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Rapid weight gain during infancy and pubic hair development onset in boys from a contemporary British cohort.

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Bachelor of Science

University of Maryland

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An abstract of

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Abstract

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By Laila Sara Noory

Specific Aims

The aim of the present study is to describe the relationship between weight gain during infancy and the entry into stage 2 or higher of pubic hair development in boys. The boys were enrolled prenatally from 1991-1992 in the Avon Longitudinal Study of Parents and Children (ALSPAC) who responded to the Growing and Changing questionnaire. Data was gathered on their self-assessed pubertal status between 8 and 14 years of age.

Methods

Repeated self-assessments of pubertal development were obtained from 3,938 boys between the ages of 8-14. Data on prenatal characteristics and weight at birth, 2, 9 and 20 months were obtained from questionnaires, birth records and clinic visits for 1,816 boys. Infant's weights were converted to weight-for-age SD scores and change values were obtained for age intervals from birth to 2 months, 2 to 9 months, 9 to 20 months and birth to 20 months. Parametric survival models were used to estimate associations with age of entry into Tanner stage 2 of pubic hair development.

Results

Maternal age at delivery, smoking in the 3rd trimester, primiparity and breastfeeding were individually associated with puberty onset. The adjusted model showed a 1-unit increase in the weight-SD-score change for the birth to 20 months age interval was associated with an earlier age of entry into stage 2 of pubic hair development (-0.11 years).

Conclusion

A few maternal prenatal and postnatal characteristics, along with weight gain during infancy, appear to be involved in the onset of puberty. These early fetal and infancy factors may play a role in the timing of puberty in boys.

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BACKGROUND

Puberty and Puberty Assessment

Puberty is the process of physical changes that transition a child into adolescence and then into an adult. Puberty is initiated by pulses of gonadotrophin releasing hormone (GnRH) that are released by the hypothalamus causing the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones stimulate the production of testosterone in boys (1, 2). Adrenarche, the secretion of adrenal androgens dehydroepiandrosterone (DHEA), DHEA sulphate and androstenedione, is related to, yet distinct from, puberty. Over time the rise in adrenal androgens leads to the development of pubic hair in addition to other pubertal characteristics such as deepening voice and body odor (2). Primary sex characteristics are associated with the development of gonads and the accompanying hormones. The secondary sex characteristics in boys are genitals and pubic hair development (3). The first physical manifestation in boys is gonadarche, enlargement of testicles, which is then followed by pubarche, appearance of pubic hair (2).

The Tanner scale is used to define the various stages of pubertal development. The scale describes five stages of development. The size and characteristics of the genitalia and testes and the development of pubic hair are used to measure physical development from childhood (Stage 1) through early adulthood (Stage 5) (4). Tanner stage 2 is considered the onset of puberty for both genital and pubic hair development. Entry into Tanner stage 2 of genital development is characterized by enlargement of the scrotum and testes accompanied by a change in the texture of the scrotal skin. Stage 3 of genital development is indicated by a growth in penis length as well as breadth. In stage 4, the testes and scrotum further enlarge joined with the development of glans. In stage 5, the genitalia are adult in size and

shape. Entry into Tanner stage 2 of pubic hair is characterized by sparse growth of long, pigmented hair appearing at the base of the penis. Stage 3 is characterized by the coarsening and darkening of the pubic hair, as well as, some expansion of the area covered by hair. In stage 4, the hair is adult-like yet the area covered is smaller than in most adults. Finally, in stage 5, the pubic hair is adult in quantity and type (5).

The age at which an individual enters sexual maturation is a mark of overall public health. An early age at onset of puberty may be an intermediary factor to many diseases and may be associated with testicular cancers, insulin resistance and obesity (6). An earlier age at entry into physical maturity also raises concerns of a possible mismatch between sexual maturity and psychosocial maturity (2, 4). Emotional immaturity may be linked to behavioral problems, such as: a difficulty in emotional and impulse control; an early sexual debut; and an increased potential for sexual abuse (2, 7). Given the importance of the age of puberty onset, studies on pubertal outcomes are necessary in understanding variation in the timing and development of secondary sexual characteristics and its determinants.

Trends in Puberty Timing

In 1969, Marshall and Tanner characterized pubertal development in institutionalized boys in the United Kingdom. This study has become vital in research and clinical settings. However, due to the possibility of a trend towards a younger age of puberty onset, and the fact that Marshall and Tanner's study population consisted of institutionalized children, the results seen by Marshall and Tanner may be less applicable in current society. One limitation to their study was that they used boys exposed to poor socio-economic conditions prior to being institutionalized and another is that entry into stages was determined using

photographs. Pubic hair visible in photos may have occurred at a later age than initial pubic hair development (5). As such, the reported age at entry into pubic hair stage 2, 13.4 years, may be a misrepresentation of the actual age for the population. However, the results of Marshall and Tanner are the current standard reference of pubertal stages.

Since the Marshall and Tanner study, various studies and reviews have reported seeing a trend toward an earlier age of puberty initiation in both boys and girls (8, 9, 10). However, the documentation of secular trends of puberty onset in girls is more common because menarche attainment is such a clear marker of sexual maturity. Although there appears to be an agreement about the secular trend in girls, the current data on puberty onset in boys is considered debatable. Reviews of studies conducted in various parts of the world have shown differing results, with some concluding there is no change compared to earlier generations, while others show an earlier onset of puberty in boys (10, 11, 12, 13).

de Muinck Keizer-Schrama and Mul examined the ages of entry for various studies conducted throughout Europe. Median ages of entry into genital stage 2 for boys were reported for studies carried out between1960 to 1997 in England, the Netherlands, Sweden and Switzerland (10). The overall trend points to a decrease in the age of entry into genital stage 2 of puberty development.

Other studies conducted in various countries show different ages for onset of stage 2 of pubic hair development. When compared to the results from the Marshall and Tanner study, boys from studies conducted across Europe and the United States appear to be entering stage 2 of pubic hair at a significantly younger age (Table 1). Marshall and Tanner

showed a median age of 13.4 years for entry into stage 2 of pubic hair development. In Denmark, using data from 1991 to 1993, a study showed a mean age of 11.9 years for entry into stage 2 or greater of pubic hair development (14). A study conducted in Italy, from 1991 to 1994, showed a median age of 11.2 years (9). In Germany, a study conducted from 2003 to 2006, showed a median age of 10.9 years for stage 2 of pubic hair (15). A study conducted in Greece in 1996 using school boys showed a mean age of 11.5 years for entry into pubic hair stage 2 (16). A review of National Health and Nutrition Examination Survey (NHANES III) data, collected from 1988-1994, on boys showed a median age of 12 years for entry into stage 2 of pubic hair development (12). An earlier study done in the United States examined boys at six month intervals for 3 years showed a mean age of 12.79 years for entry into pubic hair stage 2 (17). A more recent study done in the United States, from 2000-2006, showed a median age of 11.5 years for entry into stage 2 of pubic hair development (3). Reviewers concluded that there appears to be a trend towards an earlier age of pubic hair stage 2 onset in boys and shorter duration of between pubic hair stages. Evaluation of boys' puberty data from the United States in search of a secular trend showed that current data are insufficient to confirm a significant change due to inconsistent results (18).

Determinants of Puberty Onset

It has been suggested that factors, such as race, environmental exposures and obesity influence the onset of puberty. These factors may have a role in pubertal brain changes, such as neurogenesis, synapse formation and elimination, dendritic growth and sensitivity of neurotransmitter receptors, which allow them to have an influence on puberty onset (2). Data from NHANES III showed the influence of race on onset of puberty. In 2001,

Herman-Giddens et al. found the age of entry into pubic hair stage 2 in American boys from the NHANES III study, was different for African-American, Mexican American, and Caucasian boys. The mean ages of entry were 11.2 years for African-American boys, 12.3 for Mexican American boys and 12.0 years for Caucasian boys (12).

In addition to race, environmental factors may influence the onset of puberty. The effect of endocrine disrupting chemicals on pubertal onset is being investigated in developed countries (19). Lead has been shown to alter hormone levels and delay pubertal development in boys and girls (20). Although there are differing opinions about the size and direction of the effect of persistent organic pollutants (POPs) on puberty in boys and girls, one study found that girls exposed to polybrominated biphenyls during breastfeeding reached menarche and pubic hair stages at an earlier age (20, 21). Polychorinated biphenyls (PCBs) have been shown to delay puberty onset in boys and girls (22). In boys, Den Hond found that genital development and pubic hair growth were inversely correlated with serum concentration of PCBs.

Obesity has been suggested to play a role in the timing of puberty (10). The hormone, leptin, supports the link between body fat and puberty. Leptin is secreted by adipose tissue in relation to the amount of total fat mass (23). Leptin's role is to regulate appetite and reproductive function via hypothalamic receptors (23). There has recently been an emergence of studies showing how the interaction between leptin and kisspeptin regulates puberty onset (23). As a result, increased body fat may affect the hormonal regulation of puberty.

The concept of fetal programming, the Barker hypothesis, has provided an explanation for the growth differences seen during infancy. The overall hypothesis of fetal programming is that fetal nutrition programs the structure and function of developing organ systems (24). It also postulates that diseases originate from adaptations made by the fetus based on its nutritional status (25). Fetal programming may also have a role in early puberty initiation since infants tend to show accelerated growth to compensate for intrauterine growth restriction. The fetal environment influences birth size, and birth size significantly affects postnatal growth (26). A study was conducted in healthy post-menarchal girls, ages 11 to 19 years, recruited after discharge from a hospital in Barcelona, Spain (27). Researchers gathered birth size information from hospital records and blood samples from each girl. Their results showed girls with a birth weight that was small for gestational age (SGA) had significantly elevated dehydroepiandrosterone sulphate (DHEA-S) concentrations between 11 and 19 years of age. This was greater, approximately two times, when compared to girls born with appropriate for gestational age (AGA) birth weight. This suggests that girls who were growth restricted in utero are prone to experience elevated hormone levels during the ages of pubertal development.

Monteilh's preliminary findings show that some maternal and paternal variables appear to influence the age at puberty onset in boys (28). Variables such as, maternal age at delivery, smoking in the third trimester and paternal race appear to have an effect on the timing of puberty. Some variables associate with an earlier onset of puberty and some with a later onset of puberty. For example, maternal smoking in the third trimester and paternal race, non-Caucasian, seem to be associated with an earlier onset of puberty. Whereas, when

maternal age at delivery was greater than 30 years, it was found associated with a later onset of puberty.

Puberty and Weight Gain During Infancy

Childhood obesity may be related to rapid weight gain during infancy up to two years of age. One study found that children who gained weight rapidly during infancy had a higher weight and body mass index (BMI) comparatively (29). However, the relationship in boys was not as clear as in girls and more research is needed to elucidate the association (29). Rapid weight gain during infancy has been associated with early attainment of breast and pubic hair development and menarche in girls. One study, conducted on girls from this same cohort, found that a higher weight gain during infancy was associated with an earlier onset of puberty (30). In the United States, a longitudinal study followed Caucasian girls from age 5 to age 9 (31). Researchers used three measurements of puberty onset, Tanner stage of breast and pubic hair development and estradiol levels (31). Information from all three measurements was combined into a puberty index, which was used to assess puberty onset. It was found that girls with a higher weight status at 5 years of age were more likely to experience an advanced pubertal development at age 9. This finding is supported by another study, using girls from the National Institute of Child Health and Human Development Study of Early Child Care and Youth Development (32). Their results show a higher BMI z scores at age 36 months and a faster rate of change in BMI during childhood, ages 36 to 84 months, to be associated with an earlier onset of puberty.

The relationship between rapid weight gain in infancy and the early onset of puberty has yet to be fully explored in boys. A review of studies examining relationship of infancy and

childhood weight gain and the age at puberty onset had reviewers conclude that weight gain during infancy is likely to be a vital influence on the timing of puberty onset (33). Data on the factors that influence puberty in boys is clearly incomplete. Further studies are needed in order to establish determinants for an earlier onset of puberty in boys.

METHODS

Hypothesis

The rapid weight gain between birth and 20 months may influence the timing of pubic hair development, causing an earlier entry into stage 2 of pubic hair development in boys enrolled in the Avon Longitudinal Study of Parents and Children.

Study Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based cohort designed to examine environmental influences on health and development. Pregnant women from three districts in Avon County, Great Britain who were due to give birth between April 1991 and December 1992 were enrolled in the study. The study began early in the pregnancy and very detailed information was collected from the mother prior to the child's birth (34). The pregnancies resulted in 11,972 singleton births, of these 6,130 were boys.

Data Collection

Pubertal data was collected using recurring self-assessment questionnaires given to the boys between the ages of 8 and 14. Data collection methods and management are described elsewhere (35). Information was gathered on both genital stage and pubic hair stage. Upon examination of the data, it was found that the self-reported genital data appeared to reverse in direction as the boy aged. This inconsistency resulted in the variable being unreliable, thus not considered in this analysis. Of the 6,130 boys a total of 3,938 (64%) had valid pubic hair data from the initial cohort.

Questionnaires were administered to mothers to gather data on prenatal characteristics and behaviors. Variables to be assessed as potential confounders include: maternal pre-pregnancy BMI, age at delivery, smoking in the third trimester, alcohol consumption in the first trimester, maternal education, and parity. Maternal pre-pregnancy weight status was assigned according to the Centers for Disease Control and Prevention BMI classification: underweight (>18.5), normal (18.5-24.9), overweight (25-29.9), and obese (≥30.0). The variable was categorized based on these ranges for the purpose of analysis. Postnatal variables assessed for potential confounding include birth weight, birth height and breastfeeding.

Data on weight at birth, 2, 9, and 20 months of age were obtained from questionnaires, birth records, and records from postnatal clinic visits. Infant weight was converted to weight-for-age SD scores (z-scores) using the boy's 1990 British growth reference (12). The change in weight was assessed using the intervals birth to 2 months, 2 months to 9 months, 9 months to 20 months and birth to 20 months. The change value for the age intervals of the SD scores for weight were obtained by subtracting the weight SD score for the age at the beginning of the interval from the SD score for the age at the end of the interval (30). Associations for weight gain from birth to 20 months and pubic hair timing were assessed on 1,816 boys.

Statistical Analysis

Frequencies of maternal prenatal and postnatal variables and Pearson correlations on weight gain were used to describe the study population. Bivariate analyses were used to test potential confounders, maternal prenatal and postnatal characteristics, with the study

outcome, stage ≥ 2 of pubic hair development. Each variable was fitted separately in a survival model to assess for association with the study outcome. Any variable not found associated, having a Wald Chi-Square with a p-value greater than 0.05, was removed from further analyses.

Associations of weight change adjusted by puberty associated prenatal characteristics were modeled with the study outcome. Any change in the median age of transition into a stage and 95% confidence intervals were documented. The association of weight change, birth weight and birth length were modeled with the outcome and variables found associated with the outcome in the bivariate analysis. Weight-SD-score age intervals were modeled individually, then adjusting for previous intervals, and finally all age intervals were modeled with birth weight and birth length. For pubic hair development analysis, interval-censored parametric survival models were used, assuming a normal distribution using PROC LIFEREG in SAS (37). The interval of weight change from birth to 20 months, weight-SD score, was used in the survival models.

Institutional Review Board

This study is an analysis of secondary data and did not require contact with humans. Investigators did not have access to any identifying information on participants. Human subject protection had been previously assessed and approved by the ALSPAC Law and Ethics Committee, the Local Research Ethics Committee, the CDC Institutional Review Board, and exempt from the Emory Institutional Review Board.

RESULTS

The median age of entry into pubic hair stage 2 for this population is 11.35 years (Table 2).

Maternal Prenatal Characteristics

Frequency distributions of maternal prenatal and postnatal characteristics, potential confounders, were used to describe the study population (Table 3). The analysis of race with the outcome showed a substantial percentage, 96%, of this cohort to be Caucasian. Due to the small number of subjects having a race other than Caucasian, race was not analyzed in any models. Nearly half of the mothers were over the age of 30 at the time of delivery. Over 75% of the mothers had at least a secondary education certificate. More than half of the mothers enrolled in this cohort had at least one alcoholic beverage during their first trimester. Around 15% of mothers had at least one tobacco item during their third trimester. Pre-pregnancy BMI for mothers showed that the majority of mothers were in the normal BMI range, according to CDC classifications. Approximately 20% of mothers were classified as overweight or obese in this cohort. Roughly half of the mothers were primiparous. A small percentage (1.93%) of the boys in this cohort had a low, less than 2,500 grams, birth weight. However, nearly 7% of the boys had a high, greater than 4,300 grams, birth weight according to the weight-for-age tables from WHO. The majority (82%) of the boys in this cohort were breastfed at some point between birth and 4 weeks of age. Assessment of confounding showed none of the variables to be a confounder of weight gain from birth to 20 months (results not shown).

Pubertal Associations with Maternal Prenatal Characteristics

Bivariate analysis showed the association of each variable, individually, with the outcome. The variables associated with stage 2 of pubic hair development were maternal age at delivery, parity and breastfeeding. Smoking in the third trimester, low birth weight and birth length were found to be borderline significant (Table 4). Using a p-value of 0.05 as the cutoff for the Wald Chi-Square test, the following variables were not found associated with the study outcome: maternal education, alcohol consumption in the first trimester, and maternal pre-pregnancy BMI category.

A multivariable parametric survival model was made using the variables found to be significantly associated with the outcome. The Wald Chi-square p-values of this model showed that maternal age at delivery, parity and breastfeeding were significant (Table 5).

Fetal Growth

The mean birth weight and standard deviation in the group of boys with valid pubic hair data was 3.52 (0.51) kilograms (Table 6). The mean and standard deviation for weight at 2 months was 5.22 (0.67), at 9 months 9.22 (1.05), and at 20 months 12.17 (1.42). Weight change values were correlated with birth weight and between intervals with the exception of the change in SD from 9 to 20 months. When compared to birth weight and the change in SD from birth to 2 months, the interval from 9 to 20 months was not found to be correlated (Table 7). All other intervals were inversely correlated with birth weight.

Postnatal Weight Gain and Growth

A 1-unit increase in the weight change score estimated for the birth to 20 months age interval was found associated with an earlier age of entry into pubic hair stage 2 (-0.17 years), including after adjusting for birth weight and birth length (Table 8). Age intervals were modeled separately and associations were similar across the intervals, with each interval being significant except the 9 to 20 months interval. The 9 to 20 month interval was not significantly associated with an earlier age of entry into pubic hair development. After adjusting for weight gain in previous age intervals, the magnitude of the coefficients shifted further from the null towards an earlier age of onset. Adding birth weight and birth length into the model did not drastically influence the estimates or confidence intervals seen in the other models.

DISCUSSION

In the present study, the median age of entry into stage 2 of pubic hair development was 11.35 years. When compared to the median ages and confidence intervals from previous studies, this sample had a median age lower than the results seen from Marshall and Tanner, NHANESIII and Juul (Table 1). When compared to Marshall and Tanner's results, there is an apparent shift in the median age of pubic hair development towards a younger age of onset. The trend towards an earlier age of entry into stage 2 of pubic hair development can also be seen when the results of this study are compared to the median ages and confidence intervals obtained from previous studies (Table 1). Pubic hair development can be correlated with genital development, and thus the onset of puberty. One study examined entry into pubic hair and genital stage development in 427 boys from various locations throughout the United States (3). The results showed that boys entered into each sexual maturity stage of genital maturation prior to entering the same stage for pubic hair development. The age of entry into stage 2 of genital development occurred before the age of entry into stage 2 of pubic hair development, by a mean of 1.1 years earlier. It can be argued that if the observed mean of entry into stage 2 of pubic hair development is occurring earlier compared to previous generations then the age of entry into genital stage 2 must also be occurring earlier.

In this study, maternal age at delivery, smoking in the 3rd trimester, parity and breastfeeding were found individually associated with an earlier age of entry into pubic hair Tanner stage 2. When the variables individually associated with pubic hair were modeled together, maternal age at delivery, parity and breastfeeding remained significant. Maternal age at delivery greater than 30 years was found to be associated with a later onset of pubic hair

development. As expected, Monteilh's findings show a similar result using this cohort (28). In girls from this cohort, maternal age at delivery was not found associated with any puberty marker (30).

Smoking in the 3rd trimester was found borderline significantly associated with pubic hair development. A study conducted using the Ottawa Prenatal Prospective Study Cohort (OPPS) found that prenatal tobacco use was associated with an earlier appearance of pubertal milestones, voice change and shaving initiation in adolescent boys (38). In girls, smoking during pregnancy was found associated with an earlier entry into stage 2 of breast development and an earlier age at menarche (30). However, the association was not seen regarding entry into stage 2 of pubic hair development.

Boys born to primiparous mothers were found to enter stage 2 of pubic hair development significantly earlier, by nearly 3 months, compared to boys born to mothers who had given birth before. Parity was also found associated with an earlier age of menarche and entry into pubic hair stages in girls from this cohort (30). One speculation is the presence of a higher concentration of maternal sex hormones in first-born children compared to children born close to their previous sibling (39). Umbilical-cord blood has higher concentrations of sex hormones in firstborns compared to later born children closely spaced to their next-older sibling (39).

Breastfed boys were found to enter stage 2 of pubic hair development earlier compared to boys who were not breastfed. As expected, this result is supported by Monteilh's findings in boys from this cohort (28). Pre-pregnancy BMI was not associated with the onset of pubic

hair development, which is similar to the result seen in girls from this cohort. Yet, in girls of this cohort, a higher maternal pre-pregnancy weight was associated with an earlier onset of breast development and menarche (30).

Childhood and prepubertal obesity have been suggested to promote an early onset of puberty and may be related to an increase in gonadotrophin-initiated puberty (4; 40). The relationship between rapid childhood weight gain and earlier onset of puberty has been investigated in numerous studies (33). One from Denmark used data from school health records on boys and girls who attended from 1930-1969 (23). The study used the BMI at age 7 as the measure of obesity, and age at onset of pubertal growth in addition to the age at peak height velocity as measures of puberty onset. Body mass index was categorized based on standard deviations above or below the reference population's mean. Aksglaede found a significant difference in both the age at onset of the pubertal growth spurt and the age at peak height velocity in boys of the higher BMI categories compared to the lower BMI categories. Both outcomes occurred earlier in children in the higher BMI categories. One study looking for potential early-life risk factors for obesity used a random subsample selected from the cohort used in the present study (41). The results show catch-up growth between birth and 24 months and high rates of weight gain from birth to 12 months were both associated with obesity at age 7. Catch-up growth between birth and 24 months showed a 2.6 increase in the odds of being obese by age 7. Weight gain from birth to 12 months increased the odds of the child being obese at age 7 by 6%. Another study conducted in Germany using data from the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study investigated early life exposures and their influence on the timing of puberty (6). The results of this analysis showed that the age at

peak height velocity occurred earlier (-0.54 years) in children who experienced rapid weight gain between birth and 24 months.

Conclusion

The results of this study demonstrate that rapid weight gain during infancy is related to an earlier age of entry into stage 2 of pubic hair development in boys. In the bivariate analysis examining weight gain from birth to 20 months in relation to stage 2 of pubic hair development, there was a decrease of 0.16 years (1.92 months) for a 1-unit increase in the weight change score. Analysis of the adjusted model, adjusted by maternal age at delivery, smoking in the 3rd trimester, parity, breastfeeding, birth weight and birth length, showed a decrease of 0.11 years (1.32 months) for a 1-unit increase in the weight change score. Overall, rapid weight gain during infancy seems to have an effect on pubertal development. The pathway of this interaction is currently unclear and rapid weight gain during infancy is unlikely to be the sole factor influencing the age at puberty onset.

STRENGTHS AND WEAKNESSES

The present study has several strengths, including the detailed information prospectively collected on each respondent. The data was obtained from a large population-based prospective cohort. Also, many variables were obtained from medical records, such as, birth weight, birth length, weight at 2, 9, and 20 months, and gestational age, removing patient recall bias. Additionally, the recurring self-administered questionnaires provided descriptions of each responding boy in the cohort. Utilizing this method for data collection allowed for a comprehensive assessment of entry into pubertal stages. Drawings of pubic hair stages were provided to each individual. Drawings were developed by Morris and Udry (42). Morris and Udry showed correlations between clinician and self-reported Tanner stage (pubic hair: r=0.63; genital: r=0.59). Monteilh, has promising results that show that pubic hair is closely timed with the onset of genital development in this particular cohort (28).

There were also some limitations with this study. Genital stage information was not evaluated due to the unreliability of the data collected. Although genital stage data was not analyzed, the assumption can be made that there is a relationship between pubic hair development and genital maturation. In addition, the present study analyzed a subset of the full cohort, which may have influenced the power associated with this study. Much of the information was collected using a self-administered questionnaire, which leaves room for patient error, although self-reported Tanner stage data is often used to provide an accurate assessment of puberty in a practical manner.

FUTURE DIRECTIONS

The importance of early onset puberty and the accompanying implications place a strong urgency on researchers to fully comprehend the subject. The complete list of the public health implications of an earlier onset of puberty has yet to be uncovered. Hormone-related cancers, such as testicular cancer, have been associated with an earlier pubertal onset (6). In addition to cancers, elevated androgen concentrations, insulin resistance and obesity are also found associated with an early onset of puberty. To address gaps in the research, longitudinal studies should be employed to assess the onset of puberty because they provide the monitoring necessary to obtain accurate results. More studies are needed to specify possible early life experiences and how they influence pubertal development.

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TABLES

Table 1. Summary of results on Tanner pubic hair stage ≥2 for White boys.

Location	Author	Year	Age Range	Males (n)	Mean age of entry	95% Confidence Interval
United Kingdom	Marshall	1948-1969	9.5-17	225	13.44	[13.26-13.62]
Denmark	Juul	1991-1993	6-19.9	826	11.88	[11.69, 12.08]
*Italy**	De Simone	1991-1994	6-14	535	11.47	[11.26, 11.67]
Germany	Kahl	2003-2006	10-17	3932	10.90	[10.80, 11.10]
Greece	Papadimitriou	1996	7.8-16.2	1266	11.50	
*USA** *(NHANES III)*	Herman-Giddens	1988-1994	8-19	2114	12.00	[11.70-12.30]
USA	Biro	1991-1994	10-15	515	12.79	
USA	Susman	2000-2006	9.5-15.5	427	11.50	[11.40, 11.60]

*Median age of entry reported.

Table 2. Median age of entry into pubic hair stage 2.

Variable	Median age of entry	Standard Error	95% Confidence Interval
Pubic Hair Stage 2	11.35	0.03	[11.26, 11.42]

N=3568

Table 3. Frequency distribution of selected prenatal characteristics.

Variable	N	Percent	# Missing	Percent Missing
Maternal Age at Delivery			0	0 %
<25 years	526	14.74 %		
25-29 years	1439	40.33 %		
≥30 years	1603	44.93 %		
Maternal Education Level			7	0.20 %
Less than Secondary	793	22.27 %		
Secondary	1298	36.45 %		
More than Secondary	1470	41.28 %		
Alcohol Consumption in 1st Trimester			172	4.82 %
Yes (1 or more)	2353	69.29 %		
No	1043	30.71 %		
Smoking in 3rd Trimester			307	8.60 %
Yes (1 or more)	518	15.88 %		
No	2743	84.12 %		
Pre-Pregnancy BMI			299	8.38 %
<18.5	119	3.64 %		
18.5-24.9	2492	76.23 %		
25-29.9	490	14.99 %		
≥30	168	5.14 %		
Parity			65	1.82 %
1 or more	1906	54.41 %		
None	1597	45.59 %		
Birth Weight			1752	49.10 %
Low (<2500g)	35	1.93 %		
Normal (2500 – <4300g)	1653	91.02 %		
High (≥4300g)	128	7.05 %		
Breastfeeding			92	2.58 %
Yes	2874	82.68 %		
No	605	17.32 %		

Table 4. Unadjusted associations between maternal characteristics and transition into Tanner stage ≥2 of pubic hair development.

Variable	Estimate	St. Error	95% Confidence Interval	P-Value
*Maternal Age at Delivery **				
<25 years (Reference)	-	-	-	-
25-29 years	0.08	0.10	[-0.12, 0.27]	0.43
≥30 years	0.27	0.10	[0.08, 0.46]	0.01
Maternal Education Level				
Less than Secondary	0.08	0.09	[-0.09, 0.25]	0.35
Secondary	-0.03	0.07	[-0.17, 0.11]	0.66
More than Secondary (Reference)	-	-	-	-
Alcohol Consumption in 1st Trimester				
Yes (1 or more)	0.07	0.07	[-0.07, 0.20]	0.36
No (Reference)	-	-	-	-
*Smoking in 3rd Trimester **				
Yes (1 or more)	-0.17	0.09	[-0.36, 0.01]	0.07
No (Reference)	-	-	-	-
Pre-Pregnancy BMI				
<18.5	-0.02	0.18	[-0.37, 0.34]	0.94
18.5-24.9 (Reference)	-	-	-	-
25-29.9	-0.09	0.10	[-0.28, 0.10]	0.34
≥30	0.10	0.15	[-0.21, 0.40]	0.53
*Parity **				
1 or more	-0.28	0.06	[-0.41, -0.15]	<0.0001
None (Reference)	-	-	-	-
Birth Weight				
Low (<2500g)	-0.61	0.32	[-1.24, 0.01]	0.05
Normal(2500 – <4300g) (Reference)	-	-	-	-
High (≥4300g)	0.01	0.18	[-0.33, 0.36]	0.94
Birth Length	0.04	0.02	[0.00, 0.07]	0.06
*Breastfeeding **				
Yes	-0.23	0.09	[-0.40, -0.05]	0.01
No (Reference)	-	-	-	-

Coefficients were estimated with parametric survival models using PROC LIFEREG in SAS.

Table 5. Adjusted estimates and 95% confidence intervals in age of transition into a stage ≥2 of pubic hair development for associated prenatal characteristics.

Variable	Estimate	95% Confidence Interval	P-Value
Maternal Age at Delivery *	0.02	[0.00, 0.03]	0.03
<25 years (Reference)	-	-	-
25-29 years	-0.01	[-0.23, 0.21]	0.92
≥30 years	0.14	[-0.09, 0.36]	0.23
Smoking in 3rd Trimester			
Yes (1 or more)	-0.15	[-0.34, 0.05]	0.13
No (Reference)	-	-	-
*Parity**			
None	-0.21	[-0.35, -0.07]	0.00
1 or more (Reference)	-	-	-
Breastfeeding *			
Yes	-0.21	[-0.40, -0.02]	0.03
No (Reference)	-	-	-

* Significant at 0.05 level.

Table 6. Summary measures of birth size by age and age interval.

Variable	**Mean (SD)**	**IQR**	**Mean (SD)**	**IQR**	**Mean (SD)**	**IQR**	**Mean (SD)**	**IQR**
Age	*Birth*		*2 Months*		*9 Months*		*20 Months*	
Weight (kg)	3.52(0.51)	0.70	5.22(0.67)	0.80	9.22(1.05)	1.30	12.17(1.42)	1.80
Weight SD Score	-0.08(1.05)	1.34	0.08(1.00)	1.27	0.48(1.12)	1.52	0.26(0.99)	1.29
Age Interval	*Birth to 2 Months*		*2 to 9 Months*		*9 to 20 Months*		*Birth to 20 Months*	
Weight SD	0.17(0.81)	1.07	0.40(1.15)	1.46	-0.22(1.04)	1.31	0.35(1.17)	1.54

Table 7. Correlation matrix for birth weight and change in weight SD scores.

	Birth Weight	**Change in weight SD score 0 to 2 Months**	**Change in weight SD score 2 to 9 Months**
Change in weight SD score 0 to 20 months	-0.61*		
Change in weight SD score 0 to 2 months	-0.45*		
Change in weight SD score 2 to 9 months	-0.26*	-0.23*	
Change in weight SD score 9 to 20 months	-0.04	0.02	-0.55*

* Pearson correlation coefficients are significant at $p < 0.0001$ level, n=1816

Table 8. Adjusted estimate and 95% confidence interval for age of entry into stage ≥2 of pubic hair development for birth size and change in weight SD score.

Variables	Estimate	95% Confidence Interval	P-Value
Birth weight (g)	0.11	[-0.07, 0.30]	0.21
Birth length (cm)	0.03	[-0.01, 0.07]	0.16
Weight change (intervals modeled separately)			
0 to 20 months	-0.14	[-0.22, -0.05]	0.00
0 to 2 months	-0.12	[-0.23, -0.01]	0.04
2 to 9 months	-0.10	[-0.18, -0.01]	0.02
9 to 20 months	0.03	[-0.06, 0.11]	0.55
Weight change (intervals modeled adjusting for prior intervals)			
0 to 2 months	-0.12	[-0.23, -0.01]	0.04
2 to 9 months	-0.13	[-0.21, -0.04]	0.00
9 to 20 months	-0.07	[-0.18, 0.04]	0.19
Total Weight change (adjusted by birth weight and length)			
0 to 20 months	-0.17	[-0.27, -0.06]	0.00
Weight change adjusted by birth weight and length (intervals modeled adjusting for prior interval)			
0 to 2 months	-0.12	[-0.24, 0.00]	0.07
2 to 9 months	-0.16	[-0.25, -0.06]	0.00
9 to 20 months	-0.10	[-0.21, 0.02]	0.09

Coefficients were estimated with parametric survival models using the PROC LIFEREG procedure in SAS. Adjusted for parity, smoking in third trimester, maternal age at delivery and breastfeeding.

APPENDIX

EMORY UNIVERSITY

Institutional Review Board

TO: Michele Marcus
Principal Investigators
Emory University

DATE: July 21, 2010

RE: Notification of Submission Determination: No IRB Review Required

TITLE: Avon Longitudinal Study of Parents and Children Data Analysis

Thank you for requesting a determination from our office about conducting additional data analysis on the existing Avon Longitudinal Study of Parents and Children dataset. Research analysis of an existing dataset that doesn't contain any identifiers would not be considered Human Subjects Research. It would not meet the 45 CFR Section 46.102(f)(2) definition of "Human Subjects Research" or the definition of "Clinical Investigation" under applicable federal regulations. Secondary analysis of the ALSPAC private non-identifiable dataset would not require IRB review.

45 CFR Section 46.102(f)(2) defines "Research involving Human Subjects" as follows:

Human Subject means a living individual about whom an investigator (whether professional
or student) conducting research obtains:

(1) data through intervention or interaction with the individual, or
(2) identifiable private information

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

In addition, the IRB has determined that the study is not a "Clinical Investigation" under applicable Food & Drug Administration regulations because it does not involve a test article and does not otherwise meet the requirements of the definition of "Clinical Investigation" as set forth in 21 CFR Section 50.3(c). Please note that any additions to the dataset or additional activities could conceivably alter the status of this research under the federal regulations cited above. Accordingly, any substantive changes in the protocol should be presented to the IRB for consideration prior to their implementation in the research.

Sincerely,

Donna Dent, MS, MISM, CIP Lead, Research Protocol Analyst Emory University Institutional Review Board
This letter has been digitally signed

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