Follow-up of growth and puberty in children with premature adrenarche

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BACKGROUND

Children with premature adrenarche (PA) have enhanced prepubertal growth in height and they are more often overweight than healthy peers (1). Insulin-like growth factors (IGF) play a role in pubertal initiation (2) and elevated serum IGF-1 levels have been reported in children with PA (1,3). Earlier menarcheal timing has been reported in girls with premature pubarche and PA (4,5).

OBJECTIVE

The aim of this follow-up cohort study was to evaluate growth and pubertal development in PA children. We hypothesized that children with PA have earlier pubertal development than healthy controls. Also prepubertal factors predicting earlier menarche were investigated.

METHODS

Seventy-three PA children and 99 healthy controls were originally recruited into this study. Other causes of hyperandrogenism were excluded. Birth data were collected from medical records. Laboratory samples were taken at diagnosis/ first study examination at the mean age of 7.6 years. Altogether 61.6 % participated (36 PA, 52 control girls; 7 PA, 11 control boys) in the follow-up study including the assessment of anthropometric measures and pubertal status at the mean age of 12.1 years. Pubertal status was assessed by Tanner staging scores. Birth length SDS, birth weight SDS, height SDS and BMI SDS were calculated with current Finnish growth references. All statistical analyses were performed with the SPSS 21.0 software (SPSS Inc., Chicago, IL). Mann Whitney U ([a]) and independent samples t-test ([b]) were used to analyse differences in continuous parameters between the study groups. χ^2-test was used to evaluate statistical differences in the number of subjects with attainment of certain pubertal stage. Possible predictors of earlier menarche were analyzed by logistic regression.

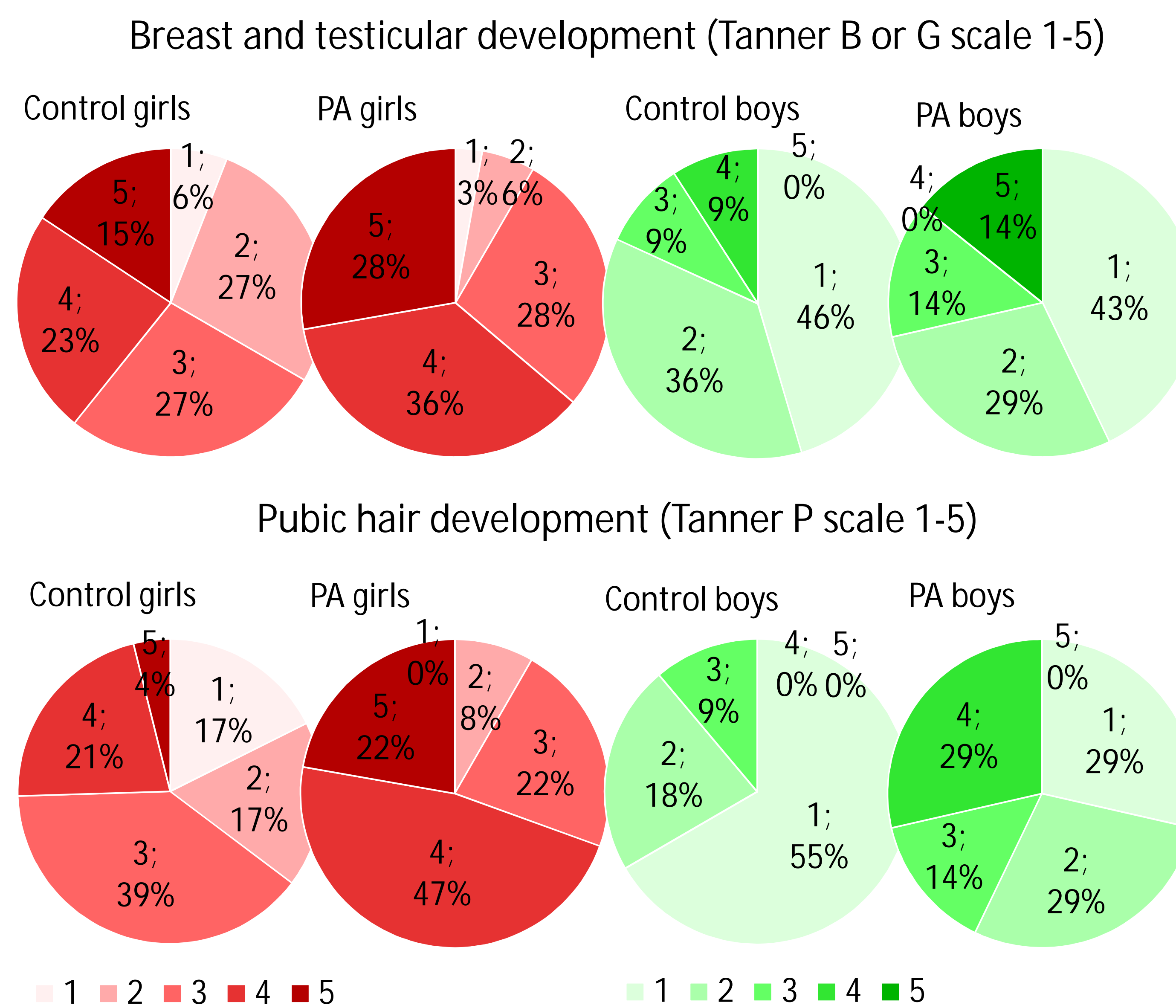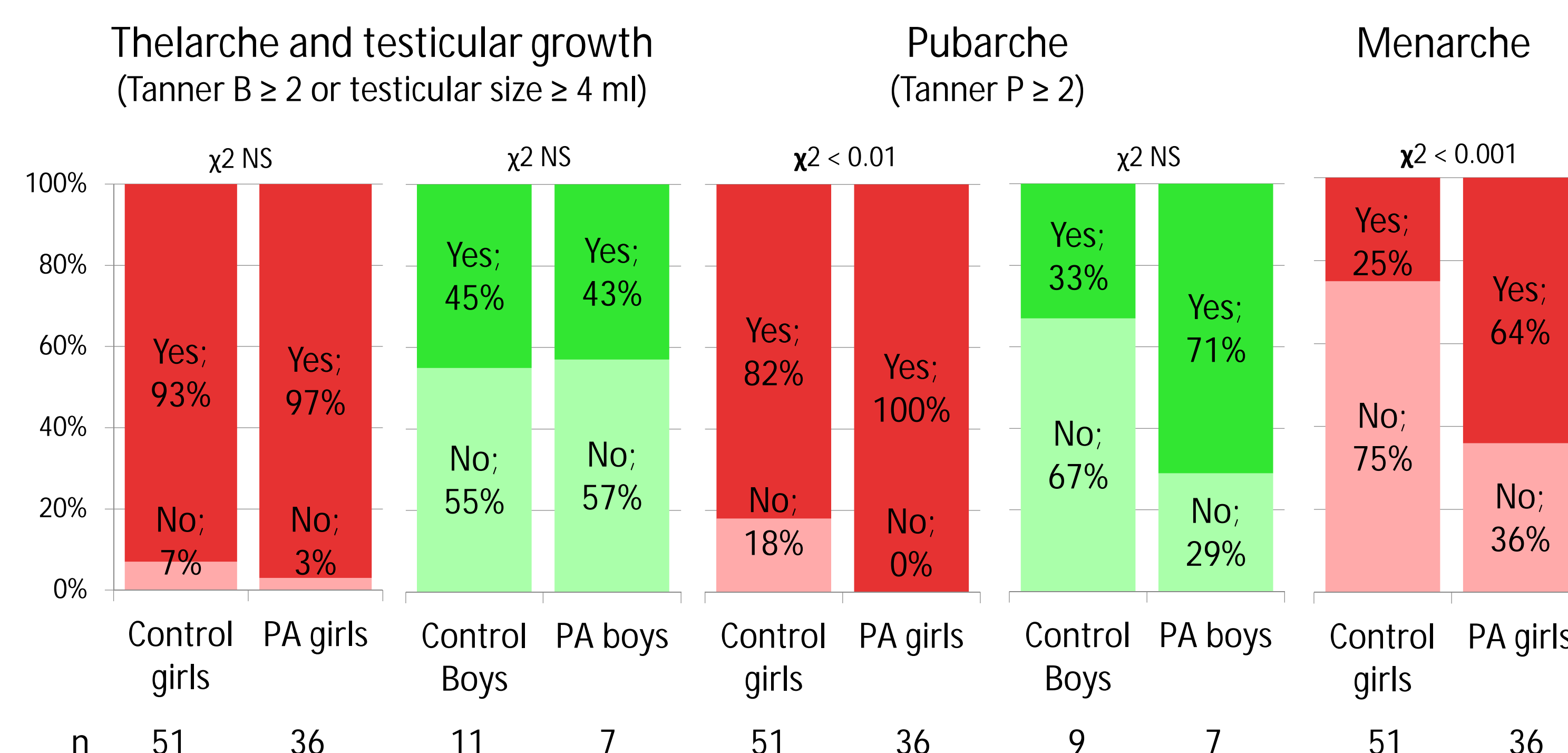Figure 1. Pubertal development in 12-year-old PA and control girls and boys.

Breast and testicular development (Tanner B or G scale 1-5)

Control girls, PA girls, Control boys, PA boys

Pubic hair development (Tanner P scale 1-5)

Control girls, PA girls, Control boys, PA boys

Table 1. Characteristics of all girls at birth (A), at the age of 7 years (B) and at the age of 12 years (C). Values are expressed as mean (95% CI). No statistical differencies were seen in boys.

A	Girls		
	Control (n=52)	p	PA (n=36)
Gestational age (weeks)	39.8 (39.1—40.4)	NS[a]	39.9 (39.1—40.7)
Birth weight (kg)	3.48 (3.30—3.66)	NS[a]	3.41 (3.18—3.63)
Birth length (cm)	50.2 (49.5—50.9)	NS[b]	49.4 (48.5—50.4)
B			
Age (yr)	7.5 (7.3—7.7)	NS[a]	7.6 (7.3—7.8)
Height SDS	-0.16 (-0.46—0.14)	<0.001[b]	1.02 (0.64—1.40)
BMI SDS	0.18 (-0.11—0.47)	<0.001[b]	1.04 (0.65—1.43)
DHEAS (µmol/l)	0.94 (0.79—1.09)	<0.001[a]	2.33 (1.94—2.72)
Androstenedione (nmol/l)	1.65 (1.39—1.92)	<0.001[a]	3.18 (2.71—3.66)
Insulin (mU/l)	4.83 (4.03—5.63)	<0.01[a]	5.98 (5.14—6.83)
IGF-1 (nmol/l)	20.3 (18.5—22.1)	<0.01[a]	25.3 (22.7—27.9)
C			
Age (yr)	12.1 (12.0—12.1)	NS[a]	12.1 (12.0—12.1)
Height (cm)	153.3 (151.4—155.2)	<0.001[b]	160.1 (157.4—162.9)
Height SDS	-0.08 (-0.35—0.20)	<0.001[b]	0.88 (0.48—1.28)
Weight (kg)	45.4 (42.6—48.2)	<0.001[a]	56.0 (51.4—60.6)
BMI (kg/m²)	19.2 (18.2—20.1)	<0.01[a]	21.6 (20.3—23.0)
BMI SDS	0.13 (-0.15—0.41)	<0.01[b]	0.81 (0.49—1.14)

Table 2. Predictive factors for menarche by logistic regression analysis. Values are expressed as OR (95% CI).

	Logistic regression analysis Dependent variable: Menarche (yes or no)			
	Univariate	p	Multivariate	p
Age (years)	0.41 (0.11—15.12)	0.63	Exc	
PA	5.17 (2.05—13.07)	<0.01	7.17 (1.24—41.34)	<0.05
Maternal age at menarche (years)	0.26 (0.13—0.55)	<0.001	0.23 (0.08—0.67)	<0.01
BMI SDS	1.96 (1.29—2.96)	<0.01	Exc	
DHEAS (µmol/l)	1.72 (1.09—2.71)	<0.05	Exc	
Androstenedione (nmol/l)	1.70 (1.18—2.44)	<0.01	Exc	
Insulin (mU/l)	1.28 (1.06—1.55)	<0.05	Exc	
IGF-1 (nmol/l)	1.14 (1.06—1.23)	<0.001	1.15 (1.01—1.32)	<0.05
	Multivariate R square:		0.68	

Figure 2. Percentage of pubertal children at 12 years of age among PA and control girls and boys.

	Control girls	PA girls	Control Boys	PA boys	Control girls	PA girls	Control Boys	PA boys	Control girls	PA girls
n	51	36	11	7	51	36	9	7	51	36

RESULTS

Cohort characteristics (here for girls only) at birth, at baseline (mean age 7.6 years) and at 12 years are presented in Table 1. At the current follow-up examination, the PA girls but not the boys were taller and heavier than the controls. A trend towards more advanced pubertal development was seen in all PA subjects (Figure 1) but only menarche and pubarche in girls reached statistical significance between the groups (Figure 2). The same percentages of the PA and control boys were at Tanner genital stage ≥2 (Figure 2). In a univariate logistic regression model, having a history of PA, earlier maternal menarche, higher childhood BMI, serum DHEAS, androstenedione, IGF1, and insulin concentrations were all associated with the earlier appearance of menarche. However, in a multivariate stepwise forward model, only the history of PA, earlier maternal menarche, and higher IGF-1 were significantly associated with early menarche (Table 2).

DISCUSSION

Our PA girls had advanced pubertal development and linear growth, and they had remained slightly heavier compared to control girls at 12 years of age. In boys, larger cohorts need to be evaluated. Future research will show if these chances in body composition persist into adulthood. Prepubertal serum IGF1 level and the history of PA are associated with earlier timing of menarche.

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