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Connections Between Obesity and Puberty:

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Abstract

The relationship between obesity and puberty remains controversial. Whereas cross-sectional and longitudinal studies show a clear shift toward earlier puberty in obese girls, the trend in obese boys remains less obvious. Overweight boys mature earlier whereas obese boys mature later compared to healthy weight boys. Newer epidemiologic studies attempt to address these knowledge gaps. This review provides a detailed overview of the recent literature regarding secular trends in pubertal onset and tempo, and the connection with obesity. Additionally, this review summarizes potential mediators that permit obesity to promote early puberty. Other factors such as socioeconomic status, in utero exposures, nutritional, and even endocrine disrupting chemicals can cause perturbation of both metabolism and the endocrine axis that can ultimately have effects on pubertal development.

Keywords

Puberty; Obesity; Socioeconomic Status; Leptin; Endocrine Disrupting Chemicals (EDCs)

Introduction

Globally, the prevalence of obesity increased in every country between 1975 to 2016 according to a study including BMI trends from 128.9 million children, adolescents and adults around the world [1]. In the US, 18.5% of children and adolescents were considered obese, a condition associated with increased risk of metabolic complications including disturbances in pubertal development [2]. Puberty is the culmination of a complex interplay between genetics, metabolic, nutritional, and hormonal factors. Thus, childhood obesity may play a role in pubertal onset and tempo. In fact, early pubertal development and central precocious puberty have been associated with childhood obesity [3, 4]. Population based

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studies from around the world have correlated high body mass index (BMI) with earlier pubertal maturation in girls [5]. The relationship between obesity and early pubertal onset in boys remains controversial. Furthermore, new mechanistic studies and data suggests that other environmental factors such as socioeconomic status, in utero exposures or endocrine disrupting chemicals maybe additional drivers of early pubertal onset.

Assessment of pubertal stages

For both girls and boys, physical palpation of breast bud development and testicular enlargement is the gold standard for determining the onset of puberty, which often is not possible in large population-based studies. In girls, the development of glandular breast tissue is the initial sign of estrogen production; however, determination of actual glandular breast tissue from adipose tissue is challenging in overweight and obese girls [6]. This may lead to misclassification of pre-pubertal obese girls as being in early puberty [5]. Age of menarche is another milestone of female puberty. There is a significant association between these two pubertal milestones, yet they are not interchangeable. The time between thelarche to menarche has been shown to be longer in girls with earlier thelarche [7]. Thus, later age of menarche does not necessarily reflect normal age of thelarche. In boys, testicular enlargement of more than 3 ml is a classic marker of pubertal onset, which requires invasive palpation. Unfortunately, there are limited simple and reliable self-reported markers for pubertal timing in boys. Most data rely solely on visual grading of genital development [6]. Subtle changes in breast development or changes in scrotal skin texture or penile size may be overlooked [5]. Other methods include questionnaires, which are prone to reporting bias. These methods include drawings of Tanner stages to collect information on puberty, including Tanner stages for pubic hair and breast or genital development, and yes or no questions for axillary hair, and acne, including age of menarche, first ejaculation of semen and voice break [8]. Pubertal onset (the start of puberty) must also be differentiated from pubertal development, which refers to the tempo of pubertal progression.

Secular trends for puberty stages - cross-sectional studies in females

Several cross-sectional studies have identified an association with obesity and earlier pubertal onset in girls. From historical data of the US and Europe in the early 19th century, the age of menarche was approximately 17 years. As a result of improved nutrition, hygiene and socioeconomic conditions, by the mid-20th century there was a dramatic decline to approximately 13 years [9, 10]. In contrast, during the past 25 years, age at menarche has only declined by 2 months [11, 12]. A recent meta-analysis evaluated secular trends of thelarche and found that onset of thelarche had declined nearly 3 months per decade from 1977 to 2013 [13]. This trend toward early pubertal onset is also true for girls with Turner Syndrome who either underwent spontaneous or induced puberty [14]. A multicenter study in the US including 3 geographically distinct locations recruited 1239 girls aged 6-8 years old from 2004-2006. Tanner staging for breast development was done by palpation and demonstrated that increased BMI was a predictor for early onset of breast development [15]. The relationship between obesity and early onset of puberty in girls has also been described in China, India, and Nigeria [16–18]. These studies support a trend of earlier pubertal onset by several months in overweight compared to normal weight girls. Additionally, pubertal

onset declined by approximately 12 months paralleling the increased prevalence of obesity in the last decade [12, 19]. Given the limitations of cross-sectional studies, a definitive conclusion cannot be made but the data is compelling.

Secular trends for puberty stages - cross-sectional studies in males

Trends in pubertal timing for boys remains less apparent and the impact of obesity on puberty remains a controversial topic. This is in part due to fewer and smaller studies, many of which are not population-based. Some studies demonstrate that boys with greater BMI enter puberty earlier [20]; however, others report boys with greater BMI entered puberty later [12]. In fact, other studies were equivocal [21]. The most recent US study assessed pubertal status by testicular palpation in 4,131 boys from 2005-2010 and found earlier puberty in overweight boys compared to normal weight, and later puberty in obese compared to overweight [22]. A Swedish study examined two cohorts of boys (born in 1945-1961 and 1981-1996) and found that for every unit increase in childhood BMI, the age of peak height velocity (PHV) was earlier by 2 months but only in normal weight boys and not for overweight boys [23]. A recent analysis of 1,306 boys aged 6-17 years old in India determined the mean age of gonadarche was 10.41 years, which was considerably earlier than a previous study (11.2 years) [24]. Being overweight or obese did not lead to earlier gonadarche [24]. Taken together, these more recent studies suggest that there are more secular trends towards earlier puberty in boys but obesity's role remains uncertain.

Secular trends for puberty stages– longitudinal studies

Longitudinal population studies offer additional insight with less risk of confounding seen in cross sectional studies. In Denmark, school health records from 350,445 boys and girls born in 1930-1983 were assessed and demonstrated that for both sexes the heavier they were at age seven, the earlier they entered puberty [25]. Further analysis revealed a drop in the age of pubertal initiation in both sexes irrespective of BMI – highlighting that the obesity epidemic is not the only factor for this secular trend. The Danish National Birth Cohort assessed 7,104 boys and 7,655 girls born from 2000-2003 starting from age 11.5 years and throughout puberty [8]. Voice break in boys occurred around 13.1 years compared to former studies from 1968 to 2005 that reported 14.0-15.5 years. For girls, age of menarche was 3.6 months earlier than their mothers. In another more recent longitudinal study in girls from the US, 946 girls enrolled at 6-8 years old were assigned an age of menarche based on parental and participant report [7]. The age of menarche (median 12.25 years) was correlated with age of breast development. Furthermore, higher BMI was associated with early onset of menarche, which suggests that increased adiposity may be linked with earlier pubertal onset in girls.

There are limited longitudinal studies that examine pubertal timing in boys. A recent large population-based retrospective cohort study in Sweden analyzed the records of 4,090 boys born between 1947 to 1996 [26]. There was a secular trend where age of PHV was 1.2 months earlier per decade increase in birth year. They found an inverse relationship between BMI and PHV that was only seen in normal and overweight boys, but not in obese boys. The most recent study on pubertal timing followed 218 obese and healthy weight boys aged 4-

17 years old in Denmark from 2009 to 2017 [27]. They used a reliable pubertal assessment technique – testicular palpation with an orchidometer. Gonadarche was significantly earlier in the obese cohort compared to healthy weight controls (11.3 years compared to 11.7 years, respectively). Overweight vs obese boys had no difference in timing of gonadarche or pubarche. Of note, the delay in puberty in obese boys as seen in other studies was not observed. These longitudinal data suggest a secular trend in early pubertal timing in both overweight and possibly obese males, but additional studies are necessary.

Association between socioeconomic status and onset of puberty

Several studies have implicated low socioeconomic status (SES) as a risk factor for the development of childhood obesity [28, 29] and suggest that SES may also modulate pubertal development. A racially diverse sample of adolescents boys and girls from Philadelphia (n=281) were studied and those with low SES experienced earlier pubertal timing [30]. Another study in the US evaluated 9,498 children (51.7% females) and correlated both low SES and traumatic stressful events with early puberty for both girls and boys [31]. However, both studies did not assess if BMI modulated pubertal onset. Another US study revealed a relationship between low SES (maternal unmarried status and low family income) and early menarche in girls; however, BMI did not mediate this association [32]. On the contrary, studies on Australian [33] and Japanese [34] children found that both low SES and higher BMI were both risk factors for early puberty. In the Australian cohort, this was true for both boys and girl and this was only true for males in the Japanese cohort.

In developing countries, the converse appears to be true in that higher SES predicts early pubertal onset. For example, girls in the upper socioeconomic class in Nigeria had earlier onset of pubertal maturation compared to girls in middle and low SES [16]. This was thought to be driven by the association of higher BMI in girls with high SES, who may have better nutritional status. Unfortunately, it is unclear if this is true in boys as there are no studies assessing males in low SES in underdeveloped countries. Ethnicity also appears to play a larger role in early puberty than obesity. Pubertal onset occurs earlier in non-Hispanic black and Mexican American girls compared to Caucasian females but this was independent of adiposity [35]. More studies are needed to understand how both SES and ethnicity interact with nutritional status and pubertal development.

Mechanistic studies regarding potential impact of overweight and obesity on puberty onset

Data from both longitudinal and cross-sectional studies show a relationship between obesity and the onset of early pubertal milestones in boys and girls albeit it is not the only influencing factor. The initiation of puberty is dependent on the enhanced pulsatile release of gonadotropin releasing hormone (GnRH), which ultimately activates the hypothalamic-pituitary-gonadal axis (HPG) [5]. Adipose tissue acts as an endocrine organ secreting adipokines including proinflammatory adipokines that promote insulin resistance. Adipokine leptin plays a specific role in the regulation of the HPG (Figure 1). Adipokine leptin is a quantitative marker for subcutaneous fat stores and signals to the hypothalamic GnRH pulse generator that there are ample energy stores for pubertal initiation. Leptin is a permissive

factor and is necessary but not sufficient for initiation of puberty [36]. Interestingly, leptin has sexually differential effects. In girls, leptin rises prior to pubertal onset and its peak precedes the gonadotropin peak. This is not the case for boys as peak gonadotropin concentrations are not associated with peak leptin levels [37]. Moreover, testosterone inhibits leptin secretion whereas estrogen stimulates leptin secretion from adipocytes. Leptin's sexually differential effects on GnRH secretion may contribute to earlier pubertal onset in obese girls and later onset in obese males. Other species of adipokines may also contribute to the regulation of the HPG axis and future studies are needed to determine which are relevant.

Increased adiposity may also have peripheral effects that promote early puberty (Figure 1). Adipose tissue has aromatase enzyme activity and can increased androgen conversion to estrogens [5]. Obesity has also been shown to promote adrenal androgen production [38]. Thus, obesity may also result in greater peripheral conversion of androstenedione to estrone and testosterone to estradiol independent of gonadotropins. In alignment, children with obesity have higher concentrations of estradiol compared to healthy weight [12]. For girls, this excess estrogen may promote earlier puberty and have the converse effect on boys. More studies are needed to understand how these peripheral hormonal changes influence pubertal onset.

Over the last several decades, we have seen a decline in pubertal timing and the reasons for this are likely related to environmental and social factors and less likely attributed to alterations in the genetic pool. Critical phases of human development, including fetal and neonatal life and onset of puberty, are characterized by the ability to respond to nutritional and other environmental factors by epigenetic programming. Epigenetic modifications allow or silence the expression of the certain genes across tissues rather than changing the underlying DNA sequence [39]. In utero exposures, improved health and nutrition, childhood obesity, and endocrine disrupting chemicals are environmental factors that drive epigenetic modifications. This is not to say that underlying genetics do not play a role in pubertal timing. Genome wide association studies have found a number of significant single nucleotide polymorphisms (SNPs) associated with pubertal development [40, 41] including SNPs related to obesity.

The in-utero environment may play a critical role in the onset of pubertal timing, but data is limited. Some risks factors for earlier pubertal onset include being a small fetus in utero, maternal obesity and maternal hyperglycemia during pregnancy [42, 43]. These associations were found for girls but not boys. Along this vein, postnatal rapid catch-up weight gain from birth to 1 year of age has been associated with higher weight, BMI and percentage of fat mass at 18 years of age in both sexes [44]. Interestingly, rapid catch-up weight was also associated with younger age of menarche in girls (12.5 vs 13.1 years). Furthermore, boys in the 1946 British Birth Cohort were studied and those who had rapid weight gain from birth to 2 years of age had higher adult fat mass and more advance voice breaking — paralleling what is seen in girls [45]. Children with chronic illness, who often have delayed puberty due to inflammatory cytokines and poor nutrition, illustrate the importance of adequate health and nutrition for puberty initiation [46]. Nutritional status, thus, likely modulates pubertal timing. Recently, novel pathways that allow for “sensing” nutritional status (SIRT1 and

AMPK) were discovered to regulate Kiss1 neurons and influence pubertal onset in rats [47, 48]. In humans, higher body weight and BMI were identified as risk factors for both precocious puberty and rapid pubertal tempo in girls with premature thelarche—suggesting that obesity is a driver of early puberty [49]. Furthermore, obesity itself may also alter secretion of sex hormones in early puberty in both sexes [50]. Contrary to this, another study demonstrated no association between serum estradiol levels and excess weight or central adiposity in prepubertal girls [51]. Thus, further studies are needed to examine the role of adiposity in pubertal development.

For the last 20 years evidence has accumulated that exposure to endocrine disrupting chemicals has impact on pubertal timing in various parts of the world: The US, England, Europe and Korea [52–54]. Establishing a causal relationship between EDCs and pubertal changes remains challenging [55]. Several studies have linked phenols and phthalates exposure with early puberty in girls including early thelarche and menarche [56, 57]. Unfortunately, the data about the effects of early exposure to EDCs on pubertal timing of boys is limited and contradictory.

Summary

In summary, longitudinal studies confirm the observation of cross-sectional studies demonstrating a potential relationship between obesity and the timing of early pubertal milestones in both boys and girls. Longitudinal studies clearly demonstrate that obesity is only one of many factors influencing timing of puberty. Both cross-sectional and longitudinal studies suggest that increased adiposity in girls is associated with earlier onset of puberty and age of menarche. In boys, the situation is more complex, with conflicting findings regarding whether overweight boys versus obese boys differ in their pubertal onset (early versus delayed, respectively). This is due in part to unreliable male pubertal assessment techniques. A more recent longitudinal study utilizing testicular palpation found that both overweight and obese boys had earlier gonadarche compared to healthy weight boys, which contradicts previous studies using other means of pubertal assessment such as voice break or peak height velocity. These epidemiological findings suggest a link between obesity, adiposity, and early puberty.

Additionally, it is not entirely clear whether obesity stimulates central nervous activation of the HPG axis. The most promising link between obesity and pubertal onset seems to be adipokine leptin. Leptin has a clear impact on the brain's ability to regulate puberty. Circulating levels of leptin differ between boys and girls and have different effects on pubertal onset, which may partially explain the sex difference concerning puberty onset between boys and girls. Understanding the link between puberty and obesity is crucial as obesity's link to earlier age of pubertal onset may have long term consequences such as impairment in adult final height or poorer psychological and behavioral outcomes [58]. Other factors such as genetic background, in utero and postnatal environment, EDCs, socioeconomic status have also been linked to both obesity and earlier puberty. Further studies are needed to understand how the interplay of these factors contribute to the development of obesity and early pubertal onset.

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Highlights

- A secular trend of earlier onset of thelarche and menarche in girls has been observed in the United States, Europe, and other countries in the last 150 years.
- Trends in pubertal onset of boys are less clear as there are fewer studies. However, recent data shows a similar trend of earlier onset of puberty and earlier pubertal growth spurt in the last 70 years.
- For girls, the association between increased adiposity and earlier onset of puberty and menarche has been documented in many studies.
- For boys, the link between adiposity and pubertal onset is less clear. Recent longitudinal data demonstrate being overweight or obese may contribute to earlier gonadarche and peak height velocity; however, these studies are not consistent with cross sectional data that has shown delayed puberty in obese males.
- The decline in pubertal timing over the last several decades is likely to be related to environmental and social factors and less likely due to alterations in the genetic pool. Several causal factors ranging from in utero exposures, improved health and nutrition, increased leptin from childhood obesity, endocrine disrupting chemicals have been implicated.

Figure 1. Hypotheses linking obesity, insulin resistance, and adipokine secretion to timing of pubertal development.

Adapted from Reinehr et al. Lancet 2019. SHBG = sex hormone binding globulin. GnRH = gonadotropin releasing hormone. HPG = hypothalamic-pituitary-gonadal

Table 1.

Summary of Recent Studies on Onset of Puberty

Authors	Year	Country	Study Design	Data Collection	Sample Size (n)	Sex	Age (y)	Pubertal Assessment	Primary Outcome
Eckert et al [13]	2020	International	Meta-analysis	1977-2013	30 studies	Girls	-	Thelarche (self report and palpation)	Pubertal onset by thelarche decreased by 3 months per decade from 1977-2013 globally.
Busch et al [27]	2020	Denmark	Mixed cross-sectional and longitudinal	2009-2017	218	Boys	4.2-17.0	Tanner stage (orchidometer)	Testicular enlargement occurs earlier in obese boys compared to normal weight.
Brix et al [8]	2019	Denmark	Longitudinal	2012-2017	7655 7104	Girls Boys	11.5 -18	Self-report questionnaire	Age of menarche has declined. Males had some decline in age of puberty.
Ohlsson et al [26]	2019	Sweden	Longitudinal	1947-1996	4090	Boys	-	Peak Height Velocity	Inverse relationship between BMI and PHV in overweight and normal weight but not seen in obese boys.
Lian et al [17]	2019	China	Cross-sectional	2012 & 2013	2996	Girls	9-19	Tanner Stage (palpation)	Obesity and overweight girls had earlier breast and pubic hair.
Biro et al [7]	2018	US	Longitudinal	2004-2007	946	Girls	6-8	Parental and Participant Report (menarche)	Age of menarche inversely correlated with BMI. Racial difference in timing of menarche.
Bygdell et al [23]	2018	Sweden	Cross-sectional	1945-1961 1981-1996	31,971 1465	Boys	6.5-22	Peak Height Velocity	Inverse association of BMI and pubertal timing (PHV) in normal weight but not overweight boys.
Woeffle et al [14]	2018	International	Longitudinal	1987-2012	7219	Turner Syndrome Girls	7-9	Tanner stage (palpation) Self report menarche	Declines in age of onset of spontaneous and induced puberty (-2.0 years) and menarche (-2.1 years).
Kubo et al [43]	2018	US	Cross-sectional	2003-2006	15,267	Girls	6-11	Tanner stage (palpation)	Maternal obesity and hyperglycemia during pregnancy associated with early breast development.
Cicek et al [49]	2018	Turkey	Longitudinal	2005-2015	158	Girls	0-8	Tanner stage (palpation)	Higher BMI predicted precocious or rapid temp of puberty in girls with premature thelarche.
Bratke et al [19]	2017	Norway	Cross-sectional	2003-2006	1481	Girls	8-15.5	Self report menarche	Earlier menarche related to high BMI (HR 1.41)
Surana et al [24]	2017	India	Cross-sectional	2013	1306	Boys	6-17	Tanner stage (orchidometer)	Decline in age of pubertal onset in Indian boys. High BMI associated with earlier pubarche but not gonadarche.
Deng et al [42]	2017	International	Meta-analysis	1946-2016	2366	Girls Boys	0-18	Age of menarche Tanner stage (orchidometer)	Being a small fetus was associated with earlier puberty in girls but no in boys.

Authors	Year	Country	Study Design	Data Collection	Sample Size (n)	Sex	Age (y)	Pubertal Assessment	Primary Outcome
Lee et al [22]	2016	US	Cross-sectional	2005-2010	3872	Boys	6-16	Tanner stage (orchidometer)	Racially diverse group with early puberty for overweight and later puberty for obese boys compared to normal weight boys.
Khadgawat et al [18]	2016	India	Cross-sectional	2013	2010	Girls	6-17	Tanner Stage and self-report (menarche)	Overweight and obese girls had 6 month earlier thelarche and menarche.
Anyanwu et al [16]	2016	Nigeria	Cross-sectional	2012-2013	1150	Girls	6-18	Tanner Stage (palpation) and self-report (menarche)	Higher SES, overweight and obesity correlated with earlier thelarche and menarche.
Crocker et al [12]	2014	US	Cross-sectional	1996-2010	627 439	Girls Boys	5-17	Tanner Stage (palpation)/ orchidometer)	Higher BMI associated with early puberty in girls. Obesity associated with smaller testicular volume and delayed puberty.
Sorensen et al [20]	2010	Denmark	Cross-sectional	1991-1993 2006-2008	1528	Boy	5.8-19.9	Tanner Staging (orchidometer)	Age of pubertal onset by testicular volume declined and was associated with increase in BMI.
Aksela et al [11]	2009	Denmark	Cross-sectional	1991-1993 2006-2008	2095	Girls	5.6-20.0	Tanner Staging (palpation)	Earlier breast development not explained by BMI.
Aksela et al [25]	2009	Denmark	Longitudinal	1930-1969	135,223 21,612	Girls Boys	0-8	Peak Height Velocity Onset pubertal growth spurt (OGS)	For both sexes, high BMI at age 7 associated with early puberty. Secular trend for pubertal onset boys and girls regardless of BMI.