with these conclusions: previously shown prepubertal differences between the PA and control girls in weight and body composition attenuated by adult age [18], CRF between the adult PA and control women were similar, and childhood BMI SD score failed to predict adulthood CRF.

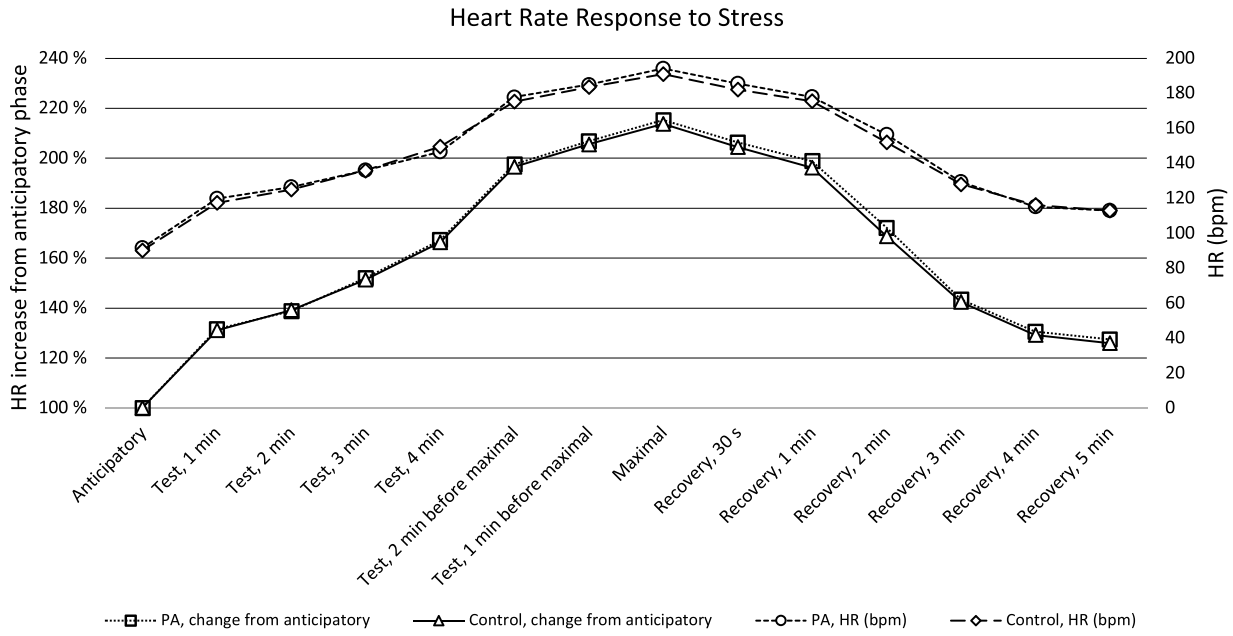

Figure 1. Heart rate (HR) response to stress during maximal cycle ergometer test in young adult women with a history of premature adrenarche (PA) and controls. The figure depicts the mean change in HR from the anticipatory phase during the test (lines with square and triangle; as %; left y-axis) and the mean absolute HRs during the test (lines with circle and diamond; beats/min [bpm]; right y-axis). HRs were recorded continuously during the test using a 12-lead electrocardiography from the beginning of the pretest until the end of the posttest recovery phase. We did not detect any statistically significant differences in HR responses to stress between the study groups.

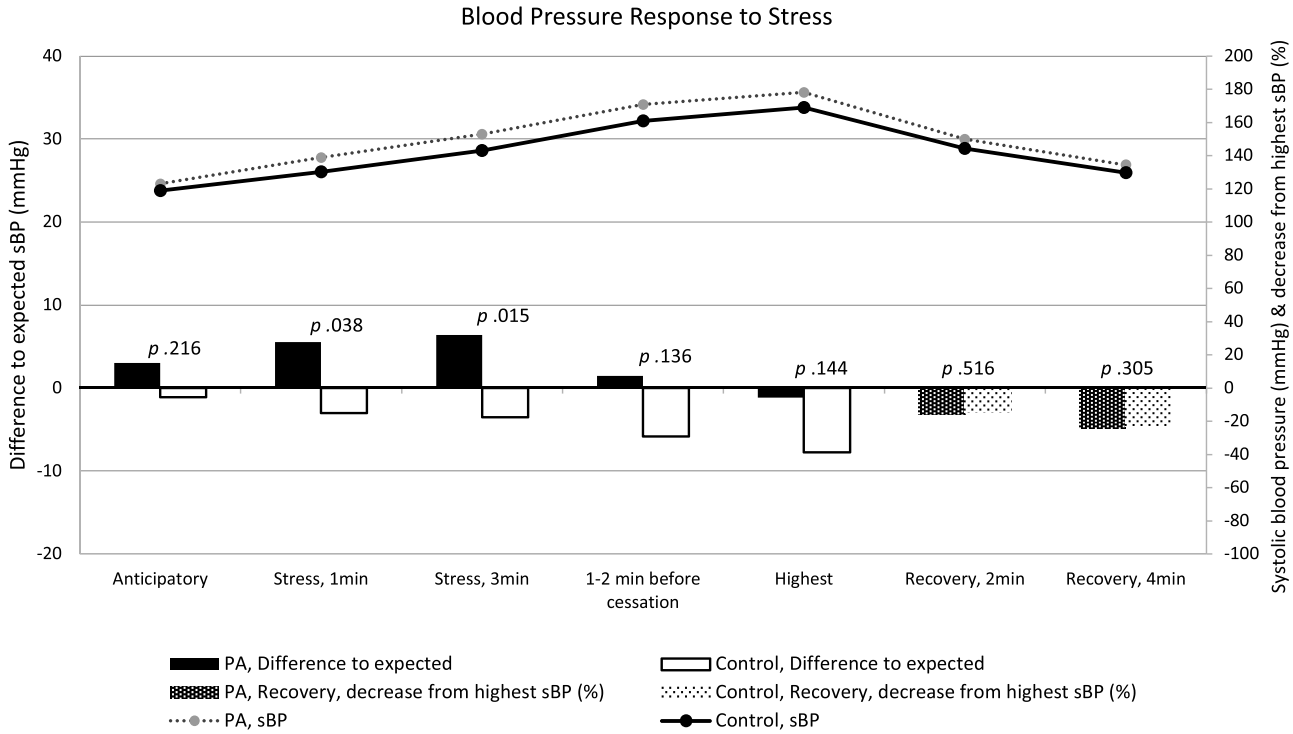

Figure 2. Blood pressure response to stress during maximal cycle ergometer test in young adult women with a history of premature adrenarche (PA) and controls. Figure depicts the mean absolute systolic blood pressures (sBP) during the different phases of the test (solid and dashed lines), the mean differences to expected sBP for the first 5 stress phases (white and black bars), and the mean percentage of sBP decrease during the recovery phases (filled bars). Blood pressure was recorded using an aneroid sphygmomanometer at anticipatory phase, in 2-minute intervals during the test, as close as possible to exhaustion, and twice during the recovery phase. Expected sBP was calculated as 120 + 0.333 × achieved load. For the 1 to 2 minutes before the cessation phase, the achieved load was calculated with the following formula: 120 + 0.333 × (maximal workload – 90 seconds × (20 W/60 seconds)). A mixed linear model for the first 3 and last 2 phases detected no significant differences between the groups ($P = .206$). sBP recovery calculated as (1 – (sBP/highest sBP)) × 100.

There is a certain degree of freedom, then, in the strength of androgen exposure, weight, and body composition during childhood and adulthood that, with other characteristics being equal, lead to no significant changes in long-term outcomes of CRF. Women with PA seem, according to this study, to be mostly within this window of outcome normalcy when it comes to CRF. Multiple factors, of which many seem more important than those associated with PA, modulate this window so that a subgroup of PA women with hyperandrogenism, overweight, and/or disturbances of glucose metabolism in adulthood might be disposed to altering of CRF similarly to women with PCOS.

The strength of our study is the prospective design, which also allows us to analyze possible predictive factors for outcome variables. Limitations include a relatively small sample size, which may affect the statistical power of the analyses, and the lack of respiratory gas analyses in the ergometer test. The findings of the present study should be confirmed by larger studies, and it remains to be seen whether a history of PA is overrepresented in elite athletes, or whether there are subgroups among women with PA who are more predisposed to deterioration of CRF than other women with PA.

In conclusion, our study suggests that PA induced prolonged and premature hyperandrogenism in childhood/adolescence, by itself, does not have a significant impact on adulthood CRF.

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Author Contributions

P.U., J.L., J.J., and R.V. designed and prepared the study; P.U. and J.L. prepared and carried out the clinical research visits; P.U., J.L., and J.J. created and constructed the database; J.T., J.L., T.L., and J.J. designed and performed statistical approaches and analyses; J.T. wrote the manuscript; J.J., P.U., R.V., T.L., and J.L. performed critical review of the manuscript; all authors read and approved the final manuscript.

Disclosures

The authors have nothing to disclose and report no conflict of interest in this work.

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.

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