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Review

Influences on the onset and tempo of puberty in human beings and implications for adolescent psychological development

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ABSTRACT

This article is part of a Special Issue "Puberty and Adolescence".

Historical records reveal a secular trend toward earlier onset of puberty in both males and females, often attributed to improvements in nutrition and health status. The trend stabilized during the mid 20th century in many countries, but recent studies describe a recurrence of a decrease in age of pubertal onset. There appears to be an associated change in pubertal tempo in girls, such that girls who enter puberty earlier have a longer duration of puberty. Puberty is influenced by genetic factors but since these effects cannot change dramatically over the past century, environmental effects, including endocrine disrupting chemicals (EDCs), and perinatal conditions offer alternative etiologies. Observations that the secular trends in puberty in girls parallel the obesity epidemic provide another plausible explanation. Early puberty has implications for poor behavioral and psychosocial outcomes as well as health later in life. Irrespective of the underlying cause of the ongoing trend toward early puberty, experts in the field have debated whether these trends should lead clinicians to reconsider a lower age of normal puberty, or whether such a new definition will mask a pathologic etiology.

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Introduction

Puberty is best considered one stage in the continuum of reproductive life rather than a single event (Styne and Grumbach, 2011). Thus, changes that begin during fetal life result in the maturation of the hypothalamic–pituitary–gonadal (HPG) axis, a process that includes suppression and then re-activation of the hypothalamic gonadotropin releasing hormone (GnRH) pulse generator, enhanced gonadotropin secretion and gonadal maturation with reproductive function.

Developmental stages of the control of puberty

Hypothalamic–pituitary–gonadal axis

Pituitary gonadotropin secretion is controlled by the hypothalamus, which releases pulses of GnRH into the pituitary–portal system to stimulate the anterior pituitary gland to episodically release gonadotropins (Styne and Grumbach, 2011). Control of GnRH secretion is exerted by a "hypothalamic pulse generator" in the arcuate nucleus which is responsive to higher central nervous system (CNS) centers and sensitive to feedback control from gonadal secretory products.

In males, LH stimulates the Leydig cells to secrete testosterone, and FSH stimulates the Sertoli cells to produce inhibin which exerts feedback on the hypothalamic–pituitary axis to inhibit FSH. In females, FSH stimulates the granulosa cells to produce estrogen and the follicles to secrete inhibin. LH appears to play a minor role in the endocrine milieu until menarche, at which point it triggers ovulation and later stimulates the theca cells to secrete androgens.

Fetal Life

During fetal life, GnRH content in the hypothalamus and gonadotropin content in the pituitary gland increase, pulsatile release of GnRH and gonadotropins develops and rise until midgestation (Styne, 2011; Styne and Grumbach, 2011). After midgestation, GnRH release decreases, due to CNS inhibition, which leads to decreased gonadotropin secretion; elevated maternal estrogens also suppress gonadotropin secretion until term. Once maternal estrogen has been cleared, postnatal peaks of serum LH and FSH occur for more than 6 months after birth (Grumbach, 2002). During the juvenile pause, the period between infancy and the peripubertal period, basal and GnRH stimulated serum gonadotropin concentrations are suppressed, although pulsatile secretion is still detectable, albeit at low levels (Aksglaede et al., 2006).

Prepuberty and puberty

Prepubertal children demonstrate a circadian rhythm of LH and FSH secretion of low amplitude with sex steroid secretion lagging behind the gonadotropin rhythm. Thus, the changes that occur at puberty do not arise de novo but are based on preexisting patterns of endocrine secretion. In the peripubertal period, endogenous GnRH secretion increases in amplitude and frequency during the early hours of sleep and serum testosterone and estrogen concentrations rise several hours thereafter. As pubertal development progresses, the peaks of serum LH and FSH occur more often during waking hours; and, finally, in late puberty, the peaks occur at all times, eliminating the diurnal variation (Styne and Grumbach, 2011).

The development of reproduction is essential to a species and thus duplicate and complex mechanisms ensure this progression. While investigators are making progress in uncovering the control of the onset of puberty, much remains to be done. Genes coding for transcription factors such as CLOCK and BMAL1 regulate cellular rhythms that are involved in the control of puberty (Tolson and Chappell, 2012). Kisspeptin, encoded by the KiSS-1 gene, is implicated as a major "gatekeeper" of GnRH function. Kisspeptins activate a G protein coupled receptor, GPR54, encoded by the KISS1R gene, that is expressed in the brain, pituitary, placenta and on GnRH neurons. Many lines of evidence suggest that KiSS-1 gene regulates puberty at the level of the GnRH pulse generator (Tolson and Chappell, 2012). While GnRH content remains relatively constant during puberty, hypothalamic kisspeptin levels rise (Tolson and Chappell, 2012). Loss of function of the GPR54 gene results in idiopathic hypogonadotrophic hypogonadism (de Roux et al., 2003; Seminara et al., 2003), while over expression of GPR54 or Kisspeptin leads to precocious puberty (Teles et al., 2011). More on the regulatory role of kisspeptins can be found in another article within this issue of Hormones and Behavior (Sanchez-Garrido MA and Tana-Sempere M).

Physical changes associated with puberty

Secondary sexual maturation and endocrine changes during pubertal development include thelarche, gonadarche, pubarche, and adrenarche. Increased growth rate is one of the first signs of puberty and peak height velocity (PHV) occurs relatively early in female puberty (Tanner and Davies, 1985). Thelarche, the onset of breast development, is caused by an increase in the secretion of ovarian estrogen and is often the first sign of puberty noted in girls during routine evaluations (Styne, 2011). Isolated premature thelarche may occur unrelated to normal GnRH dependent puberty. Gonadarche marks the increase in sex steroid secretion from the gonads under the control of the hypothalamic pituitary axis; in boys, gonadarche is associated with increased testicular volume (Styne, 2011). The maturation of the adrenal gland and increased secretion of adrenal androgens, adrenarche, contributes to pubarche, the onset of pubic hair development, which is independent of the HPG axis.

The staging system Tanner developed to describe normal progression of puberty in males and females over 50 years ago is utilized for clinical descriptions in terms of Sexual Maturation Rating (SMR) or Tanner Stages (Marshall and Tanner, 1969, 1970). Marshall and Tanner also observed variations in children's progression through these stages, specifically describing differences in pubertal timing, described as "variation in the chronological age at which adolescence begins and different stages of physical maturity are reached" and pubertal tempo, described as "variation in the time taken to pass through the various stages of development" (Marshall and Tanner, 1969).

Body composition changes with puberty

While prepubertal boys and girls have equal lean body mass, skeletal mass, and body fat, at maturity men have approximately 1 1/2 times the lean body mass, skeletal mass, and muscle mass of women, whereas women have twice as much body fat as men. Attainment of peak values of these tissues occurs several years earlier in girls than in boys, in a manner similar to the earlier peak of height velocity and velocity of weight gain in girls. Girls reach peak bone mineralization between 14 and 16 years of age, whereas boys reach a later peak at 17.5 years; both milestones occur after peak height velocity (Loomba-Albrecht and Styne, 2009).

Determining onset of puberty

Females

The method used by the examiner to determine breast development can affect results of a study evaluating the age of thelarche. Thus palpation, observation without physical palpation, review of a photograph of the subjects (as Tanner used in his classic studies), or self-rating by the subjects themselves may lead to different levels of certainty as to degree of development, especially in overweight girls in which inspection alone may not accurately determine that puberty has started. Discrimination between breast tissue from fat (adipomastia) may add further difficulty, especially during the epidemic of obesity (Bonat et al., 2002). While menarche occurs on an average 3 years after the onset of puberty and is a late marker for the onset of puberty, it is often used as a surrogate for the onset of puberty because it is a sentinel event that is often well remembered within 12 months of accuracy, even up to 30 years later (Must et al., 2002). Contemporaneous determination of the age of menarche is often performed with the probit method of asking a subject whether they are menstruating with an answer of "Yes" or "No". Pubarche in girls is controlled by androgens that mainly emanate from the adrenal glands, with smaller contributions from ovarian androgens (Ankarberg and Norjavaara, 1999), and thus do not necessarily represent maturation of the HPG axis, although the two are usually temporally coordinated.

Males

Palpation of testes is considered the most accurate method of determining the onset of pubertal development in boys but there is controversy over the cutoff point to be used. The first sign of normal puberty in boys is generally considered to be an increase in testicular volume of ≥4 mL (Juul et al., 2006; Styne and Grumbach, 2011). It typically takes 6–12 months from the increase in testicular size to the appearance of other signs of puberty, such as increase penis length and increased growth rate, which depend on increasing testosterone secretion (Tanner and Whitehouse, 1976). SMR pubic hair stage 2a (absence of pubic hair in the presence of a testicular volume of 3 mL or more) was proposed as an addition to the classic five stages of pubertal development based on a longitudinal study that showed that most boys begin endocrine puberty with testicular enlargement of this degree (Biro et al., 1995), although this stage has not been formally accepted into medical use. An older longitudinal Swiss study also proposed 3 mL as an indicator of the onset of puberty 30 years ago (Largo and Prader, 1983). Most of the increase in testicular size is due to seminiferous tubular development stimulated by follicle-stimulating hormone (FSH), with a smaller component due to stimulation of Leydig cells by lutenizing hormone (LH).

Pubic hair development in boys is induced by a combination of adrenal and testicular androgen secretion, and thus there is closer correlation between genital and pubic hair development in boys than breast and pubic hair development in girls (Mul et al., 2001). Peak height velocity (PHV) is reached toward the end of male puberty, in comparison to earlier occurrence of PHV in girls, and some boys do not reach PHV until attainment of adult genitalia (Marshall and Tanner, 1970). There is no sentinel event in males that is remembered as accurately as menarche in girls.

Secular trends in puberty

Females

Aristotle stated in "Historia Animalium", that menarche occurred when a girl was "twice 7 years old", an age far younger than found in recent centuries of recorded history; remarkably he also noted 14 years as the age that the male begins to engender seed (Marshall, 1911). While there is no peer review for this statement, if accurate it suggests that girls several thousand years ago in Greece may have been healthier than in recent centuries in Europe! From a menarcheal age between 17 to 18 years recorded in the 18th century, there has been a decline in age of menarche of 1–4 months per decade in industrialized European countries and the United States over the last 150 years (Demerath et al., 2004b; Freedman et al., 2002; Onland-Moret et al., 2005; Wyshak and Frisch, 1982). This trend has been thought to be associated with improved socio-economic and health status (Lehmann et al., 2010; Parent et al., 2003) and plateaued in most industrialized countries in the 1960s (Sorensen et al., 2012). However, over the past two decades, there is a reappearance of a trend toward earlier age at thelarche in the United States (Chumlea et al., 2003; Herman-Giddens et al., 1997; Wu et al., 2002), and a lesser decrease in the age at menarche (Anderson et al., 2003; Chumlea et al., 2003; Morris et al., 2011b).

One of the earlier studies regarding timing of onset of puberty in the United States was that of the National Health Examination Survey III (NHES III), which included observations of sexual maturation in 3130 boys and girls between 1966 and 1970. This major US study started following children at 12 years when many had already begun puberty, thus impeding the ability to determine the lower limits of puberty in normal US children. While the National Health and Nutrition Examination Survey (NHANES III) enrolled 2300 children >8 years of age between 1988 and 1994, there is still a group of children who enter puberty prior to 8 years of age who would have been missed. European standards of onset and progression of puberty from Marshall and Tanner (Marshall and Tanner, 1969) were modified for use in the United States (Tanner and Davies, 1985). It is important to note that the girls observed by Marshall and Tanner all lived in a children's home, mainly came from the lower socio-economic sector of the population, and may not have received optimal nutrition or medical care before entering the home. Given that the population studied by Marshall and Tanner are different from that of the general US population, American standards are needed to accurately trend secular changes in puberty.

The AAP's Pediatric Research in Office Settings (PROS) practice-based research network conducted by specially trained pediatricians studied a convenience sample of 17,077 non-Hispanic white (NHW) and non-Hispanic black (NHB) girls starting as young as 3 years of age who were seen for routine care (Herman-Giddens et al., 1997). The study revealed that 3% of NHW girls reach stage 2 breast development (as determined by trained clinicians via visual inspection) by 6 years of age and 5% by 7 years, whereas 6.4% of NHB girls had stage 2 breast development by 6 years of age 15.4% by 7 years. Although the study participants did not represent a population-based sample, this is the largest study available, and led to the Lawson Wilkins Pediatric Endocrine Society statement that precocious puberty may be defined as secondary sexual development starting prior to 6 years in NHB girls and prior to 7 years in NHW girls (Kaplowitz and Oberfield, 1999). It cannot be overemphasized that such limits refer only to girls who are otherwise healthy, as various serious or even potentially fatal conditions that can cause precocious puberty must not be missed. This study only included observations until 12 years, limiting the ability to determine the upper limit of normal puberty in the sample by observation although statistical inferences were invoked. A smaller, more recent longitudinal study found an even higher proportion of NHW and NHB girls who reached SMR stage

2 breast development by 7 years of age (10.4% and 23.4%, respectively) (Biro et al., 2010). This study also included Hispanic girls, and found that 14.9% had SMR stage 2 breast development by 7 years of age.

The secular trend toward earlier thelarche is reported in European countries as well. A study of 2095 Danish girls found that the mean age at thelarche decreased from 10.88 years to 9.86 years, while the mean age of menarche showed a lesser decrease from 13.42 years to 13.13 years (Aksglaede et al., 2009). The trend in earlier thelarche was significant even after adjusting for BMI, although the trend for menarche was not (Aksglaede et al., 2009).

However, some expert opinions have expressed concerns about the new guidelines, stating that liberalizing the definition of "normal" carries with it the risk of overlooking pathology (Herman-Giddens et al., 2001a; Pathomvanich et al., 2000; Rosenfield et al., 2000). It may be inferred that if the physician looks for signs and symptoms of disease, such as headaches, abnormal fundoscopic or neurological exam, or rapid progression, rather than just relying on the age criteria, less than 10% of true precocious puberty will be missed; of those cases, many will be so mild as to not need intervention and may actually represent variations of normal. While these lower ages of onset of puberty are now generally invoked, controversy over the lower age of normal puberty in girls remains.

Males

While the data Marshall and Tanner published on age references for males (Marshall and Tanner, 1970) exhibit the same limitations as the references for females for use in the US population, most studies in the US and Europe found similar age of onset of male puberty (Harlan et al., 1979; Lee, 1980; Mul et al., 2001). Analyses of NHANES III data (1988–1994) on male puberty showed a significant decrease in median age at genital maturation and pubic hair development compared to previous studies (Herman-Giddens et al., 2001b; Karpati et al., 2002). However, the study was limited by the fact that testicular volume was not assessed and thus perhaps genital development could have been overestimated by inspection only. In Europe, a few studies that performed orchidometry in addition to genital staging have shown no significant trend toward earlier age at pubertal onset in boys from the mid-1960s to the late 1990s (Juul et al., 2006; Mul et al., 2001).

In the past decade, a secular trend in male puberty has now been reported. The Copenhagen Puberty Study documented a decline of 3 months in age at onset of puberty in males (11.92 years versus 11.66 years), evaluated by both genital staging and orchidometry, between their 15 year study period (Sorensen et al., 2010). A subsequent study in the United States recruited clinicians from the PROS network specifically trained to assess SMR and testicular volume to conduct a cross-sectional study to determine the current age of male puberty (Herman-Giddens et al., 2012). The median age of entering SMR stage 2 for genital development among 4131 boys aged 6–16 years was 10.14 years, 9.14 years and 10.04 years for NHW, NHB, and Hispanic boys, respectively. Compared to boys studied by Marshall and Tanner (Marshall and Tanner, 1970), NHW and Hispanic boys now enter SMR stage 2 genitalia 1.5 years earlier and NHB boys enter puberty more than 2 years earlier according to this PROS study. On the other hand, compared with Marshall and Tanner's original study, NHW boys in the PROS study reached SMR stage 5 genitalia roughly 6 months later. The most widely used indicator for onset of puberty in boys is a testicular volume of ≥4 mL. The median age at reaching testicular volume of ≥4 mL in the PROS study was 11.46, 11.75, and 11.29 for NHW, NHB, and Hispanic boys, respectively, even earlier than noted in the Copenhagen Puberty Study. However, it may not be accurate to directly compare data regarding puberty of US boys to European boys, and previous US studies did not include testicular palpation when determining onset of puberty. Ongoing surveillance of pubertal trends in boys via testicular palpation is needed to clarify the significance of these recent observations.

The tempo of puberty

Paralleling the decrease in age of onset of puberty is the decrease in correlation between onset of puberty in girls and menarche (Biro et al., 2006). Several studies report an increase in the interval between thelarche and menarche (Aksglaede et al., 2009; Herman-Giddens et al., 1997), which may be due to changes in the tempo of puberty. Girls who enter puberty later progress faster to menarche and those entering earlier take longer to progress to menarche, suggested to be a compensatory response (Biro et al., 2001, 2006; Marti-Henneberg and Vizmanos, 1997; Pantsiotou et al., 2008). This could account for the greater decrease in the age of thelarche compared to the decrease in the age of menarche in recent decades, as is most apparent when graphically represented (Fig. 1). The observation that the age of onset of thelarche has decreased more dramatically than the age of onset of menarche may be due to estrogen or estrogen like effects from tissues other than the ovary (Nelson and Bulun, 2001) without earlier awakening of the GnRH pulse generator (Aksglaede et al., 2009).

Influences on onset and tempo of puberty

Genetic effects on puberty and menarche

Twin and familial studies indicate that 49–82% of the variance in timing of puberty in girls can be explained by heritable factors, with closer age at menarche between relatives with increased degree of genetic similarity (Anderson et al., 2007; Morris et al., 2011a; Towne et al., 2005). Correlation between monozygotic twins ranges between 0.51 and 0.95, whereas the correlation between dizygotic twins range between 0.17 and 0.58 (Anderson et al., 2007). More than 30–50 novel genetic loci have been identified in genome-wide association studies (GWAS) for age at menarche (Dvornyk and Waqar ul, 2012; He and Murabito, in press), but no single gene has been discovered, which suggests that the genetics of puberty likely follows a non-Mendelian mode of inheritance.

Studies regarding the genetics of male puberty are scarce. Heritability for the age at onset of growth spurt and age at peak height velocity in a Swedish cohort of male monozygotic and dizygotic twins was 0.91 and 0.93, respectively (Silventoinen et al., 2008), similar to reported heritability estimates from a Belgian twin study, 0.93 and 0.92, respectively (Beunen et al., 2000). However, a Polish twin study reported lower heritability estimates (Silventoinen et al., 2008). There has only been a modest correlation ($r = 0.36$) reported between age at peak height velocity and age at onset of puberty in girls (Biro et al., 2006), and thus the heritability of growth may not be representative of the heritability of pubertal onset.

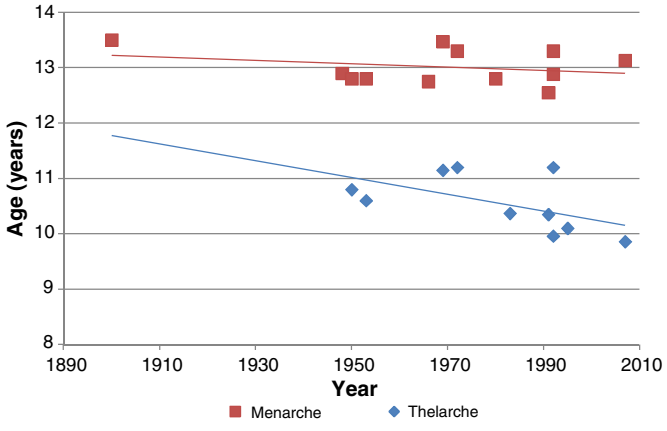

Fig. 1. Secular trends of thelarche and menarche. Although a trend toward earlier onset of both thelarche and menarche is evident, there is a clear divergence between the two trends (Aksglaede et al., 2009; Chumlea et al., 2003; Herman-Giddens et al., 1997; Lee, 1980; Marshall and Tanner, 1969; Wu et al., 2002). This appears to be a compensatory mechanism, such that girls who enter puberty earlier progress through puberty slower.

Weight and nutrition

The recent secular trend toward early puberty parallels that of the obesity epidemic (Anderson et al., 2003; Foster et al., 1977; Kaplowitz et al., 2001; Mumby et al., 2011; Wang, 2002). Recent analysis of data from NHANES III showed that children of normal BMI values rarely had breast or pubic hair development before 8 years (3.2% and 0.6%), but overweight and obese girls had earlier thelarche, pubarche, and menarche, independent of race or ethnicity (Rosenfield et al., 2009). Thelarche was determined by inspection only in the NHANES III study population, but thelarche determined by palpation in a proportion of the study subjects of the PROS study was also associated with increased BMI z-scores (Kaplowitz et al., 2001). The question of whether increased adiposity precedes or is a result of early puberty remains. Many studies report that higher adiposity in childhood is associated with earlier thelarche (Davison et al., 2003; Freedman et al., 2003; Lee et al., 2007) and menarche (dos Santos Silva et al., 2002; Frontini et al., 2003; St George et al., 1994; Tam et al., 2006). However, one longitudinal study found that BMI differences in girls were evident only after the onset of puberty in early maturing US girls (Demerath et al., 2004a). Furthermore, the association between higher adiposity and pubertal advancement does not prove a causal link.

Frisch and Revelle suggested that there may be a critical weight or amount of body fat required for the establishment of normal menstrual cycles (Frisch and Revelle, 1970, 1971). These theories are controversial. However, the discovery of leptin in 1994 (Zhang et al., 1994) provided a candidate hormone that might link body fat to endocrine changes of puberty. While an early small longitudinal study of 8 boys showed a small peak in leptin level prior to the onset of puberty (Mantzoros et al., 1997), other larger, longitudinal studies, instead described a slow and steady rise in leptin levels prior to puberty (Ahmed et al., 1999; Blum et al., 1997). Plasma leptin concentrations trend differently in boys and girls; in girls, leptin continues to rise after the onset of puberty, whereas in boys, leptin declines sharply (Ahmed et al., 1999; Blum et al., 1997). Leptin deficient children cannot enter puberty until leptin is replaced (Farooqi, 2002), but leptin treatment did not bring about precocious puberty in a leptin deficient 2 year old. Further, leptin receptor deficient individuals have hypogonadotrophic hypogonadism (Clement et al., 1998; Strobel et al., 1998). These and other studies suggest that leptin is necessary for pubertal development and may play a role in the tempo of its progression, but is not sufficient to trigger puberty. Recent studies have found no association between common polymorphisms in the leptin or leptin receptor genes and age at menarche (Banerjee et al., 2006). The role of leptin in the control of puberty is further discussed in another article within this issue of Hormones and Behavior (Sanchez-Garrido MA and Tana-Sempere M).

In boys, there has not been a consistent association between adiposity and markers of pubertal onset. Some studies report that increased adiposity is associated with earlier onset of puberty (Sandhu et al., 2006), while others report an association with later onset of puberty (Lee et al., 2010; Vizmanos and Marti-Henneberg, 2000; Wang, 2002). An increase in BMI has been found to be associated with increase in estradiol and decrease in testosterone concentrations (Rohrmann et al., 2011), which may be a result of increased activity of aromatase which coverts androgens into estradiol within adipose tissue (Nelson and Bulun, 2001). The suppressive effects of testosterone on gonadotropin secretion is mediated by aromatization of testosterone to estradiol (Bagatell et al., 1994), and estrogen provides negative feedback inhibition to both the hypothalamus to decrease GnRH pulse frequency and the pituitary gland to decrease responsiveness to GnRH (Hayes et al., 2000). Therefore, it is plausible that those boys with increased BMI and delayed puberty may have increased estradiol which suppresses gonadotropin secretion.

One study found that prepubertal body composition was not associated with the pubertal growth spurt (used as a marker of onset of puberty), but rather associated with the tempo of puberty. In both boys and girls, higher BMI before the pubertal growth spurt was associated with a shorter duration of puberty, with significantly earlier attainment of PHV and, in girls, the attainment of menarche (Buyken et al., 2009).

Ethnic differences

Analysis of data from NHANES III showed that while children of normal BMI values rarely have breast development before 8 years (3.2%), significantly more NHB girls with normal BMI achieved breast development by age 8 years compared to NHW girls (12.1% vs. 1.3%, respectively) (Rosenfield et al., 2009). Breast development in Hispanic girls with normal BMI was similarly early (19.2%). Leptin levels are greater in NHB girls, even with adjustment for fat mass and pubertal maturation (Wong et al., 1998), which may provide one factor relating to the ethnic difference in onset of puberty. Studies have also reported that NHB girls reach menarche earlier than NHW girls (12.14 years versus 12.60 years), after controlling for age and weight (Anderson et al., 2003). In general, NHB girls start to menstruate the earliest, followed by Hispanic girls and finally NHW girls (Chumlea et al., 2003; Wu et al., 2002). Furthermore, the racial difference was most evident in girls who enter puberty earliest (Wu et al., 2002), and the racial difference appears to have widened over the past half century (Freedman et al., 2002).

NHANES III data showed that NHB boys showed pubic hair growth approximately 9 months earlier than NHW boys and more than 1 year earlier than Hispanic boys, in agreement with NHANES II data (Herman-Giddens et al., 2001b). In the recent PROS study, there was a higher percentage of NHB boys at any given age with both genital and pubic hair development compared to NHW and Hispanic boys, but NHW and Hispanic boys showed no difference (Herman-Giddens et al., 2012).

Stress

Various types of stress are associated with decreased age of pubertal processes in girls. One theory explaining the effect of environmental factors on pubertal development is the life history theory (described in more detail in another article by Ellis BJ published in this issue of Human and Behavior). Factors such as an unrelated male present in the house, absence of father or poor father daughter relationship and maternal mood disorders are associated with earlier menarche (Bourguignon and Parent, 2010).

Perinatal influences and the fetal origins of adult disease

There are long-lasting effects of abnormalities in fetal and neonatal growth. Decades after birth, there is an inverse relationship between lower birth weight and an increased risk for adult disease, such as Type 2 diabetes, dyslipidemia, hypertension, and other cardiac diseases as first reported by Barker et al. in 1989 (Barker et al., 1989; Curhan et al., 1996a, 1996b). This is attributed to developmental plasticity, the ability for organisms to modify structure and function in response to environmental cues, usually occurring during critical windows during development, such as fetal and neonatal life; the modifications made are often long lasting or even irreversible (Gluckman and Hanson, 2004).

Some responses made by the developing organism to environmental conditions may not have immediate adaptive value, but are designed for predicted benefits to optimize survival and reproduction after birth (Gluckman et al., 2005). Thus, a fetus with restricted intrauterine growth that predicts a limited postnatal nutrient environment may undergo epigenetic metabolic changes that ensure that the fetus develops a physiology and metabolic homeostasis designed for the uncertain future. The environment has changed dramatically such that high-calorie food is now plentiful and energy expenditure has become reduced; hence the mismatch between predicted scarcity and experienced plenty leads to ultimate metabolic compromise and disease.

The intrauterine growth environment also affects aspects of puberty. Cross sectional and longitudinal studies have found that girls who had

lower birth weights, especially those with more rapid early postnatal growth, achieve PHV and tall childhood stature (Wehkalampi et al., 2011), thelarche, adrenarche, and menarche earlier (Adair, 2001; Ibanez et al., 2006; Koziel and Jankowska, 2002; Ong et al., 2004; Persson et al., 1999; Wang et al., 2012), and may have reduced adult height (Ibanez et al., 2000). A lower expected birth weight ratio (i.e., ratio of observed infant's birth weight to median birth weight appropriate for maternal age, weight, height, parity, infant sex, and gestational age) and a higher body mass index (BMI) at 8 years led to an earlier age of menarche (Sloboda et al., 2007; Tam et al., 2006). Rapid weight gain in the second to ninth neonatal months but not thereafter correlated with a greater BMI at 10 years and with earlier menarche in a longitudinal study (Ong et al., 2009). Lower birth weight is associated with higher serum concentrations of androstenedione and DHEAS levels in both boys and girls at adrenarche (Ong et al., 2004) with highest adrenal androgen levels among small infants who gained weight rapidly during early childhood (0–3 years).

Environmental endocrine disruptors and puberty

The concern that endocrine disrupting chemicals (EDCs), defined as "an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function" (Diamanti-Kandarakis et al., 2009) arose nearly 50 years ago. In 1996, the US Congress formally recognized EDCs as a public health concern and passed the Food Quality Protection Act and amendments to the Safe Drinking Water Act which includes a mandate to the US Environmental Protection Agency (EPA) to develop a program to identify EDCs that may have health consequences to humans. In response, the EPA has worked over the past 10 years to develop the Endocrine Disruptors Screening Program, a formal system of screens and tests that would be used to identify potential EDCs in the environment.

One of the earliest suggestions that exogenous estrogen-like compounds may affect normal development is the association between the exposure to synthetic estrogen diethylstilbestrol (DES) in the first trimester of pregnancy and the development of adenocarcinoma of the vagina in the offspring (Herbst et al., 1971). Analysis of historical data regarding infant girls who were prenatally exposed to DES revealed an association between DES exposure and an increased risk in being a preterm and/or small for gestation age birth, as well as a small elevation in risk of early menarche (Hatch et al., 2011). The findings of abnormal development of genitalia in boys, risk of low sperm count, and susceptibility to testicular cancer as adults is related to fetal exposure to pesticides suspected to cause perinatal disruption of normal testis differentiation, the Testicular Dysgenesis Syndrome (TDS) (Wohlfahrt-Veje et al., 2012).

There is evidence now that EDCs not only affect steroid based hormonal systems (i.e., sex steroids and thyroid), but are also involved in other hormone receptor types and functions, including those of metabolism, obesity, and various CNS signaling pathways (Mouritsen et al., 2010). EDCs may also cause epigenetic and transgenerational endocrine disruption (Bourguignon and Parent, 2010), with animal studies showing that exposure to EDCs at the time of gonadal sex determination results in alterations of DNA methylation that are transferred to several subsequent generations (Anway et al., 2005). Far more conclusive evidence of an adverse effect of EDC's comes from animal, rather than human studies, and some of the data on human beings derives from industrial accidents and very high level exposure rather than the lower level exposures most individuals experience. The limited research regarding EDCs on human puberty is reviewed below (Table 1 and Table 2).

Sources of EDCs

Human beings are exposed to EDCs from a wide range of sources, many that are unbeknownst to the consumer. Endocrine disrupting chemicals include organohalogens and other synthetic chemicals used as industrial solvents and lubricants, plastics, plasticizers, pesticides, fungicides, and pharmaceutical agents. On the other hand, there are natural estrogen-like chemicals found in human and animal food, such as phytoestrogens found in soy. Most organohalogens of public health concern are organochlorines that resist degradation and are lipophilic, allowing them to bioaccumulate in adipose tissue exerting long lasting effects after exposure (Longnecker et al., 1997). One study in Japan found that even house dust is an important human exposure source to endocrine disrupting chemicals (Uzumcu and Zachow, 2007).

Dioxin and dioxin-like compounds

Dioxins and dioxin-like compounds have anti-estrogenic properties, and although are present at much lower concentrations than other EDCs, their extreme potency makes it possible that health effects could occur (Longnecker et al., 1997). In 1976, a chemical explosion in Seveso, Italy, exposed the surrounding population with the highest levels of the most toxic congener of dioxin, tetrachlorodibenzo-*p*-dioxin (TCDD), in a human population. Despite this high exposure, there was no association between serum TCDD levels and reported age of menarche in females who were premenarcheal during the explosion, in spite of a 10 fold increase in TCDD levels (Warner et al., 2004). On the other hand, studies in populations exposed to lower levels of dioxins and dioxin like compounds, but perhaps at a more critical time period, showed a delay in thelarche but no change in pubarche or menarche (Den Hond et al., 2002; Leijs et al., 2008). Certain dioxin-like compounds have also been associated with delayed age at first ejaculation (Leijs et al., 2008), but results are inconsistent (Den Hond et al., 2002).

Halogenated aromatic compounds

In 1973, fire retardant was inadvertently fed to livestock in Michigan, exposing residents to animal and dairy products contaminated with polybrominated biphenyls (PBBs). Breastfed daughters of mothers with a high estimated serum PBB level at the time of pregnancy were found to have an earlier menarche than non-breastfed daughters of mothers with a low estimated serum PBB level at the time of pregnancy (Blanck et al., 2000), but no association was found with breast development.

The activity and half life of polychlorinated biphenyls (PCBs) vary according to the specific congener (Hansen, 1998; Wolff et al., 1997), which explains why some studies involving PCB congeners with known anti-estrogenic or phenobarbital-type cytochrome P450 enzyme inducing effects have been reported to be associated with delayed thelarche (Wolff et al., 2008) or menarche (Den Hond et al., 2011), whereas PCB congeners with estrogenic effects have been reported to be associated with premature menarche (Denham et al., 2005). Most studies, however, have found no relationship between the PCB exposure and changes in female puberty (Blanck et al., 2000; Den Hond et al., 2002; Gladen et al., 2000; Vasiliu et al., 2004; Yang et al., 2011).

A small study reported that boys exposed prenatally to PCB contaminated cooking oil in Taiwan were associated with abnormal sperm morphology, motility, and activity (Guo et al., 2000). While PCB congeners described to have anti-estrogenic effects were associated with delayed genital development in boys and those with enzyme inducing effects were associated with delayed pubic hair development (Den Hond et al., 2002), others have shown that PCB congeners with mixed anti-estrogen and estrogen inducing effects resulted in advanced genital development (Den Hond et al., 2011) or had no association (Gladen et al., 2000; Mol et al., 2002).

A recent analysis of NHANES 2003–2004 data on exposure to polybrominated diphenyl ethers (PBDEs), a group of chemicals structurally like polyhalogenated biphenyls, found that higher PBDE levels were associated with earlier menarche (Chen et al., 2011a), however, a smaller study found no association (Leijs et al., 2008).

Table 1
Endocrine disrupting chemicals and puberty in girls.

Compound	Suspected mechanism of action	Timing of exposure	Type of exposure	Thelarche	Pubarche	Menarche	Reference
Dioxin and dioxin-like compounds	Anti-estrogenic	Premenarchal	Explosion	■	■	–	Warner et al. 2004
		Ongoing	Proximity to Source	Delayed	–	–	Den Hond et al. 2002
		Perinatal	Background	Delayed	–	–	Leijs et al. 2008
PBB	Estrogenic, Anti-estrogenic	Perinatal	Contamination	–	Earlier	Earlier	Blanck et al. 2000
	Agonist or antagonists of estrogen/thyroid receptorsor Antagonists of and rogen/progesterone receptors	Ongoing	Background	■	■	Earlier	Chen et al. 2011
	Agonist or antagonists of estrogen/thyroid receptors or Antagonists of and rogen/progesterone receptors	Perinatal	Background	–	–	–	Leijs et al. 2008
	Estrogenic	Ongoing	Background	■	■	Earlier	Denham et al. 2005
	Mixed (Anti-estrogenic, Enzyme Inducing)	Ongoing	Background	Delayed [b]	–	■	Wolff MS et al. 2008
	Mixed (Anti-estrogenic, Enzyme Inducing)	Ongoing	Background	–	–	Delayed	Denhond et al. 2011
	Dioxin-like activity (Anti-estrogenic)	Ongoing	Proximity to source	–	–	–	Den Hond et al. 2002
	Anti-estrogenic	Ongoing	Background	■	■	–	Denham et al. 2005
	Enzyme inducing	Ongoing	Proximity to source	–	–	–	Den Hond et al. 2002
	Enzyme inducing	Ongoing	Background	■	■	–	Denham et al. 2005
	Unspecified	Ongoing	Background	–	–	–	Blanck et al. 2000
	Unspecified	Perinatal	Background	–	–	–	Gladen et al. 2000
	Unspecified	Perinatal	Contamination	■	■	–	Vasiliu et al. 2004
PCBs [a]	Unspecified	0-20 years of age	Contamination	■	■	–	Yang et al. 2011
DDT	Weakly estrogenic	Postpubertal	Textile Mills	■	■	Earlier	Ouyang et al. 2005
		Perinatal	Contamination	■	■	Earlier	Vasiliu et al. 2004
		Perinatal	Background	–	–	–	Gladen et al. 2000
DDE	Androgen antagonist	Ongoing	Background	■	■	–	Denham et al. 2005
		Ongoing	Background	–	–	–	Denhond et al. 2011
Lead	Decreased GH and other growth factors	Ongoing	Background	Delayed	Delayed	Delayed	Selevan et al. 2003[c]
		Ongoing	Background	–	Delayed	–	Wu et al. 2003
		Ongoing	Background	–	Delayed	–	Den Hond et al. 2011
		Ongoing	Background	■	■	Delayed	Denham et al. 2005

This table summarizes a selection of studies investigating common EDCs and their associations with pubertal changes in girls.
■ Black shading indicates that the particular pubertal aspect was not investigated.
– indicates that there was no effect found.
[a] Activity of PCB congers based off Wolff et al., 1997.
[b] In a subset of girls with below-median BMI and ≥ median PCB levels.
[c] Higher BLLs associated with all three pubertal markers in African American girls. Higher BLLs only associated with thelarche and pubarche in Mexican Americans, and similar but not significant trend between BLL and puberty in non-Hispanic Whites.

Organochlorines

Dichlorodiphenyltrichloroethane (DDT) has weakly estrogenic effects whereas dichlorodiphenyldichloroethylene (DDE) has been found to have anti-androgen effects (Kelce et al., 1995). Earlier menarche has been associated with populations exposed to higher levels of DDT through work exposure (Ouyang et al., 2005) and DDE through consuming marine animals bioaccumulated with pollutants

Table 2
Endocrine disrupting chemicals and puberty in boys.

Compound	Proposed mechanism of action	Timing of exposure	Type of exposure	Findings	Reference
Dioxin and dioxin-like compounds	Anti-estrogenic	Pubertal	Background	Delayed age at first ejaculation	Leijs et al. (2008)
		Ongoing	Proximity to source	–	Den Hond et al. (2002)
PCBs	Unspecified	Perinatal	Contamination	Abnormal semen quality	Guo et al. (2000)
	Anti-estrogenic	Ongoing	Proximity to source	Delayed genital development	Den Hond et al. (2002)
	Enzyme inducing	Ongoing	Proximity to source	Delayed pubic hair development	Den Hond et al. (2002)
	Mixed (anti-estrogenic, enzyme inducing)	Ongoing	Background	Advanced genital development	Den Hond et al. (2011)
	Mixed (anti-estrogenic, enzyme inducing)	Perinatal	Background	–	Mol et al. (2002)
	Unspecified	Perinatal	Background	–	Gladen et al. (2000)
DDE	Androgen antagonist	Perinatal	Background	–	Gladen et al. (2000)
		Ongoing	Background	Advanced genital development	Den Hond et al. (2011)
Lead	Decreased GH and other growth factors	Ongoing	Proximity to source	Delayed onset of puberty	Hauser et al (2008), Williams et al. (2010)
		Ongoing	Background	–	Den Hond et al. (2011)
Endosulfan	Unknown	Ongoing	Proximity to source	Delayed pubic hair and genital development	Saiyed et al. (2003)

This table summarizes a selection of studies investigating common EDCs and their associations with pubertal changes in boys.
– indicates that there was no effect found.

(Vasiliu et al., 2004). Populations exposed to background levels of either DDT or DDE have not been found to have any effects on male (Gladen et al., 2000) or female puberty (Den Hond et al., 2011; Denham et al., 2005; Gladen et al., 2000), although DDE was associated with advanced genital development in one study (Den Hond et al., 2011).

Endosulfans

Endosulfan is a broad-spectrum insecticide and acaricide (a category of pesticides used against mites and ticks), and has been classified as a moderately hazardous pesticide by the World Health Organization. In a village in northern India, boys with higher endosulfan levels had significantly lower SMR staging for pubic hair ($p < 0.001$) and genital development ($p < 0.01$) (Saiyed et al., 2003).

Lead

Animal studies suggest that lead exposure decreases concentrations of growth hormone, insulin-like growth factor 1, testosterone, and other hormones responsible for growth and pubertal development (Ronis et al., 1998). Two studies analyzing NHANES III data found higher blood lead concentrations (>3 μg/dL) associated with delays in puberty (Selevan et al., 2003; Wu et al., 2003). Other studies have confirmed delays in pubarche (Den Hond et al., 2011) and menarche (Denham et al., 2005) with elevated lead levels. A study in Russian boys found that that time to pubertal onset was significantly later for boys with high blood lead levels (≥5 μg/dl) compared with those with lower levels (Hauser et al., 2008; Williams et al., 2010).

Barriers to understanding the effect of EDCs on human population

Although it is widely accepted that the human endocrine system is a biologically plausible target for disruption by the large number of man-made chemicals released into the environment, the full extent of such chemicals have on human health remains unknown. The effects of EDCs on human health have been difficult to understand for several reasons. First, human studies have been small, have had conflicting results, and report associations rather than causality. The mechanism of action of EDCs can be quite complex and it may be difficult to determine their specific target (Safe et al., 1997). In addition, human beings are usually exposed to mixtures of EDCs, which makes it difficult to parse out the effects of each component. To add more complexity, some EDs only become active in mixtures, such that the sum of the effects of several individual EDCs does not predict the effect of the whole. Furthermore, timing of exposure may play a critical role in the severity and reversibility of their adverse effects, and there may be a lag between exposure and manifestation of a disorder. In addition, individual differences in metabolism and body composition will create variability in the half-life and persistence of EDCs (Diamanti-Kandarakis et al., 2009). Lastly, as is generally true of most lines of investigation, variations in methodology between studies adds to the difficulties of interpreting results.

Variation in methodology awakens other concerns for the health in children. Cattle in the US and some other countries are routinely treated with estrogen or synthetic alternatives to increase rate of weight gain; this adds estrogenic effect to the natural estrogens found in all animal tissues without treatment (this practice is banned in the European Union.) The FDA set the limits on the hormone content of animal products decades ago as 1% of the production rate of hormones in children. These production rates and the hormone content in a standard serving of meat were established by less sensitive methods of detection than are available today, raising the concern that although the hormone content of animal tissues in our diet pass US standards, the hormonal content may actually be relatively high using newer technologies (Aksglaede et al., 2006).

Neurodevelopmental consequences of EDCs

The prevalence of neurodevelopmental disorders such as attention-deficit disorder and autism spectrum disorders has increased in recent years, which may be due to many factors including increased awareness and diagnosis (Meeker, 2012). However, the National Academy of Sciences suggests that the etiology of 3% of theses developmental disorders may be attributed to a toxic environmental exposure, including EDCs, and another 25% may result from an environmental insult occurring in conjunction with a genetic predisposition (Miodovnik, 2011). Higher BPA levels at birth were associated with higher scores for measure of anxiety, hyperactivity, emotional control, and behavioral inhibition at 3 years of age, and the effects were larger among girls than boys (Braun et al., 2011).

Clinical consequences

Premature puberty

Girls who enter puberty early are more likely to have psychological outcomes, including internalizing and externalizing problems (Graber et al., 1997; Kaltiala-Heino et al., 2003b; Marceau et al., 2012). There are two popular hypotheses regarding the association between pubertal timing and negative behavioral outcomes. The *early timing* or *developmental readiness* hypothesis predicts that "the early maturer is less prepared for the sudden intensifications of drive in adolescence" (Peskin, 1973). This theory is supported by studies that found that early maturing girls have higher rates of depression (Ge et al., 2003; Graber et al., 1997; Kaltiala-Heino et al., 2003a; Kaltiala-Heino et al., 2003b), substance abuse or dependence (Deppen et al., 2012; Graber et al., 1997; Kaltiala-Heino et al., 2003b, 2011; Tschann et al., 1994), disruptive behavior disorders (Caspi and Moffitt, 1991; Graber et al., 1997; Kaltiala-Heino et al., 2011), eating disorders (Graber et al., 1997; Kaltiala-Heino et al., 2001, 2003b), and precocious sexuality (Deppen et al., 2012).

The *off-time* or *maturational deviance* hypothesis proposes that adolescents who develop either earlier or later relative to their peers experience psychological distress and manifest behavioral problems. Adolescents who have a deviant tempo of puberty in which they progress unusually quickly or slowly through puberty may also be at risk for psychological problems. Studies that support this hypothesis have found that girls who deviate from "normal" onset of puberty (i.e., both early- and late-maturers) suffer from psychological consequences (Reynolds and Juvonen, 2012), behavioral and social problems in adolescence (Graber et al., 1997), substance use (Bratberg et al., 2005), including higher rates of conduct problems (Burt et al., 2006).

There has been less research regarding timing of puberty and psychosocial consequences in boys, and the findings have been inconsistent. A majority of more recent studies have found that early puberty is associated with internalizing and externalizing disorders in boys (Ge et al., 2006a; Kaltiala-Heino et al., 2003b). Earlier maturing boys have increased behavioral problems (Kaltiala-Heino et al., 2011), earlier substance use (Ge et al., 2006b; Kaltiala-Heino et al., 2011; Tschann et al., 1994) as well as early sexual activity (Marceau et al., 2011). While some studies found that late maturation in boys was associated with poor psychosocial development (Graber et al., 1997, 2004), other groups found that late maturating boys are protected against certain adverse outcomes, such as reduced risk of alcohol drinking (Bratberg et al., 2005).

Recently, the *maturational compression* hypothesis was proposed to explain the relationship between tempo of puberty and psychosocial and behavioral problems (Mendle et al., 2010). This hypothesis predicts that those who have a rapid tempo of puberty and progress unusually quickly may not have time to acclimatize to the biological and social changes and thus develop psychological problems. Ge et al. investigated symptoms of major depression in African American children in relation to pubertal timing and pubertal change (Ge et al., 2003). For girls, early pubertal timing significantly predicted a more severe level of depressive

symptoms, but there was no association with rate of pubertal change. For boys, early pubertal timing as well as accelerated pubertal change predicted increased symptoms of depression. Mendle et al. reported similar findings as Ge et al., but added that for boys, the relationship between pubertal tempo with depressive symptoms was significantly greater than that of pubertal timing (Mendle et al., 2010). A more recent study found that both earlier timing and faster tempo are associated with more internalizing problems in girls (Marceau et al., 2011), but results were inconclusive with boys.

Beyond these social consequences, early pubertal development and menarche are related to an array of pathological conditions. There is substantial evidence to link earlier age at menarche with a greater risk of development of breast cancer (Ahlgren et al., 2004; Clavel-Chapelon and Gerber, 2002; De Stavola et al., 2004; Gao et al., 2000; Hamilton and Mack, 2003; Tehard et al., 2005). A recent meta-analysis from 117 epidemiological studies of 118,964 women with breast cancer showed that breast cancer risk increased by a factor of 1.050 (95% CI 1.044–1.057; $p < 0.0001$) for every year younger at onset of menarche (Collaborative Group on Hormonal Factors in Breast, 2012). Evidence from the Fels Longitudinal Study of NHW females revealed that girls with self-reported menarcheal age of less than 11.9 years (classified as early menarche; 23% of the sample) had adverse cardiovascular risk factors such as elevated blood pressure and glucose intolerance unrelated to body composition (Remsberg et al., 2005). Earlier age at menarche is associated with the development of postmenarcheal asthma (Al-Sahab et al., 2011), as well as a higher risk of Type 2 diabetes in later life, which is most strongly attenuated by adolescent and adult adiposity (Chen et al., 2011b; Pierce et al., 2012). There is indirect evidence relating earlier menarche to increasing likelihood of hepatocellular carcinoma (Mucci et al., 2001). Indeed, there was a 1.17 increased risk of all cause mortality in Japanese women who had menarche younger than 12 years (Tamakoshi et al., 2011) and an inverse relationship between age at menarche (Sobotnik et al., 2010) and total mortality.

Conclusions

Puberty is a complex process resulting in maturation of the HPG axis and physical changes of secondary sexual development. There has been a secular trend toward earlier puberty in both males (Herman-Giddens et al., 2012; Sorensen et al., 2010) and females (Aksglaede et al., 2009; Chumlea et al., 2003; Herman-Giddens et al., 1997; Wu et al., 2002); in particular, a decrease in the age at thelarche appears to be the most dramatic. The cause of this trend, whether due to activation of the HPG axis or to gonadotropin-independent estrogenic effects, remains an open question. Concerns regarding lowering the lower limit of normal pubertal onset, which would theoretically risk masking those presenting with true precocious puberty and perhaps a pathologic etiology, also remain in the minds of some (Sorensen et al., 2012). The onset of puberty has long been known to be affected by a combination of genetic and environmental cues including geographic location, chronic diseases, and diet (Danker-Hopfe, 1986). Since genetic influences do not change dramatically from one generation to the next, the significant secular trends noted are more likely a result of environmental changes (Golub et al., 2008), such as endocrine disrupting chemicals, or a result of the obesity epidemic. Associations between EDCs and adverse health effects have been seen after toxic accidents as noted above. However, these types of high, single exposure incidences are not representative of the constant widespread exposure to chemicals that have contaminated our environment. Studies investigating background exposures to a variety of EDCs have been inconsistent and limited by several factors, such as exposures to mixtures that potentially could exert opposing affects and the timing of the exposure. The most consistent evidence is that increased lead levels may be associated with delayed pubertal markers. The observed changes in onset and tempo of puberty have an array of clinical consequences, including adverse behavioral and psychosocial outcomes. This makes it all the more urgent that more investigation to answer these questions be carried out.

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