Socioeconomic Status Is Related to Pubertal Development in a German Cohort

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Keywords
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Abstract
Introduction: Current health literature suggests that there has been a decline in the age of pubertal onset and that pubertal onset/duration of puberty may, besides weight status, be influenced by socioeconomic context. Objective: The goal of this study was to determine whether pubertal onset/duration and puberty-triggering hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) vary according to socioeconomic status (SES). Moreover, we aimed to propose cutoff values of serum LH and FSH for predicting gonadarche in boys. Methods: 2,657 apparently healthy children and adolescents between 5.5 and 18 years from the area of Leipzig were recruited from the LIFE Child study. Age at pubertal onset/end of puberty was given in 738/573 children, respectively. Anthropometric parameters of pubertal blood measurements of LH and FSH, and questionnaires assessing SES were evaluated. Results: Lower SES was associated with earlier thelarche and longer duration of puberty in overweight/obese girls, whereas age of menarche was not affected. In boys with low SES, a trend versus earlier puberty onset can be seen. Lower SES was significantly associated with boys’ age at mutation. No significant differences in boys’ and girls’ serum levels of LH and FSH during puberty according to SES were observed. Serum LH levels of 0.56 IU/L and serum FSH levels of 1.74 IU/L showed the best prediction of gonadarche in boys. Conclusion: Puberty onset/duration and boys’ age at mutation is affected by SES. The proposed cutoff levels for serum LH and FSH could provide a serological tool to determine gonadarche in boys.

Introduction
For a better understanding of children’s and adolescents’ sexual and reproductive health, it is important to have access to up-to-date, region-specific data on pubertal timing. Puberty as a critical time of growth and development is influenced by a range of genetic, environmental, and lifestyle factors [1, 2]. Variation in pubertal timing may affect health risks. Previous studies showed that early puberty [3] or early menarche [4, 5] might lead to adverse outcomes such as increased substance use [3], earlier sexual activity [4], and increased risk of breast can-

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In addition, late maturity among boys has been associated with behavior problems [6] and lower educational attainment [7]. For quite some time, research discusses the association of elevated BMI with earlier puberty [8]. Additionally, growing scientific evidence points to an association of children’s socioeconomic status (SES) with a wide array of health-related, cognitive, and socio-emotional outcomes [9–11]. The German Health Survey for Children and Adolescents (KiGGS) showed that children and adolescents with low SES are half as likely to have good general health as those with high SES [11]. We could recently demonstrate a strong association between SES and child health and development [9]. A low SES was, for example, associated with emotional disorders, behavioral problems, a less healthy lifestyle, and less physical activity [9, 12, 13]. Despite the strong link between SES and different aspects of child health, research results are inconclusive with regard to the influence of SES on pubertal timing. An Australian cohort study showed that exposure to socioeconomic disadvantage predicts earlier puberty onset in both girls and boys [14] and a Canadian study found that adolescents with high SES were less likely to have entered puberty by the age of 13 [2]. Other studies from the USA and Germany showed that lower SES is associated with earlier menarche [11, 15, 16]. However, a recent meta-analysis, that also included studies from less developed countries, did not find a significant association between low SES and early pubertal timing [17]. So far, little research activity has focused on associations between SES and the duration of puberty.

Our study provides current data on critical steps during pubertal development in healthy adolescents from the German LIFE Child study cohort. Moreover, we investigated whether there is an association between SES and pubertal onset/duration as well as age at menarche and mutation. Finally, we investigated whether SES relates to serum values of the puberty-triggering hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and propose a cutoff value of serum LH and FSH for predicting gonadarche in boys.

Methods

Study Population

Our study originates from the LIFE Child Study, which is a part of the Leipzig Research Centre for Civilization Diseases (LIFE). LIFE Child aims at a better understanding of the etiology of lifestyle diseases. It collects detailed longitudinal and cross-sectional information from children and adolescents with mostly Caucasian ethnic background aged 0–20 years as well as from their parents. Precise study characteristics are described elsewhere [18]. For the present study, data from children and adolescents between 5.5 and 18 years with annual visits from 2011 to 2019 were analyzed. After applying the exclusion criteria (Fig. 1), the sample consisted of 7,986 visits from 2,657 children.
Anthropometric Indicators of Puberty and BMI

The pubertal stage was assessed for both sexes according to Tanner [19, 20] by well trained, qualified personnel. The breast developmental stage (B) in girls was evaluated by palpation of glandular breast. The median age at onset of puberty was estimated as the age at which 50% of the study subjects entered pubertal stage 2 (defined as age when both of the following conditions meet: (a) for males testicular volume >3 mL [21] and pubic hair stage (PH) 1 or 2 and (b) for females B2 and PH1–3). Therefore, pubertal onset in girls was mainly defined by the onset of thelarche. Pubertal stage 5 was considered as mature and defined both as a testicular volume ≥7 mL and PH5 or PH6 in boys and both B5 and PH4–6 in girls. Median end of puberty was estimated as the age at which 50% of the study subjects entered pubertal stage 5. Because too few subjects had both a known entry and end of puberty, the duration of puberty was defined by the time interval from the median pubertal onset to the median end of puberty in each subgroup. Age at menarche was obtained from 576 girls. 452 boys provided information about their age at mutation (voice change). Children's height, weight, and BMI-SDS were assessed as described before [18]. All subjects were assigned to 1 of 2 weight groups according to the criteria of the German Obesity Task Force Group [22]. BMI-SDS from −1.28 to +1.28 was defined as normal weight (NW) and above +1.28 as overweight or obese (OW). Children with a BMI-SDS below −1.28 were excluded from analyses.

Socioeconomic Status

The SES of children was assessed at their first visit recorded in the data using the “Winkler-Stolzenberg-Index” [9, 12, 13, 23]. This index comprises 3 scales measuring parental education, occupational status and household equivalized disposable income (for more information see [23]). In the case of missing values in 1 of the 3 scales, it was substituted by the mean of the remaining 2 indicators. The resulting scale ranges from 3 to 21 points. Based on the score, 3 categories of SES were defined: low (3–8 points), mid (9–14 points), and high (15–21 points).

Laboratory Measures

Blood samples were collected between 7.30 and 10.30 a.m. in a fasting state. Samples were sent to the Institute of Laboratory Medicine, University Hospital of Leipzig, for analysis on the same day. LH and FSH were analyzed by electrochemiluminescence immunoassay (Roche, Mannheim, Germany). The assay was performed according to the specification of the manufacturer. The detection limit was 0.1 IU/L. For LH, intra-assay coefficients of variation (CV) were ≤1.2% and inter-assay CVs were ≤2.2% at the concentration range of 6.2–164 IU/L. For FSH, intra-assay CVs were ≤2.8% and inter-assay CVs were ≤4.5% at the concentration range of 6.0–178 IU/L.

Statistics

BMI was transformed into age- and sex-adapted standard deviation scores (SDS) according to the German standards [22]. For determining puberty onset, hierarchical logistic regression analyses were conducted stratified by sex. To account for multiple measurements per person, hierarchical models were applied, adding the subject as a random intercept. LH and FSH levels were compared between the different pubertal stages applying an ANOVA.
followed by the Tukey Honest Significant Difference test. LH- and FSH-cutoffs for puberty onset were obtained using ROC analysis. All statistical analyses were performed with the statistical software R V.3.4.0.

**Results**

**Study Characteristics**

2,657 children (48.7% female) with a total of 7,986 visits were included. Demographic background characteristics of the study sample are presented in Table 1. A low SES was less frequently observed than a mid or a high SES. Children with low SES were more likely to be OW compared to children with middle or high SES.

**Anthropometric Parameters of Pubertal Development**

Puberty started earlier and lasted longer in girls than in boys (Table 2). The median age of pubertal onset was 10.18 years in girls and 11.01 years in boys. The median age when reaching pubertal stage 5 was 14.77 years in girls and 15.24 years in boys. The duration of puberty was 4.59 years in girls and 4.23 years in boys. In girls, the median age at menarche was 12.55 years, whereas in boys the median age of voice break was 13.26 years. In girls, higher BMI values were significantly associated with an earlier pubertal onset (NW: 10.3 years vs. OW: 9.51 years, \( p < 0.05 \)) and an earlier age at menarche (NW: 12.6 years vs. OW: 12.22 years, \( p < 0.05 \)). In boys, however, pubertal onset was not significantly associated with weight group. Lower SES values were associated with earlier puberty in OW girls (Fig. 2). Girls with low SES entered puberty at a median age of 8.97 years, whereas girls with mid- and high SES did not enter puberty until the age of 9.65 and 10.02 years, respectively. In other terms, at the age of 8.97 years, 50% of the girls with low SES had already entered puberty compared to 23% of the girls with mid-SES (\( p = 0.17 \)) and 3.8% of the girls with high SES (\( p = 0.05 \)). Furthermore, in OW girls with low SES, the duration of puberty was 1.15 years longer than in girls with high SES (4.91 vs. 3.76 years). In both NW and OW boys with low SES, a trend toward earlier puberty was observed but did not reach statistical significance.

| Table 2. Parameters of pubertal development by gender, weight group 2 and 3, and SES |
|----------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                                        | Female           |                  |                  | Male             |                  |                  |
|                                        | age at pubertal onset, yr (n) | age at end of puberty, yr (n) | duration of puberty, yr | age at pubertal onset, yr (n) | age at end of puberty, yr (n) | duration of puberty, yr |
| All                                    | 10.18 (372)      | 14.77 (379)      | 4.59             | 11.01 (366)      | 15.24 (194)      | 4.23             |
| NW2                                    | 10.3 (301)       | 14.99 (295)      | 4.69             | 11.02 (301)      | 15.27 (154)      | 4.25             |
| Low SES                                | 10.23 (20)       | 14.65 (34)       | 4.42             | 10.73 (22)       | 15.24 (9)        | 4.51             |
| Mid-SES                                | 10.27 (192)      | 14.94 (178)      | 4.67             | 10.97 (170)      | 15.26 (79)       | 4.27             |
| High SES                               | 10.38 (80)       | 15.14 (58)       | 4.76             | 11.17 (102)      | 15.14 (57)       | 4.17             |
| OW3                                    | 9.51 (74)        | 13.94 (99)       | 4.43             | 10.95 (65)       | 15.12 (45)       | 4.17             |
| Low SES                                | 8.97 (25)        | 13.88 (29)       | 4.91             | 10.97 (15)       | 14.76 (10)       | 3.78             |
| Mid-SES                                | 9.65 (35)        | 14.05 (49)       | 4.4              | 10.92 (37)       | 15.10 (28)       | 4.18             |
| High SES                               | 10.02 (10)       | 13.78 (14)       | 3.76             | 11.24 (9)        | 15.41 (5)        | 4.17             |

Age is expressed as median. Importantly, lower SES values in OW girls were associated with earlier puberty onset and longer duration of puberty and in NW/OW boys with a trend toward earlier puberty onset and with higher/lower age at mutation. NW, normal weight; OW, overweight or obese; SES, socioeconomic status. 1 As defined by the time interval from the median pubertal onset to the median end of puberty in each subgroup. 2 NW = normal weight, as defined by BMI-SDS from −1.88 to 1.28. 3 OW = overweight or obese, as defined by BMI-SDS >1.28.
Fig. 2. The probability of puberty onset at each age according to gender (a, male; b, female), weight group\(^1,2\), and SES. Lower SES values were associated with earlier puberty in OW\(^2\) girls. \(^1\)NW as defined by BMI-SDS from −1.88 to 1.28. \(^2\)OW as defined by BMI-SDS >1.28. NW, normal weight; OW, overweight and obese; SES, socioeconomic status.
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In summary, lower SES values were (a) associated with earlier and longer puberty in OW girls and (b) with a trend towards earlier puberty and with later/earlier age at mutation in NW/OW boys.

**Gonadotropin Measurements**

The mean and standard deviation of serum LH and FSH values in boys and girls across different stages of puberty are shown in Figure 3. In boys, mean serum LH levels increased significantly from pubertal stages 1–5, mean serum levels of FSH changed significantly from pubertal stages 1–4 ($p < 0.001$). Based on the ROC-curve, the best cutoff value of serum LH for predicting gonadarche in boys was 0.56 IU/L with a sensitivity and specificity of 86 and 88%, respectively (Fig. 4). The area under the curve was 0.906 (CI: 0.892–0.921). The cutoff value of serum FSH was 1.74 IU/L with a sensitivity and specificity of 76%. The area under the curve was 0.841 (CI: 0.823–0.859). In girls, there was no significant change in LH levels between pubertal stages 1 and 2. An increase can only be seen from stages 2–4. Although serum levels of FSH rise significantly from pubertal stages 1–3, a possible cutoff for thelarche as determined by ROC analysis showed only poor sensitivity and specificity. Therefore, cutoff

**Fig. 3.** LH and FSH serum values in boys (a) and girls (b) during puberty. The black dot within the boxplot represents the mean (additionally labeled with mean ± SD). LH, luteinizing hormone; FSH, follicle-stimulating hormone; SD, standard deviation.
values of both LH and FSH seem inappropriate as serological markers for determining thelarche. No significant differences in girls’ and boys’ LH and FSH levels between the different SES groups were observed during puberty (results not shown).

Discussion

Pubertal Timing, BMI, and Socioeconomic Status in the Light of Existing Literature

Many countries are experiencing an epidemic of pediatric obesity, which is more prevalent in lower SES groups [24]. However, although it is well known that a critical body weight and/or fat mass must be achieved for the onset of puberty [25], the influence of BMI on pubertal development is still controversial [26–29]. In our study, elevated BMI was significantly associated with earlier thelarche in girls but not with earlier puberty in boys. This is in line with a large body of literature that supports the hypothesis that higher BMI is associated with earlier puberty in girls [28, 30–33]. However, a few controversial results in European cohort studies have also been published [26, 34]. In boys, the relationship between pubertal onset and BMI is less consistent [8, 11, 28, 29]. Despite the possible influence of BMI on pubertal timing, BMI was not found to (solely) mediate the associations between SES variables and pubertal onset [14], age at menarche [15], or breast development [24]. Our findings, too, suggest an effect of SES beyond the weight group effect. Especially, OW girls with low SES had earlier thelarche and longer puberty than OW girls with high SES. A Canadian study found girls from low SES enter puberty earlier and go through puberty at a slower pace [2]. A study from Australia, too, found an association of socioeconomic disadvantage and early puberty [14], whereas a recent meta-analysis did not find a significant association [17]. Regarding menarchal age, we found no associations with SES contrary to the German KiGGs study and studies from the US reporting a positive correlation [11, 15, 16]. In boys with low SES, we observed a trend of earlier puberty and an association of SES with age at mutation in both NW and OW boys. Interestingly, low SES was significantly associated with later mutation in NW boys, but, on the contrary, with earlier mutation in OW boys. However, these findings are based on self-reported data and should be viewed critically. Additionally, a comparison of pubertal timing between studies should be made carefully. Differences in design and composition of study cohorts, the methodology of measuring puberty onset and ongoing puberty as well as regional conditions differ widely and have to be seen in a geographical or ethnic context.
Socioeconomic Status and Pubertal Timing

Pubertal timing may play a mediating role between early social disadvantages and health disparities later in life as suggested by Sun et al. [14]. The mechanisms by which socioeconomic disadvantage might contribute to the risk of early puberty are not yet clear and thus, speculative. We discussed the possible impact of BMI on early puberty. BMI was not found to exclusively mediate the associations between SES variables and pubertal timing. There may be other environmental, behavioral, and physiological effects by which SES influences early pubertal development. An alternative pathway by which SES might mediate puberty onset is through increased exposure to stress associated with lower SES [2, 13, 35–39]. Results from the German KiGGS study suggest that children and adolescents with low SES are half as likely as those with high SES to have good general health; they were significantly more affected by psychological and behavioral difficulties [11]. Exposures to stress could influence physiological and psychological processes, resulting, for example, in cell/molecular damage [36], poorer emotional health [12], and health behavior, like reduced physical activity and poor diet [13]. Moreover, exposure to early life stress could influence both the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes and thus provide a link to advanced pubertal maturation [40]. Hochberg and Belsky [41] reviewed the understanding of pubertal maturation from an evolutionary life-history perspective. The life-history theory as a branch of evolutionary biology provides a theoretical framework for explaining the individual reproductive strategies that organisms use to allocate their limited time and energy to shaping the stages of their life. According to this theory, exposure to different childhood environments biases children toward different reproductive strategies that may include early pubertal timing [14, 37, 42]. The theory constitutes a set of assumptions. Belsky (1991) and Ellis (2004) proposed the psychosocial acceleration/developmental theory to account for the relationship between early pubertal maturation and environmental stressors, characterized by high levels of familial interpersonal stress and untrustworthy pair-bonds [37, 42]. Under such adverse conditions, girls show earlier and accelerated puberty because paternal investment is unreliable/not related to the reproductive success of offspring. Therefore, early puberty and a longer period of reproduction in children from disadvantaged contexts may also be seen as an advantage, though, according to Belsky (1991), probably more an advantage of quantity, less of quality [37]. On the metabolic level, the early stressful environment is supposed to lead to an internalization of problems, changes in metabolism and body fat and thus to an earlier onset of puberty [14, 37, 42]. Our study neither delivered data on early adverse life events nor biochemical markers of stress, and it gives no answer to the question of how this could influence centrally induced pubertal onset. Further research is needed to investigate the possibility of an evolutionary benefit of earlier puberty onset in case of a more demanding early environment.

Luteinizing Hormone- and Follicle-Stimulating Hormone-Serum Levels as Markers for Puberty Onset

It is well known that LH and FSH as mediators of pubertal development increase with advancing puberty. To estimate a cutoff value for serum LH (0.56 IU/L) and serum FSH (1.74 IU/L) as serological predictors of gonadarche in boys, we compared these measures to testicular volume, a widely used anthropometric standard in the determination of puberty onset in boys [43]. An earlier Argentinian study found an optimal LH-cutoff of 0.65 IU/L and an FSH-cutoff of 2.5 IU/L in boys based on laboratory measures of 20 boys [44]. An Indian study found an optimal LH-cutoff value comparable to ours (0.53 IU/L, AUC: 0.59) [45]. The AUCs of the present study indicates that pubertal boys can be distinguished from prepubertal boys by determining LH and FSH with high sensitivity and specificity. The cutoff value could help to verify the puberty onset, though its validity is yet uncertain. A single hormone measurement during clinical practice may not always predict pubertal onset among individual boys [46]. If verification of pubertal onset is needed, LH measurements following stimulation with gonadotropin-releasing hormone (GnRH) or a gonadotropin-releasing hormone analog may be required [47]. In girls, LH and FSH show a larger variability across all puberty stages (as indicated in Fig. 3). It was, therefore, impossible to determine a cutoff level for puberty onset with good validity measures for either parameter.

Strengths and Limitations

Our study has limitations worth noting. We determined the duration of puberty based on median values of onset and end of puberty. Longitudinal data from a larger sample would allow for determination of individual puberty courses. Despite the large amount of study subjects, case numbers at least in some subgroups are small. We did not evaluate data on diurnal rhythm of LH and FSH serum values. As is true for most population-based studies, families with mid- and high SES are over-represented...
in our study sample. Personal initiative and interest in health issues are necessary prerequisites and probably less pronounced in people with lower SES [48]. Because our study cohort includes an unintended selection of presumably more health-conscious families, it is possible that the observed effects may be even more pronounced in the target population. Our study does not contain data on SES in early childhood. In some cases, the SES at first visit might not be equal to the SES in early life years crucially relevant for child development. The main strengths of our study are the large sample size and the standardized assessment that allowed us to provide a variety of pubertal parameters. To the best of our knowledge, this is the first European study that examines the impact of SES not only on pubertal turning points like menarche and puberty onset but on the duration of puberty. Cutoff values for LH and FSH in boys were determined with high diagnostic sensitivity and specificity. LIFE Child is 1 of the largest running cohorts of healthy children and adolescents in Europe and, therefore, well suited for the determination of representative pubertal and hormone parameters.

Conclusion

In summary, we established pubertal parameters including puberty onset and duration, age of menarche/mutation, and pubertal hormone values of LH and FSH in a large sample of German children and adolescents. We showed that low SES is associated with earlier thelarche and longer puberty especially in OW girls and with a trend toward earlier puberty in boys. Finally, we propose cutoff values of serum LH and FSH to predict gonadarche in boys.

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Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent to publish their case (including publication of images). All examination methods were in accordance with the principles of the Declaration of Helsinki and with the ethical standards of the national research committee. This study was approved by the Ethical Committee of the University of Leipzig (reference number: Reg. No. 264-10-19042010) and is registered under the trial number: NCT02550236.

Conflict of Interest Statement

There are no competing interests to declare.

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Author Contributions

Wieland Kiess (W.K.) and Jürgen Kratzsch (J.K.) conceived the presented idea. Lea Oelkers (L.O.), Hans Surup, and Mandy Vogel (M.V.) developed the theory and performed the computations. M.V. verified the analytical methods. W.K., J.K., M.V., Agnes Kalenda, and Antje Körner discussed the results. L.O. drafted the manuscript, which was critically revised by all the authors.

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