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Children with a History of Premature Adrenarche Have Good Health-Related Quality of Life at the Age of 12 Years

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Background/Aim: Children with premature adrenarche (PA) are taller and more overweight than their healthy peers, and PA girls have a slightly accelerated pubertal development. There is some evidence that early exposure to androgens may have an influence on psychosocial development. The aim of this cross-sectional case-control study was to evaluate health-related quality of life (HRQoL) in PA children at the age of 12 years. **Methods:** The HRQoL was assessed for 43 PA (36 girls) and 63 control children (52 girls) at the median age of 12.0 years using the standardized 16D instrument, and the scores of the PA children were compared to those of the control children and reference population. **Results:** The mean overall HRQoL scores did not differ between PA and control girls, PA and control boys, or all PA and control children or the reference population. Independently of PA, overweight girls had a lower mean overall HRQoL score than lean girls, and both overweight girls and boys were on average worse off on the dimension of appearance than their lean peers. **Conclusions:** PA children have as good self-rated HRQoL as their peers at the age of 12 years. Overweight is associated with a

worse HRQoL profile independently of PA.

Abstract Second Language

Abstract Third Language

Key Messages

Body

Introduction

Premature adrenarche (PA) is diagnosed when early adrenal androgen exposure leads to clinical signs (adult-type body odor, oily hair and skin, comedones/acne, axillary or pubic hair) before the age of 8/9 years in a girl/boy and other causes of hyperandrogenism have been excluded [1, 2]. Children with PA have slightly advanced bone age, and they are typically tall for age and overweight already in early childhood [1]. Girls with a history of PA [3] or higher serum dehydroepiandrosterone sulfate (DHEAS) concentrations [4] have accelerated pubertal development. Despite the relatively high prevalence, long-term outcome of PA has not been well studied. Especially, the psychosocial burden of PA is not known.

Adrenal androgen precursors, dehydroepiandrosterone and DHEAS, are neuroactive and neuroprotective steroids capable of remodeling neuronal network and functions [5]. It has recently been suggested that earlier timing of adrenarche and higher concentrations of adrenal

androgens may be associated with psychopathology in children [6]. In one case-control cohort, prepubertal girls with premature pubarche (PP), some with low DHEAS concentrations, had a higher rate of oppositional defiant disorder and higher symptom counts reflecting anxiety, mood or disruptive behavior disorders than the control girls [7]. In another study, however, there were no differences in psychological assessments between prepubertal PA girls and girls with early normal or precocious puberty [8].

Exaggerated androgenic signs, overweight, enhanced growth and pubertal development, and possible psychopathological effects of earlier exposure to adrenal androgens might all have an impact on emotional and social well-being in PA children. Non-disease-specific and multidimensional health-related quality of life (HRQoL) instruments are multipurpose tools to evaluate a self-rated state of health encompassing emotional, physical, and social components. Based on the 15-dimensional HRQoL (15D) instrument for adults [9], there is also a modified 16-dimensional (16D) instrument for adolescents [10]. Overweight is known to be negatively associated with an individual's HRQoL [11], but to date there are no published studies investigating HRQoL in children with PA. In this study, our objective was to determine the association between PA and self-reported HRQoL at the age of 12 years using the 16D instrument.

Patients and Methods

Subjects and Study Design

Our original case-control cohort included 73 children with PA and 99 age- and gender-matched healthy controls, all Caucasian, evaluated at the mean age of 7.6 years [12]. We invited all these children to attend a follow-up visit at the age of 12 years. Altogether 106 children participated (61.6%; 36/7 PA and 52/11 control girls/boys, respectively) and they were re-examined at the pediatric outpatient clinic at Kuopio University Hospital. The PA children had

presented with at least one clinical sign of adrenal androgen action before the age of 8/9 years (girls/boys, respectively) together with a serum DHEAS concentration exceeding 1 $\mu\text{mol/L}$ (=37 $\mu\text{g/dL}$), and other causes of hyperandrogenism had been excluded. More detailed clinical follow-up data of the cohort at the age of 12 years have been published recently [3]. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, and informed consent was obtained from the children and their parents in accordance with the ethical principles stated in the Declaration of Helsinki.

HRQoL Instrument

For measuring self-reported HRQoL, we used the standardized 16D instrument [10]. The dimensions of the 16D questionnaire include mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, school and hobbies, mental function, discomfort and symptoms, depression, distress, vitality, appearance, and friends. For each dimension, the respondent was asked to choose the level (on a scale of 1--5, with 1 indicating the best and 5 the worst level) that best describes her/his current state of health. The single index score (16D score), representing the overall HRQoL on a 0--1 scale (1 = full health, 0 = being dead) and the dimension level values, reflecting the goodness of the levels relative to no problems on the dimension (=1) and to being dead (=0), are calculated from the health state descriptive system (questionnaire) by using a set of population-based preference or utility weights. These weights have been elicited from a sample of 12- to 15-year-old adolescents from schools in the Helsinki metropolitan area. The mean dimension level values are used to draw 16D profiles for groups. The minimum clinically important difference in the 16D score was assumed to be similar to that for the 15D score, i.e., 0.015 [13]. The HRQoL scores of the PA subjects were compared to those of the controls and the age- and gender-standardized general population from 4 schools in the Helsinki metropolitan area.

Clinical Evaluation

Height was measured with a calibrated Harpenden stadiometer (Holtain Ltd., Crymych, UK) and recorded to the nearest 0.1 cm as the mean of three repeated measurements, and weight was measured with a calibrated scale recorded to the nearest 0.1 kg. Anthropometric standard deviation scores (SDS) were calculated with the current Finnish growth references [14]. BMI SDS cut-off values for overweight were 1.16 and 0.78 for girls and boys, respectively, which both correspond to a BMI of 25 kg/m² at the age of 18 years. Pubertal development was evaluated with Tanner staging scores, and menarche was recorded by interviewing the girls and their parents.

Statistical Analyses

All statistical analyses were performed with the SPSS 23.0 software (IBM corp., Armonk, NY). The Shapiro-Wilk test was used to evaluate the distribution normality of all continuous parameters. Statistical significances of the differences in the means between the study groups were tested with the independent samples *t* test and those in the distributions (medians) with the Mann-Whitney U test (normally/nonnormally distributed parameters, respectively). A univariate linear model was used to assess whether the differences between the study groups in HRQoL results were independent of confounding factors, and the Pearson χ^2 test was used to compare differences between the study groups in crosstab settings. *p* values <0.05 were considered statistically significant.

Results

Cohort characteristics with anthropometry and pubertal development are shown in [Table 1](#) [for more detailed background data, see [3](#)]. The data were analyzed separately for girls and boys. The PA girls were on average taller with higher BMI SDS, and a higher percentage of the PA girls had reached menarche compared to the control girls at the age of 12 years. Altogether

41.7% of the PA girls (15/36), 21.2% of the control girls (11/52), 42.9% of the PA boys (3/7), and 45.5% of the control boys (5/11) were overweight or obese.

HRQoL Analyses

HRQoL results are illustrated in [Figure 1](#) a–c: PA versus control girls; PA versus control boys, and the whole PA cohort versus the control cohort or general population. The mean overall 16D scores were similar in these three comparisons. In more detailed analyses at the dimensional level, the PA girls were on average worse off on the dimension of speech than the control girls (0.96 vs. 1.00, $p = 0.044$) and both all PA and control children were on average better off on the dimensions of depression, distress, and vitality compared to the population reference ([Fig. 1](#)). The difference on the dimension of speech between the PA and control girls remained significant also after adjustment for BMI SDS. No other statistically significant differences were found between the PA and control children or the reference population.

When comparing the mean HRQoL scores in the whole cohort between the overweight and nonoverweight children, overweight girls, but not boys, had a lower mean 16D score than their nonoverweight peers (0.952 vs. 0.975, $p = 0.042$ and 0.949 vs. 0.949, $p = 0.994$, respectively). At the dimensional level, both overweight girls and boys were on average worse off on the dimension of appearance than the normal-weight girls and boys (0.861 vs. 0.957, $p = 0.015$ and 0.778 vs. 0.972, $p = 0.014$, respectively). These differences in the mean overall 16D score between the overweight and nonoverweight girls and in the mean score on the dimension of appearance between the overweight and nonoverweight girls and boys remained also significant after adjustment for PA. When analyzing only overweight children, no significant differences in the HRQoL scores were found between the PA and control girls or boys.

Discussion

This case-control study investigated the association between PA and HRQoL at the age of 12 years and showed that the mean overall 16D scores did not differ between PA and control girls, PA and control boys, or all PA and control children. At the dimensional level, only one statistically significant difference was found between PA and control girls/boys: the PA girls were on average worse off on the dimension of speech than the control girls, and the difference remained significant also after adjustment for BMI SDS. On the speech dimension, the respondent was asked about difficulties to produce clear talk on a 5-level scale. The worst level (5) describes that the respondent can communicate only with gestures and the best level (1) that he/she has no difficulties in speaking. The levels between 1 and 5 include abrupted or quiet voice and stammering. The difference seen on this dimension may reflect that the PA children in our cohort may be more insecure in social interactions than the control girls. However, the mean score on the dimension of speech for the PA girls did not differ when compared to the reference population.

To date, there are no published reports investigating HRQoL in PA cohorts. However, a previous study investigated psychosocial health in a cohort of prepubertal girls with PP [7]: PP girls had a higher rate of oppositional defiant disorder and more symptoms related to anxiety, social and specific phobias, depression and hyperactivity than the control girls. Additionally, these PP girls had more parent- and/or teacher-reported internalizing and externalizing symptoms, social and behavioral problems, and aggressive behavior [7]. On the other hand, psychological assessments were similar in PA girls and girls with early normal or precocious puberty in another study [8]. One may assume that if PA children have mental health problems or difficulties with social interaction due to psychopathology, worse self-rated quality of life could be expected. Our results suggest that children with PA have as good HRQoL as their peers at the age of 12 years, but we are not able to compare in a straightforward manner the data with previous studies as our setting was different without direct analyses of mental health and psychosocial symptoms.

Being overweight (often associated with PA) is negatively correlated to self-reported quality of life, and weight loss seems to improve HRQoL scores in overweight children [11]. In our cohort, independently of PA, overweight girls had a lower overall HRQoL score, and both overweight girls and boys were on average worse off on the dimension of appearance than their lean control peers. These findings are well in line with the previous studies showing a worse HRQoL profile in overweight children [11] probably reflecting dissatisfaction with their self-appearance.

Our present case-control study is the first one to evaluate HRQoL in PA children. The limitations include a relatively small sample size. The number of male participants was too small to come to any definite conclusions. Additionally, both PA and control cohorts were on average better off on the dimensions of depression, distress, and vitality than the reference population. This may indicate a potential study bias in which: (1) children with problems on these dimensions may not have been willing to participate in this follow-up study (i.e., participation bias) or (2) children participating in this study may be more prone to embellish their answers in the HRQoL questionnaire (i.e., self-report response bias).

In conclusion, self-reported HRQoL in children with PA is good and does not differ from peers at the age of 12 years. Overweight is associated with lower HRQoL independently of PA.

Disclosure Statement

H.S. declares that he is one of the developers of the 16D instrument. J.L., P.U., R.V., and J.J. declare no conflict of interests. No financial support has been received from anyone benefitting from the results, and the institutions above had no role in: (1) study design; (2) the collection, analysis, and interpretation of data; (3) writing the report, and (4) the decision to submit the paper for publication.

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Appendix after References (Editorial Comments)

Legend(s)

Fig. 1. Self-reported HRQoL comparing PA and control girls (**a**), PA and control boys (**b**), and the whole PA and control cohorts or general population at the age of 12 years (**c**) using the 16D HRQoL instrument. For each dimension, the respondent was asked to choose the level (on a scale of 1–5, with 1 indicating the best and 5 the worst level) that best describes her/his current state of health. The index scores on a 0–1 scale represent the overall HRQoL (0 = being dead, 1 = no problems on any dimension). The differences between the mean level values of the PA and controls or general population are

compared using the independent samples *t* test. The differences in the mean overall 16D scores between the study groups were not statistically significant. Statistically significant differences between the PA and control girls (*) or all PA children and the reference population (+, #, §): 0.962 versus 1.000, **p* = 0.044; 0.959 versus 0.897, +*p* = 0.003; 0.927 versus 0.878, #*p* = 0.034; 0.965 versus 0.831, §*p* < 0.001. PA, premature adrenarche; 16D score, overall score in the 16-dimensional HRQoL test.

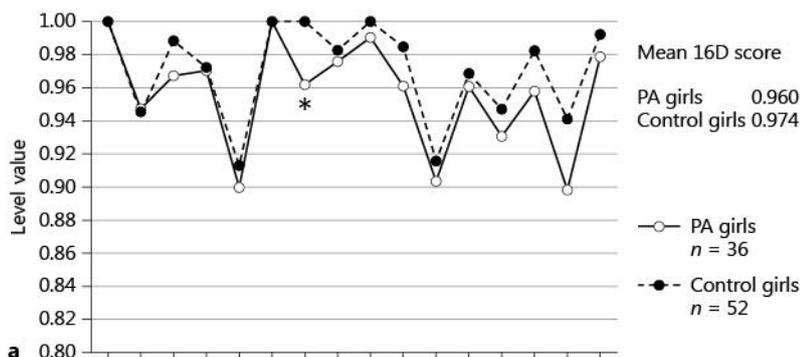
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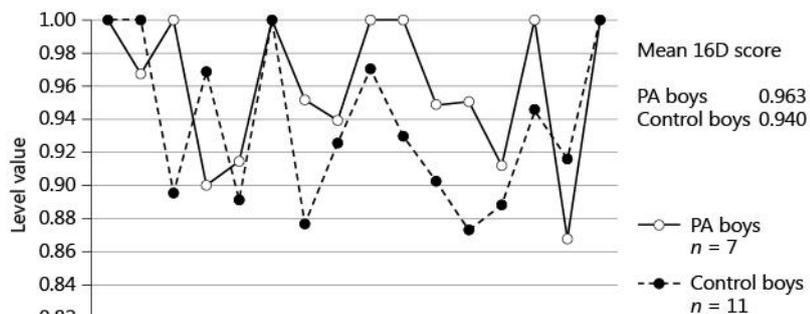
Table 1. Characteristics of the PA and control children at the age of 12 years [modified from 3]

	Girls			Boys		
	PA (<i>n</i> = 36)	control (<i>n</i> = 52)	<i>p</i>	PA (<i>n</i> = 7)	control (<i>n</i> = 11)	<i>p</i>
Age, years	12.0 (12.0 to 12.1)	12.0 (12.0 to 12.1)	0.42 ^a	12.2 (11.9 to 12.3)	12.0 (11.9 to 12.1)	0.13 ^a
Height SDS	0.88 (0.48 to 1.28)	-0.08 (-0.35 to 0.20)	<0.001	0.19 (-1.46 to 1.84)	0.16 (-0.44 to 0.77)	0.97
BMI SDS	0.81 (0.49 to 1.14)	0.13 (-0.15 to 0.41)	<0.01	0.92 (-0.23 to 2.06)	0.66 (-0.12 to 1.44)	0.66
Thelarche or testicular enlargement, yes % ¹	97.2	94.1	0.50 ^b	57.1	54.5	1 ^c
Menarche, yes %	63.9	25.0	<0.001^b	Not applicable		

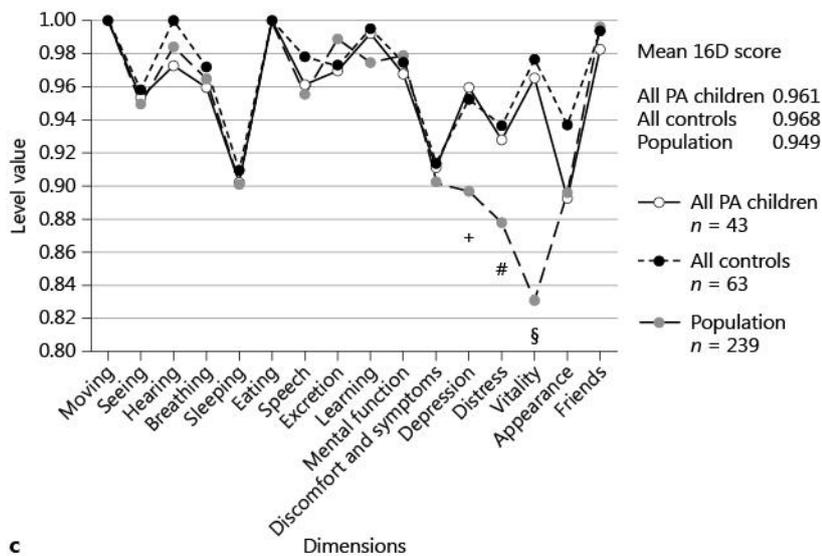
Values are expressed as mean (95% confidence interval), and statistical significance of the differences between the study groups is analyzed using independent samples *t* test, unless noted otherwise. PA, premature adrenarche; SDS, standard deviation score; BMI, body mass index. ^a Median (interquartile range) and Mann-Whitney U test for nonnormally distributed variables. Percentage and ^b Pearson χ^2 test or ^c Fisher's exact test for categorical variables. ¹ Tanner B \geq 2 for girls or testicular volume \geq 4 mL for boys, *n* = 51 for control girls.



a



b



c