

The Intricate Relationship between Chronic Undernutrition, Impaired Linear Growth and Delayed Puberty: Is 'catch-up' growth possible during adolescence?

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THE INTRICATE RELATIONSHIP BETWEEN CHRONIC UNDERNUTRITION, IMPAIRED LINEAR GROWTH AND DELAYED PUBERTY: IS 'CATCH-UP' GROWTH POSSIBLE DURING ADOLESCENCE?

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EXECUTIVE SUMMARY

The global nutritional crisis, which forms the backdrop for the lives of the 1.8 billion adolescents in low- and middle-income countries (LMICs), has made stunted growth and the delayed onset of puberty common in many regions. These undernourished individuals experience various manifestations, beginning with low birth weight and height-for-age z-scores (HAZ) scores, followed by slow linear growth rates during childhood and culminating in the delayed commencement of puberty. This delay, one can logically assume, is due to the body's prioritization of more critical processes over physical growth and reproductive capacity.

The first 1000 days of life have been articulated as the optimal window for implementing stunting recovery interventions. While this remains true, certain researchers have also investigated whether interventions outside this window were effective (1). The highest rated question in a most recent review on the relationship between stunting and wasting was "Can interventions outside of the 1000 days, e.g. pre-school, school age and adolescence lead to catch-up in height and in other developmental markers?" (2). The potential for a catch-up growth (CUG) window in adolescence has been suggested for some time but has not yet been substantiated (1, 3, 4).

What do we know about catch-up growth during adolescence?

Difficulties in determining CUG during adolescence arise from incomplete data on the subject. During early adolescence, it is difficult to differentiate growth during the pubertal growth spurt from CUG. Here, sexual maturation data is vital because a person who experiences early puberty may not necessarily be catching-up in growth. For example, at the same chronological age, girls who have experienced menarche will be taller (with some normally assumed variation) than premenarcheal peers. As such, the extent to which CUG has occurred during adolescence may be best determined following puberty when adult height has been reached.

In this review, we highlight studies examining: CUG in observational longitudinal studies in LMICs; CUG in children born small-for-gestational age (SGA); and CUG in children who have migrated or are adopted into better environments. Several LMIC observational birth cohorts illustrate the fluid nature of CUG with transitions in and out of stunting during childhood and adolescence, until adult height is reached. Studies measuring the growth of children born SGA imply that CUG during childhood predisposes one to increased risk of metabolic syndrome and short stature due to early puberty. Additionally, immigration and adoption studies suggest that the timing of the change in environment is critical. There exists an increased risk of precocious puberty, as well as early onset puberty and shorter adult stature, if migration or adoption occurs in younger childhood years. This is thought to be due to a change in environment with improved socioeconomic standards, which can trigger endocrine responses.

Research gaps and recommendations for future research

Despite the available evidence on CUG in adolescence, there still exists a paucity of high-quality data. Specifically, there are several limitations inherent in the heterogeneity of study designs, populations, secular trends and statistical methods. As there is currently no global standard to identify CUG in adolescence, mainstreaming results is a challenge. Additionally, in terms of representative populations, little is known about CUG in boys, as most studies are conducted within predominantly female populations. Moreover, underlying biological mechanisms with regards to the role of epigenetics still require delineation.

These limitations are important given that interventions aimed at ameliorating stunting by augmenting CUG during adolescence will be compromised without knowing the timing of puberty onset, duration and completion. All in all, understanding CUG in its entirety will require significant stakeholder investment and consensus on research methods in order to strengthen existing findings.

INTRODUCTION

Chronic undernutrition is characterized by long-term exposure to food of insufficient quality and inadequate quantity, including restricted intake of energy, protein, fat, micronutrients, essential amino acids, vitamins and minerals. Physiologically, in a state of chronic food insufficiency, the human body conserves energy by prioritizing essential metabolic processes resulting in impaired linear growth and delayed reproductive maturation. Consequently, height can theoretically be considered a measure of an individual's cumulative health and nutrition. Therefore, a deviation from the 'normal' height relative to one's age represents a deviation from one's optimal growth and, potentially, the presence of other issues. Similarly, the delayed onset of puberty is another common physiological response to food insufficiency, often accompanying impaired linear growth. Chronic undernutrition can arise from chronic disease, congenital abnormalities and insufficient food intake. In this review, we will explore the hypothesis of CUG during adolescence, given the relationship between impaired linear growth and the delayed onset of puberty in children suffering from chronic undernutrition due to a lack of sufficient quality and quantity of food.

Linear growth

Linear growth is determined by measuring one's height and is an inherited trait with genetics accounting for about 50 per cent of its variation (5, 6). Height is thought to be sensitive to nutrition until adequate nutritional levels are achieved. After this, height is determined by genetic factors – provided no other restraints exist (5). Long-term exposure to an inadequate diet, repeated exposure to infection and the inability to engage in 'catch-up' growth are characteristics of chronic undernutrition and the resulting impaired linear growth can be quantified in height-for-age z-scores (HAZ) scores. Stunting is the indicator for undernutrition and is identified by an HAZ-score of less than -2 standard deviations of the World Health Organization - Growth Standards (WHO-GS) median (7). The complex relationship between stunting and factors which span community, household, maternity and individual traits is outlined elsewhere in the WHO Conceptual Framework on Childhood Stunting (8).

Fetal and neonatal growth

It is generally accepted that size at birth is an important indication of fetal health, neonatal health and, ultimately, adult health. Birth size is affected by two factors: (a) time – the length of gestation and (b) growth rate – i.e. increase in fetal size. A newborn's size is the result of the average growth rate over the gestation period. Growth may have taken place in periods of rapid, slow and/or steady growth. Body size continues to be affected by gestation time and growth rate during childhood and into puberty until long bone skeletal fusion is achieved.

Growth during early childhood is routinely monitored and suboptimal growth conditions are detected at birth via indicators like possessing a low birth weight or being small for one's gestational age. Once born, an infant can be categorized according to gestational age and size. Based on standard sex-birth-weight-for-gestational-age conventions, an infant is SGA when its body size at birth falls below a specific cut-off for gestational age (7).

Another term used to describe early suboptimal growth is intrauterine growth retardation (IUGR). IUGR is diagnosed during pregnancy after at least two ultrasound assessments of reduced growth are apparent when compared to a standard fetal growth chart. Whereas SGA refers to the size of

the infant at birth, IUGR refers to a decrease in growth of the unborn infant; therefore, they are not synonymous. SGA is often related to IUGR, but not all SGA infants have suffered from IUGR and infants who are born after a short period of IUGR are not necessarily destined to be SGA.

Adolescent growth

Adolescence is generally associated with the chronological period in life that encompasses puberty. Critically, adolescents represent future human resources, economic growth and the potential to reproduce. The World Health Organization (WHO) defines adolescence as falling between the ages of ten and nineteen years, with early adolescence taking place between ten and fourteen years of age and late adolescence occupying years fifteen to nineteen (9). These young people represent a quarter of the global population, currently 1.8 billion, 90 per cent of whom live in low- and middle-income countries (LMICs) (9). During adolescence, growth and development do not necessarily follow parallel paths, potentially leading to differences between chronological age and stage of maturation (10). While growth refers to quantitative increases in weight or height, development reflects progress towards sexual and behavioural maturation. Although growth and development are genetically determined, they are susceptible to nutritional, environmental and hormonal factors and, subsequently, possible modifications. Growth during adolescence is not assessed or reported in any systematic manner and therefore, both worldwide historical rates and current prevalence of stunting among adolescents are, frustratingly, unknown.

In developed countries, the decreasing age at which the onset of puberty occurs in females seems to be stabilizing (11) and the differences in average timing of puberty onset remain small; in most western countries they are less than one year (12). It seems intuitive that under optimal living conditions similar to those in developed countries, this process is only slightly influenced by nutritional and environmental signals. Conversely, in LMICs, where undernutrition is more prevalent, living conditions would seem to play a more substantial role; however, epidemiological studies neither support nor contradict this perception. Difficulty in comparing the age at the onset of puberty in girls among epidemiological studies most likely arises from the different methods used to evaluate breast development. In girls with excess adiposity, breast stage assessment can be particularly difficult unless visual inspection is accompanied by palpation.

While fewer studies examine puberty onset in boys, a secular trend of a declining age at the onset of puberty can also be detected; onset in boys, however, seems to be impacted less by undernutrition than in the case of girls. While most studies examine testicular volume by using a graded series of standard ellipsoid beads based on the Prader orchidometer (13), there exists some debate on whether or not pubertal onset occurs at a testicular volume of 3 or 4 mL (14). Therefore, the age at puberty onset in boys is also impacted by assessment methodology.

Children with early growth impairment have a different epidemiology of puberty resulting from their *developmental origins*. Weight gain CUG in children born SGA predisposes this group to precocious puberty due to its tendency for increased central adiposity (15). Here, the mechanism for precocious puberty is similar to that resulting from obesity. SGA children who did not catch-up in linear growth had the onset of puberty occur at a normal age and follow a normal progression. However, the fact that puberty onset occurred relatively early in relation to their height subsequently led to the inability to overcome their height difference during the pubertal growth spurt (16). While existing evidence is incomplete, an initial study indicates that the mechanisms of puberty are influenced by either the transition from SGA to normal weight or the failure to catch up, thus remaining short.

EVIDENCE FOR CATCH-UP GROWTH DURING ADOLESCENCE

Catch-up growth defined

Accelerated linear growth or growth spurts occur twice before one reaches adult height; first, from conception until two years of age and second, during adolescence. During growth spurts, 'windows of opportunity' or plasticity in growth may enable individuals to ameliorate their previous growth trajectories, thereby allowing previously stunted individuals to achieve their genetic height potential (1). Evidence for plasticity of linear growth in epidemiological studies is clear prior to two years of age (17). However, the timing, sensitivity and mechanism of a second 'window of opportunity' for CUG during adolescence remain uncertain. With about 15–20 per cent of total stature and 45 per cent of adult bone mass achieved during adolescence, this phase may represent the final opportunity to influence adult height and mitigate stunting (1, 18-21).

CUG is commonly defined as height velocity above the statistical limits of normal for age and/or maturity during a defined period of time following a period of growth inhibition (22). CUG may occur at any stage of growth but has been most studied after intrauterine growth retardation during the first 1–2 years of life (23). CUG is determined retrospectively over a course of months or years up to adult height. While this definition is generally agreed upon, the basis for determining CUG has multiple variations including a change in height-for-age Z-score (HAZ) of greater than 0.67; achieving an HAZ of >-2 SD or >1.3 SD; or growth above the third percentile for height (for age) at any time during follow-up (24).

Hypotheses for catch-up growth during adolescence

Two hypotheses exist for CUG during adolescence: a neuroendocrine hypothesis; and an epiphyseal growth plate hypothesis. However, it is likely that the process of CUG involves both factors to varying degrees (25). Both the epiphyseal growth plate and puberty onset are sensitive to energy homeostasis at multiple levels (26, 27). Support for a combined neuroendocrine and epiphyseal growth plate hypothesis stems from evidence that prior to CUG in height, the undernourished child must regain 85 per cent of its weight (25). If CUG and the pubertal growth spurt coincide, it is possible that the child's final height may be compromised due to hastened bone maturation (22). Conversely, if there is delayed puberty, bone maturation may progress slowly for a longer period of time allowing the child to reach an actual height well beyond the expected final height. The extent of recovery that can be attributed to CUG depends on the timing, severity and duration of the underlying cause of the initial growth faltering, which must disappear, or at the very least diminish, with age (28). Still, others postulate that a reduction of disease burden during pubertal growth is the mechanism for stunting recovery (1, 29).

In the following sections, we review some of the key literature and highlight main findings on CUG during adolescence. We used Medline to locate English literature (from 1990 to 2018) that included CUG in height. The impact of puberty on CUG and its reverse effect are also considered. Studies are divided into three main categories. *Longitudinal cohorts* were selected as they provided information on CUG without intervention and the impact of puberty on growth (see Table 1). Studies on *CUG in children born SGA* illustrate the impact of early growth restriction on outcomes later in life (see Table 2) while *migration and adoption studies* (see Tables 3 4) provide information on the impact of a change in environment as a 'natural experiment' on CUG.

Catch-up growth from longitudinal cohorts in LMICs

Longitudinal cohorts reporting growth without intervention in LMICs show inconsistent CUG and stunting recovery. Some studies report an increase in stunting while others report decreases. In fact, stunting status appears to be fluid until adult height is attained with transitions in and out of stunting, quite possibly related to the timing of the pubertal growth spurt (see Table 1).

Table 1. Catch-up Growth During Adolescence in Longitudinal Cohort Studies

Author	Country	Population	Outcomes
Svefors P, et al., 2016. (30)	Bangladesh	<i>n</i> = 1034 (enrolled at birth; followed until age 10) G: 513 B: 541	<ul style="list-style-type: none"> Prevalence of stunting was highest at 2 years (50%) decreasing to 29% at 10 years.
Stein A, et al., 2015. (31)	South Africa 'Birth to Twenty Cohort'	<i>n</i> = 1918 (enrolled at birth; followed until age 20)	<ul style="list-style-type: none"> Rapid passage through puberty was associated with a lower adult height and higher body mass index (BMI). (Note: mathematically, a lower adult final height results in higher BMI, which is not always due to obesity).
Teivaanmaki T, et al., 2015. (32)	Malawi	<i>n</i> = 767 (enrolled at birth; 522 followed until age 15) G: 264 B: 258	<ul style="list-style-type: none"> Prevalence of stunting was highest at 2 years (80%) decreasing to 37% at 15 years. Between 12 and 15 years of age, 9.1% became stunted and 9.1% recovered from stunting. 84.7% of those stunted at 2 years recovered at least once by 15 years. By 15 years of age, only 9.0% of boys and 19.6% of girls reached advanced puberty.
Tanner S, et al., 2014. (33)	Bolivia, rural indigenous population	<i>n</i> = 483 (enrolled at 2–10 years; followed until 7–15 years)	<ul style="list-style-type: none"> Stunting at baseline was associated with lower BMI, body fatness and arm muscularity across a period of 6 years. No puberty data available.
Fink G, et al., 2014. (34)	Vietnam India Ethiopia Peru	<i>n</i> = 976 <i>n</i> = 976 <i>n</i> = 974 <i>n</i> = 678 (enrolled at birth; follow-up at age 8, 12 and 15)	<ul style="list-style-type: none"> At 8 years of age, 31% of children were stunted. Of children classified as stunted at 8 years of age, 36% recovered from stunting by age 15. No puberty data available.
Lundeen EA, et al., 2014. (35)	Brazil Guatemala South Africa Philippines India	<i>n</i> = 966 (1yr to adult) <i>n</i> = 266 (birth to adult) <i>n</i> = 1179 (1 yr to adult) <i>n</i> = 1806 (birth to adult) <i>n</i> = 1070 (birth to adult)	<ul style="list-style-type: none"> The prevalence of stunting was highest at 24 months [range of stunting prevalence at 24 months: 13.2% (Brazil) to 81.2% (Guatemala)]. The prevalence of stunting decreased from 24 months to adulthood [range at adulthood: 3.2% (Brazil) to 41.1% (Philippines)]. By adulthood, a small proportion also became stunted [range of becoming stunted was 15% in the Philippines to 3% in Brazil]. By adulthood, many recovered from stunting [range of stunting recovery highest in Brazil at 82% to 35% in the Philippines]. No puberty data available.
Bosch A, et al., 2018. (36)	Bangladesh	<i>n</i> = 707 (enrolled at birth to 5 years; follow-up at 12–16 years)	<ul style="list-style-type: none"> Adolescent stunting was associated with childhood stunting and childhood underweight. No puberty data available.

Author	Country	Population	Outcomes
Adair LS, et al., 1999. (37)	Philippines	n = 2011 (enrolled at birth; followed to age 12) G: 955 B: 1056	<ul style="list-style-type: none"> ■ At 2 years of age, 62.5% were stunted. ■ Of the 1,252 children stunted at 2 years of age, 379 (30.3%) were not stunted at age 8.5, and 407 (32.5%) were not stunted at age 11–12. ■ Only 1.3% of 11-year-old and 5.1% of 12-year-old girls achieve menarche. ■ Among girls who achieved menarche, there was less stunting.

Catch-up growth of children born small-for-gestational age

Globally, approximately 16 per cent of all births are SGA, ranging from 7 per cent in industrialized countries to 41.5 per cent in South Asia (38, 39). In 2010, 32.4 million infants (27 per cent of live births) were born SGA in LMICs, of whom 29.7 million were full-term (FT)-SGA (39). A landmark study in 1995 reported that 90 per cent of children born SGA eventually reach a normal height (40). Since then, lay and other scientific literature has stated that approximately 90 per cent of children born SGA reach normal height without intervention, but it is unclear if a high degree of growth can be reproduced elsewhere due to the use of different definitions for SGA and CUG.

Among the literature, three research teams noted that different cut-offs and references make a considerable difference for measurements of SGA and/or CUG. Karlberg et al. (1995) first highlighted the impact of different definitions of SGA on the relative risk of short adult stature. Using different cut-off points for SGA based on birth weight or birth length and a consistent reference population, the study's SGA population contained different numbers of children which was reflected in the different outcome measures of stature (41). More recently, the prevalence of SGA has also been shown to vary significantly depending on reference populations (42, 43). Using 26 different reference populations, Katz et al. (2013) calculated the prevalence of SGA based on the 10th percentile using two birth data sets: one from Nepal and one from South India (42). They found that the prevalence of SGA varied between 10.5 and 72.5 per cent in Nepal and between 12.0 and 78.4 per cent in South India amongst the 26 reference populations (42). In addition, a systematic review by Chrestani et al. (2013), examining associated factors for accelerated growth in childhood also remarked on the lack of uniformity in CUG definitions and the need for standardization (44). Given this great variability in definitions and reference populations in many studies reporting CUG of SGA infants, it is difficult to determine if later studies support earlier findings.

Nevertheless, a recent review noted that most authors agree that children born with low birth weight (LBW) and/or SGA who experience CUG are at higher risk of developing obesity and metabolic syndrome (15). Children with early growth impairment have a different epidemiology of puberty resulting from their *developmental origins*. Weight gain CUG in children born SGA predisposes this group to earlier puberty due to their tendency for increased central adiposity and the mechanism is similar to precociousness resulting from obesity (45–47). SGA children who remain short begin puberty within a normal age range and follow slightly faster puberty progression and earlier menarche in girls. This results in an inability to overcome their height difference during the pubertal growth spurt (16). Table 2 highlights some of the more significant recent findings. Other long-term health consequences exist due to CUG of children born SGA, LBW or pre-term and these have been recently reviewed in-depth by Mericq et al. and Singhal (45, 48).

Table 2. Catch-up Growth in Children Born SGA or LBW

Author, year (country)	Initial HAZ or height (cm) mean (SD)	CUG before puberty onset (age)	Age at puberty onset	Age at puberty completion	Final adult height (cm), [age]	CUG possibility		
SGA								
Bogueszewski MC, et al., 2011. (49) (Latin America)	At birth: <-2HAZ	By the age of 4, higher velocity	Early pubertal onset in those with early rapid weight gain Normal pubertal timing for SGA children without previous CUG	Earlier menarche if rapid weight gain in first months of infancy No previous CUG, early or within normal range	Greater final adult height if no previous CUG	■ Yes, CUG possible with treatment >+0.5 HAZ		
Ibanez L, et al., 2000. (50) (Spain)	At birth: <1.5 HAZ ≥ -1.5	N/A	8.6 ±0.1 [128.6±2.7] 8.6 ±0.1 [132.8±1.4]	11.3±0.3 12.9±0.2	-1.5 ±0.3 (153.0cm±1.8) -0.6±0.2 (158.3±1.0)	■ CUG in puberty by slower progression to menarche and longer pubertal growth spurt		
Lazar L, et al., 2003. (51) (Israel)	Boys SGA: 3.4±0.6y Height: -1.8± 0.4 SD AGA 3.7±0.4y Height: -1.7± 0.2 SD	Girls SGA: 3.6±0.8y Height: -1.8± 0.4 SD AGA 3.3±0.6y Height: -1.8 ±0.5 SD	No CUG in infancy or childhood (2.5–4y)	Boys SGA: 12.0± 0.9y Stage III AGA 13.0±1.1y Stage IV-V	Girls SGA: 10.4± 1.5y Stage II AGA 11.4±1.3y Stage III-IV	Boys – n/a SGA Girls 12.6±1.6y AGA Girls 13.0±1.4y Menarche occurred within normal age range but was significantly earlier in the SGA girls	Boys SGA 169.5±5.1cm AGA 168.3±4.0 cm Girls SGA 153.6±5.7cm AGA 152.8±3.8cm	■ In SGA children, early acceleration in height (stage 3 for boys and 2 for girls) increased adult height but also resulted in a deceleration of height velocity back to -1.6 SD by end of puberty. Significant height deficit is seen between final adult height and target height. ■ In AGA children, height gain was seen throughout puberty in boys and remained stable after stage 3 in girls. Final adult height and target height were similar.

Author, year (country)	Initial HAZ or height (cm) mean (SD)	CUG before puberty onset (age)	Age at puberty onset	Age at puberty completion	Final adult height (cm), [age]	CUG possibility
Albertsson -Wikland K, et al., 1994. (52) (Swedish girls)	At birth, CUG group:-2.4 SD At birth, non- CUG group:-2.7 SD	At 8 years: CUG group: -0.7 SD Non- CUG group: -2.2 SD	Age at peak height velocity (PHV) was half a year lower than non-catch-up group PHV identical to control group, puberty onset at normal time or slightly earlier than normal height	n/a	CUG group: -0.7 SD Non-CUG group: -1.8 SD	■ CUG obtained a greater final adult height
Ghirri P, et al., 2001. (53) (Italy)	At birth: SGA girls: 46.5±1.86 cm	n/a	SGA girls 9.9y	SGA girls: menarche at 11.9y	Mean final adult height:160.1±6.7cm	■ CUG was seen during pubertal growth
Low birthweight (LBW)						
Odberg MD, et al., 2010. (54) (Norway)	n/a	LBW children were shorter than normal birthweight (NBW) at 5 and 11y.	n/a	n/a	Boys LBW 175.0 cm (CI 95%, 171.0, 181.0) Final adult height of LBW girls slightly lower than NBW 161.0cm (CI 95%, 159.0, 167.0cm)	■ Pubertal growth spurt seen from 11 to 15y in boys and then remained stable ~20y ■ Girls: Pubertal growth spurt 10–13y. LBW girls caught up to NBW during this period.
Saigal S, et al., 2001. (55) (Canada)	n/a	At 8 years, Significant improvement in height, mean HAZ -0.69	n/a	In girls, Menarche LBW: 12 y Control: 12.2y	n/a	■ Significant CUG between 8y and adolescence (12–14y). At adolescence, mean HAZ -0.50

Catch-up growth through a change in environment: Migration and adoption

In addition to SGA and LBW studies, an environmental lens or a *natural experiment* on CUG in adolescents is observed through both migration and adoption studies. A *natural experiment* is defined as a “naturally occurring circumstance in which subsets of the population have different levels of exposure to a supposed causal factor, in a situation resembling an actual experiment where human subject[s] would be randomly allocated to groups” (56). Migration and adoption alter the negative growth trajectories of children by physically changing their environment. They therefore act as *natural experiments* through which we can observe the effect of the change in environment on CUG (see Table 3 and Table 4).

Several migration studies including Houghton et al. (2014) and Pak et al. (2010), suggest that early life health shocks relating to economic and nutritional deprivation can be recovered from following migration (57, 58). In fact, these recoveries occurred sooner if migration occurred earlier in a child's life. In contrast, it does not appear that rural-to-urban migration due to seasonality and labour is associated with linear CUG effects in adolescence (59).

Moreover, there appears to be a general consensus favouring CUG in years post-adoption. Several researchers have reported precocious puberty amongst stunted children adopted from poor environments into affluent families. Viridis et al. (1998) and Proos et al. (1993) both suggest that children were significantly shorter at adoption (60, 61). At follow-up, early puberty occurred in children adopted into European families from India, as compared to reference populations. Likewise, analysis of 36 institutionalized Romanian children showed that children's mean weight rose from below the fourth percentile at the time of adoption to the eighth percentile after only 11 months in their adoptive homes. By the time these children were 4.5 years of age and thus had spent approximately 2.5 years in their adoptive homes, their mean weight was nearing the 50th percentile. By phase three, the Romanian children's physical growth had reached North American norms and there were no longer differences between them and the comparison groups in either height or weight (62).

Table 3. Catch-up Growth After Migration

Author (year)	Country of origin and migration	Population	Outcomes
Zhang N, et al., (2015). (63)	Migration from China	<i>n</i> = 865 (different stages of left-behind children – only child, left behind in early childhood, left behind in early and later childhood and left behind in late childhood) Reference population (never left behind) <i>n</i> = 1690 G: 721 B: 969	<ul style="list-style-type: none"> ■ On average, by teenage years, boys who were left behind before age 6 appeared not to grow as tall as boys who were never left behind. ■ By age 14, boys who were never left behind were 153.7 cm tall, on average, while boys who were left behind before age 6 were only 150.9 cm. ■ The predicted heights for girls suggested that, by teenage years, those who were left behind before age 6 were shorter, on average, than those never left behind– though the difference was not significant.
Houghton LC, et al., (2014). (58)	Bangladesh origin, with migration to the U.K	<i>n</i> = 419 Girls (5–16 years): <ul style="list-style-type: none"> ■ 165 Bangladeshi ■ 42 first generation Bangladeshi in the UK ■ 162 second generation Bangladeshi in the UK ■ European descent 	<ul style="list-style-type: none"> ■ In comparison to the reference population in Bangladesh, first and second generation Bangladeshi girls as well as European girls were significantly heavier (WAZ: first-generation = 0.1; second-generation = 0.3; Europeans = 0.8) and taller (HAZ: first-generation = -0.8; second-generation = -0.2; Europeans = 0.1) than the girls living in Bangladesh (WAZ = -1.2; HAZ = 21.2; all <i>p</i>,0.05). ■ First-generation migrants had a median age at adrenarche (5.3 years) that was significantly lower than that of second-generation (7.4), and European (7.1) girls.
Pak S, et al., (2010). (57)	North Korean origin, with migration to South Korea	<i>n</i> = 1406 (6–19.9 years): NK Girls: 717 NK Boys: 689	<ul style="list-style-type: none"> ■ North Korean refugee boys and girls were shorter and weighed less than their South Korean peers in all age groups. The disparity in height and weight between North and South Korean children and adolescents tended to increase in the early-teen years, peaking in the mid-teen years (for boys, the 13.5-year-old group in both cases; for girls, the 11.5 and 13.5-year-old groups for height and weight respectively), and then decreased in the late-teen years. ■ The difference in BMI of the North and South Korean boys ranged from 0.1 to 1.9, with pronounced differences throughout the teen years. There were no such differences between the North and South Korean girls, perhaps because the weight difference – when adjusted for the height difference – between the two groups of girls was insignificant. ■ HAZ differed significantly according to age at escape (ANOVA: <i>df</i> = 3, <i>F</i> = 41.001, <i>Sig.</i> = .000). Those who escaped in their early- to mid-teens were the shortest relative to their South Korean peers. Those who escaped in their mid- to late-teens were the next shortest, and those who escaped during their pre-teen years were the tallest.

Author (year)	Country of origin and migration	Population	Outcomes
Coly AN, et al., (2006). (59)	Senegal (rural to urban migration)	<p>$n = 3977$ (6–19.9 years): Girls: 1456 (at preschool survey 3.4 ± 1.4 years) (at adolescent survey 20.5 ± 1.6 years) Boys: 1418 (at preschool survey 3.4 ± 1.4 years) (at adolescent survey 20.4 ± 1.6 years)</p> <p>Full catch-up was derived if they had similar mean heights among stunting categories and partial catch-up if there was a greater height increment in comparison to non-stunted counterparts.</p>	<ul style="list-style-type: none"> ■ In childhood, mean HAZ was slightly greater for girls. The prevalence of stunting was 27.6%, with no difference between boys and girls. It varied by age, with the greatest prevalence during the second and third years of life. ■ At the follow-up survey, boys were taller and heavier than girls, but the latter had greater BMI, arm circumference and skinfold thickness. ■ A severe delay in sexual maturation was noted for females: 6.9% of 18 to 19-year-olds were still premenarcheal. This proportion varied with the degree of preschool stunting (3.5, 5.5 and 11.2% for nonstunted, mildly stunted and markedly stunted subjects, respectively, $P < 0.05$). ■ For girls, the mean height increment from early childhood to late adolescence varied with the total duration of migration to the city after adjusting for age and an independent measurement of preschool HAZ. However, the relation was not linear; girls who never migrated to Dakar had increments similar to those of women who migrated for long durations, whereas those with a short duration of migration had the greatest increments. ■ Among boys, there was no association between the height increment and any of the migration variables.
Bogin B, et al., (2002). (64)	Guatemalan origin, with migration to the USA	<p><i>Migration population</i> $n = 431$ (5–12 years) <i>Reference Guatemalan population</i> $n = 1347$ (5–12 years)</p>	<ul style="list-style-type: none"> ■ Maya children living in the US are significantly taller at all ages as compared to Maya living in Guatemala.

Table 4. Catch-up Growth after Adoption

Authors	Country of origin and adoption	Population	Outcomes
Teilmann G, et al., (2007). (65)	Multi-country adoptees to Denmark	<i>n</i> = 99 (girls only – mean 6.92 years) Reference population <i>n</i> = 93 (of Danish origin)	<ul style="list-style-type: none"> ■ Height and weight were significantly lower in adopted girls compared with Danish girls in all age groups ($P \leq 0.005$), except for weight in 8-yr-old girls. ■ Mean \pm SD height SD was -0.80 ± 1.3 and -0.36 ± 1.1 in the 5- and 8-year-old adopted girls respectively ($P = 0.012$). ■ There was no significant difference in BMI between the two groups, but the proportion of obese children (BMI SD>2) was higher among controls compared with adopted girls ($P=0.045$).
Teilmann G, et al., (2006). (66)	Multi-country adoptees to Denmark	<i>n</i> = 655 (children identified with precocious puberty(PP)) G: 577 B: 78 <i>n</i> = 51 (adopted children identified with precocious puberty) G: 45 B: 6	<ul style="list-style-type: none"> ■ Inter-country adoptees were 10 to 20 times more likely to develop PP compared with the Danish reference group. Adoptees born in India and South America had the highest risk of PP, whereas the risk of PP was not increased in the large group of children adopted from Korea. ■ Older age at adoption significantly increased the risk of PP in adoptees independent of the region of origin ($P = 0.00057$). ■ In contrast to adopted children, the risk of developing PP was not significantly increased among children who immigrated to Denmark with their family.
Le Mare L, et al., (2006). (62)	Institutionalized Romanian (RO) children, adopted into Canadian families	<i>n</i> = 36 (9 to 53 months) Girls: 19 Boys: 17 Reference group: Canadian Born (CB), non-adopted, non-institutionalized (<i>n</i> =42); Early-adoption comparison group (<i>n</i> = 25)	<ul style="list-style-type: none"> ■ At the time of adoption, the RO children, as a group, had dramatically fallen off their growth curves, with the average weight at adoption dropping to the fourth percentile. ■ At 11 months post-adoption, although the children were still significantly underweight (mean weight below the eighth percentile), improvements could be seen, with only 22.2% (<i>n</i>=6) falling below the third percentile. By phase 2, when the RO children were, on average, 4.5 years of age, almost complete weight catch-up could be seen, with their mean weight near the 50th percentile and only 8.6% (<i>n</i>=3) below the third percentile. There was, however, still a statistically significant difference between the RO and CB children's weight ($P < 0.05$). ■ In phase 3, when the children were, on average, 10.5 years of age, their weight catch-up continued, with the mean weight nearing the 60th percentile and only 2.8% (<i>n</i>=1) below the fifth percentile. Moreover, there were no longer statistically significant differences among the groups.

Authors	Country of origin and adoption	Population	Outcomes
Krstevska-Konstantinova M, et al., (2001). (67)	Multi-country migration and adoption to Belgium	<i>n</i> = 145 children with precocious puberty Migration (non-adopted): 12 (mean age 3.9 years) Adopted: 29 (mean age 3.3 years)	<ul style="list-style-type: none"> ■ The patients from adopted and migration groups were similar in mean age at diagnosis of precocious puberty (7.8 years and 8.3 years respectively). ■ Using Western European references, the mean height SD of adopted children at immigration was retarded and shorter (-1.4), but not significantly, as compared to the migrated non-adopted children (-0.7). This difference became significant at diagnosis of precocious puberty (+0.7 – adopted versus +2.3 migrated non-adopted; <i>P</i> <0.05). ■ There was an increase in BMI SD in both adopted and migration groups by diagnosis, and the mean was greater in the migration group as compared to the adopted group (+2.3 versus +0.9 respectively; <i>P</i> <0.01).
Virdis R, et al., (1998). (60)	Indian children, adopted into Italian families	<i>n</i> = 19 (girls only) Group 1: 10 adopted before 4 years (mean 2.4 years ± 1.2) Group 2: 9 adopted after 5 years (mean 6.6 years ± 0.9)	<ul style="list-style-type: none"> ■ At adoption, height SD score was similar in the two groups: -0.9 (0.4) in group 1 and -0.7 (1.3) in group 2. The weight defect was greater, and the BMI significantly smaller, in the girls who were adopted later. ■ Age at onset of puberty was similar in the two groups (group 1: 6.5 years ± 0.8; group 2: 7.2 years ± 1.1), indicative of precocious puberty.
Proos L, et al., (1993). (61)	Indian children adopted into Swedish families	<i>n</i> = 107 (girls only) mean age at adoption 2.8 years ± 2.1)	<ul style="list-style-type: none"> ■ At arrival, the adopted girls were short (- 2.8 mean SD) and, in spite of considerable catch-up growth, they were still below the reference mean (- 0.8 mean SD) at the onset of puberty. ■ The onset of puberty occurred, on average, 1.5 years earlier (than in the Swedish reference population, about 1 year earlier than in affluent Indian girls and more than 2 years earlier than in less privileged Indian girls, assuming that onset of pubertal growth occurs approximately 3 years before menarche in Indian reference populations. ■ Catch-up growth after arrival in Sweden was defined as completed when the annual height velocity at the onset of puberty was less than +2.0 SD above the mean. These criteria were met by 66 girls.

BIOLOGICAL MECHANISMS

In an effort to understand the CUG mechanisms during puberty we examine the physiological processes of puberty and linear growth in relation to undernutrition. This includes regulation of pubertal onset and hormonal responses during both sufficient food intake and undernutrition, as well as genetic and epigenetic interactions.

Puberty onset

The age at onset of puberty and the growth rate during the pubertal growth spurt are two important parameters in determining adult height. Both are sensitive to undernutrition and contribute to sexually dimorphic adult height. On average, girls enter and complete each stage of puberty earlier than boys; however, it is difficult to determine a *normal* age of puberty onset due to differences between populations and the impact of secular trends. In girls, the onset of puberty is usually at around the age of 10.9 years and is marked by thelarche – the breast bud stage – which is clinically assessed as Tanner Stage Breast 2 (68). In boys, puberty onset is usually at around 10.4 years and is marked by an increase in the size of the testes reflecting the start of spermatogenesis, wherein a testicular volume of 3–4 mL is clinically assessed as Tanner Stage Genital 2 (14).

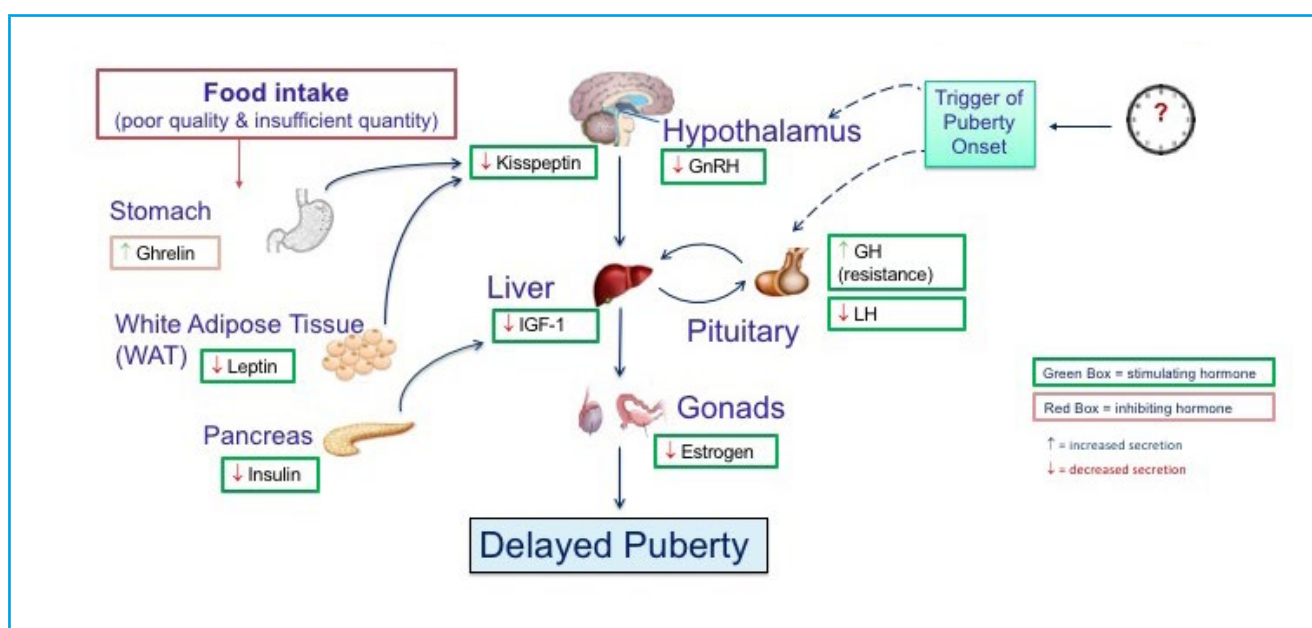
Puberty begins with a gradual increase in pulsations from the hypothalamic-pituitary-gonadal axis (HPG-axis) releasing gonadotropin-releasing-hormone (GnRH) which triggers the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). In boys, LH acts on the interstitial Leydig cells of the gonads to stimulate testosterone and FSH stimulates Sertoli cells to produce inhibin, which exerts feedback on the hypothalamic-pituitary axis to inhibit FSH. The Sertoli cells also support the initiation of spermatogenesis resulting in testicular growth. In girls, FSH stimulates the production of estrogen and the secretion of inhibin by the follicles, after which LH appears to play a minor role until menarche (69).

Hormonal consequences of undernutrition for puberty

Human adaptation to unfavourable environments would suggest that puberty is delayed in situations with suboptimal nutrition to prolong growth of the individual and to delay reproductive ability until conditions to support reproduction exist. Current comprehension of energy sufficiency or insufficiency signalling pathways takes into account the HPG-axis to re-activate (*see Figure 1. Endocrine Response to Poor AND Insufficient Food Intake on Puberty Onset*). However, research using animal models continues to uncover new factors important in energy homeostasis. Of particular importance are leptin, ghrelin, Kisspeptin, adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR). Leptin levels are directly related to adipose stores and act within the hypothalamus to adjust energy requirements. The gradual increases in GnRH are highly sensitive to body energy reserves that are influenced by leptin. In obesity, excess levels of leptin permit the gradual increase of GnRH leading to earlier puberty onset (70), whereas in chronic undernutrition, leptin levels are low and no such permissive action exists. Ghrelin is secreted from the stomach as a result of energy insufficiency and acts as an inhibitory control on puberty onset in girls (71). Kisspeptin also stimulates directly and indirectly the GnRH neurons that drive HPG axis maturation and puberty onset. Elucidation of the leptin/Kiss pathways require further study, but recent discoveries support a direct connection in undernutrition between leptin deficiency, reduced Kiss1 mRNA expression and reduced kisspeptin immunoreactivity (71). Much remains to be gleaned about the Kiss – ghrelin interaction with the onset of puberty.

AMPK and mTOR jointly control energy homeostasis through the activation of AMPK during states of low energy, which senses energy changes at the metabolic level by detecting changes in the intracellular adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio (71). The mTOR signalling pathway has been proposed to link hormonal and nutrient signals to cellular physiology. In rat models, dietary restriction decreases mTOR levels that affect the hypothalamic expression of *Kiss1* and delay puberty's onset (72). AMPK works to liberate energy in two ways: (1) it activates metabolic pathways which result in ATP generation, and (2) it downregulates metabolic pathways which need ATP consumption. This joint effect on puberty remains to be demonstrated *in vivo*.

Figure 1. Endocrine Response to Poor AND Insufficient Food Intake on Puberty Onset (13, 71-77)



Normal puberty onset is controlled by the interaction between stimulating hormones (green box) and inhibiting hormones (red box). The effect that poor and insufficient intake has on these hormones is indicated by the arrows. Green arrows (↑) indicate an increased secretion and red arrows (↓) indicate decreased secretion in states of undernutrition. (Insulin-like Growth Factor-1 (IGF-1); Growth Hormone (GH); Gonadotropin-releasing Hormone (GnRH); Luteinizing Hormone (LH); Insulin-like Growth Factor Binding protein-1 (IGFBP-1))

Final adult height affected by pubertal onset

In normally developing boys and girls, the age of puberty onset and adult height is impacted by childhood height. Taller subjects enter puberty earlier and experience slow growth velocity and pubertal progression, while puberty onset in shorter subjects occurs later but has a faster tempo and features a greater velocity of height increase. This compensatory phenomenon leads to similar adult height regardless of one's initial height (78, 79). Conversely, another study presented evidence that the onset of puberty at an early age was related to shorter stature in girls but not boys (80). However, it is important to note that neither of these studies considered body size at puberty's onset. A study of boys and girls with normal BMI reported that early puberty had a negative impact on adult height, whereas delayed puberty led to greater adult height (81). In states of chronic undernutrition, decreased secretion of estrogen, which signals senescence at the bone plate, may allow for a longer period of linear growth and augmented height or CUG (82, 83).

Epiphyseal growth plate elongation (bone growth)

Increases in height occur in the long bones of the body, which elongate at their proximal and distal ends in segments called epiphyseal plates. Epiphyseal plate chondrogenesis, the process of cartilage formation, controls linear growth. In the epiphyseal plate, chondrogenesis is regulated by many systems, including intracellular and extracellular matrix factors as well as endocrine mechanisms like growth hormone insulin-like growth factor-1 (GH/IGF-1) axis, insulin, sex hormones and leptin. During chondrogenesis, cell differentiation is regulated by gene expression at stage-gates from chondrocyte emergence to final hypertrophy (84). Multiple feedback loops, among growth factors like IGF-I, Indian hedgehog, parathyroid hormone-related protein (PTHrP), fibroblast growth factors, bone morphogenetic proteins and vascular endothelial growth factor interact to coordinate cell stage transitions and quiescence (85, 86). Undernutrition negatively affects the endocrine system, pancreatic, renal and the vascular systems, which in turn affect chondrogenesis. Growth ceases with senescence of chondrogenesis and epiphyseal closure at the end of puberty when adult height is reached.

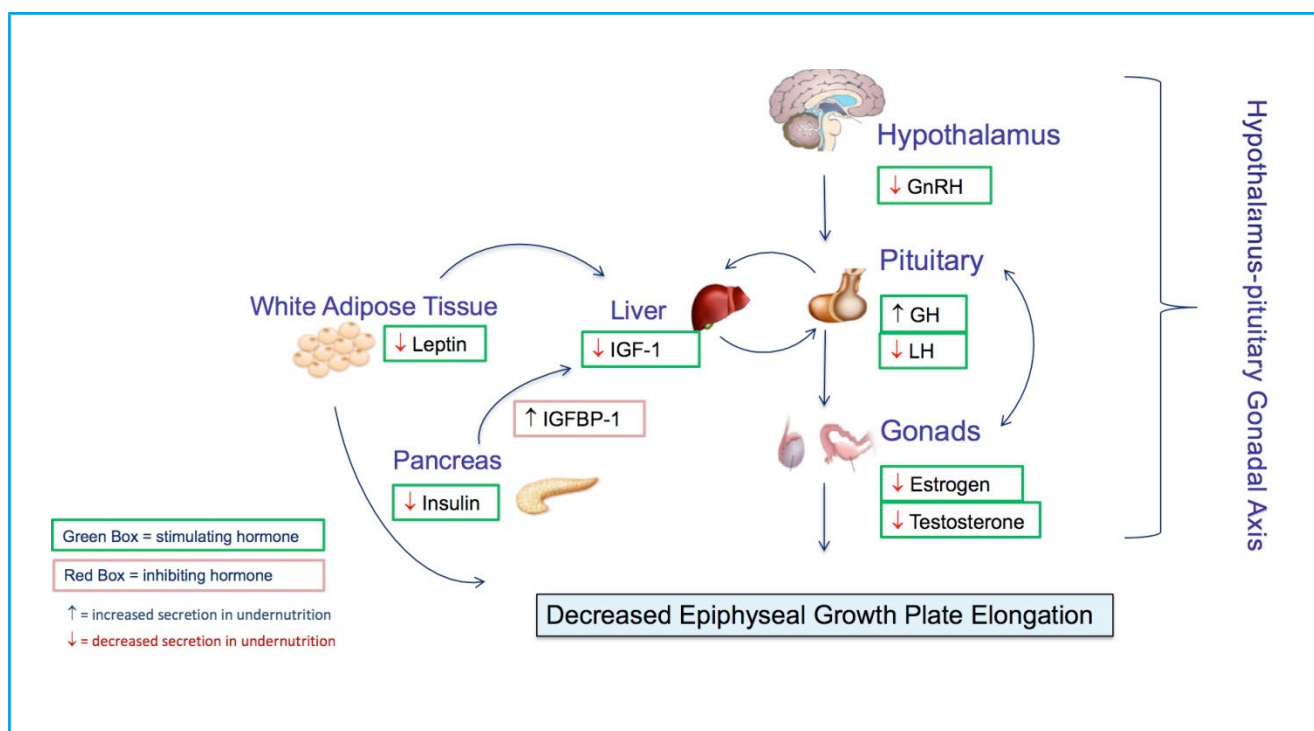
Malnutrition and epiphyseal growth plate elongation

Adequate bone mineralization during puberty requires the essential building blocks of bone. Food intake provides skeletal constituents like calcium, phosphorus, zinc, vitamin D, vitamin A and protein to support bone growth. Zinc deficiency can severely impact zinc-dependent collagenolytic proteases that facilitate changes in matrix proteins. These proteins allow for bone deposits and thus decreasing elongation in the hypertrophic zone of the growth plate - the stage which adds the greatest contribution to variability in growth. In addition, vitamin D metabolites regulate the hedgehog pathway both as morphogenetic inducers or repressors (84). Specific amino acids act on chondrocyte maturation in the proliferation zone by disrupting or inhibiting growth plate elongation when they are in limited supply (87, 88). When one's diet lacks the essential building blocks of bone during puberty, optimal bone proliferation and elongation will not be accomplished.

Hormonal consequences of undernutrition on epiphyseal growth plate elongation

Hormonal regulation of augmented epiphyseal growth plate elongation during the pubertal growth spurt is intricately linked to the onset of puberty. At this time, thyroid hormone and cortisol continue to be necessary for bone growth but the activity in the GH/IGF-1 axis is amplified by its interaction with sex steroids. Thyroid hormones are required for proper functioning of all cells and act both directly and indirectly on the epiphyseal growth plate (85). Thyroxine (T4) and Triiodothyronine (T3) are hormones that control bone turnover, bone mineral density and chondrogenesis (106). In young children, a linear relationship has been observed between the severity of undernutrition and decreased serum concentrations of T3 and T4 (90). Precise consequences of undernutrition on an amplified GH/IGF-1 axis are not known but numerous studies have shown that undernutrition creates a state of GH resistance where the IGF-1 axis is altered by raising GH concentration and decreasing plasma levels of IGF-1 (27, 91-94). This is an adaptive response, as high GH levels are required to maintain normal glucose concentrations and decreased IGF-1 levels help to conserve energy. GH resistance in cases of undernutrition appears to be the result of elevated cortisol, reduced insulin and a decrease in a number of essential amino acids in the blood due to protein deficiency. In boys and girls, testosterone and estrogen increases at puberty onset are accompanied by increased GH (95). Low serum IGF-1 is also associated with vitamin A and B6 deficiency, as well as low levels of zinc, magnesium and potassium (92). IGF-1 acts both as a mediator of GH action and an independent growth factor (*see Figure 2*).

Figure 2. Endocrine Response to Poor and Insufficient Food Intake on the Epiphyseal Growth (13, 71-77)



Normal growth plate elongation is controlled by the interaction between stimulating hormones (green box) and inhibiting hormones (red box). The effect that poor and insufficient intake has on these hormones is indicated by the arrows. Green arrows (↑) indicate an increased secretion and red arrows (↓) indicate decreased secretion in states of undernutrition. (Insulin-like Growth Factor-1 (IGF-1); Growth Hormone (GH); Gonadotropin-releasing Hormone (GnRH); Luteinizing Hormone (LH); Insulin-like Growth Factor Binding protein-1 (IGFBP-1))

Undernutrition has also been shown to impact the role of Fibroblast Growth Factor-21 (FGF-21) and Growth and Differentiation Factor 5 (GDF-5) in animal models. FGF-21 concentrations are directly related to GH levels. Undernutrition increases the expression of FGF-21 and this signalling is linked to GH insensitivity, bone growth inhibition and reduced growth plate chondrogenesis (92, 96). Growth differentiation factors form part of the process of cartilage proliferation (97). Specifically, GDF-5 initiates chondrogenesis by promoting cell adhesion, thus stimulating growth in bone length. It also increases the size of skeletal elements and stimulates extracellular matrix production in chondrocytes (98). Further studies are required to confirm the role of FGF-21 and GDF-5 in humans.

Hormonal consequences of undernutrition for bone growth and puberty onset

Undernutrition impacts hormonal production, which interferes with both puberty onset and the epiphyseal growth plate. In general, undernutrition decreases the secretion of hormones that promote epiphyseal growth plate elongation and increases the secretion of hormones that inhibit epiphyseal growth plate elongation (*see Figure 1*). During adolescence, undernutrition also delays puberty in a similar fashion (*see Figure 2*). A summary of key consequences of food restriction on hormonal regulation of long bone growth and puberty onset is outlined below (*see Table 5*).

Table 5. The Consequences of Food Restriction for the hormonal regulation of long bone growth and puberty onset

Hormone and other factors	Role	Effect of food restriction	Impact on bone growth (99)	Impact on puberty onset
Glucocorticoids	Hormones produced by the adrenal glands that are involved in glucose metabolism. (100).	Increased secretion	Inhibits	-
Ghrelin	A hormone secreted by the stomach that stimulates the secretion of growth hormone and increases appetite.(101).	Increased secretion	-	Delays
Growth hormone (GH)	A hormone secreted by the pituitary that affects mainly postnatal growth and stimulates hepatic IGF-1 production and chondrogenesis in the growth plate.(102).	Increased secretion	Stimulates	Triggers
Insulin-like growth factor binding protein-1 (IGFBP-1)	A protein that is the main carrier of IGF-1 in the body.(103).	Increased secretion	Inhibits	-
Fibroblast growth factor 21 (FGF-21)	A protein that is a mediator of fatty acid oxidation and lipid metabolism.(85).	Decreased/ Increased secretion	Inhibits	-
Leptin	A hormone that regulates fat storage by suppressing appetite. Regulates GH secretion and stimulates chondrogenesis (104).	Decreased secretion	Stimulates	Delays
Insulin	A hormone secreted by the pancreas that binds to the IGF-1 receptor and increases growth velocity. (105).	Decreased secretion	Stimulates	Triggers
Insulin-like growth factor-1 (IGF-1)	A hormone that is similar to that of insulin and has an important role in childhood growth. Stimulates uptake of amino acids from the circulation and chondrogenesis. (103).	Decreased secretion	Stimulates	Triggers
Thyroid hormones	Thyroxine (T4) and Triiodothyronine (T3) are hormones that control bone turnover, bone mineral density and chondrogenesis. (106).	Decreased secretion	Inhibits (but is required for normal functioning of all cells)	-
Growth differentiation factor-5 (GDF-5)	A protein that is involved in skeletal and joint development.(85).	Decreased secretion	Stimulates	-
Vitamin D	A fat-soluble vitamin that plays a role in the maintenance of healthy bones and teeth.(99).	Decreased secretion	Required for proper growth, inhibits chondrocyte proliferation at high concentrations	-

Hormone and other factors	Role	Effect of food restriction	Impact on bone growth (99)	Impact on puberty onset
Sex hormones	Estrogen and testosterone are hormones involved in regulating GH secretion and numerous functions including skeletal maturation. (82, 107).	Decreased secretion	Stimulates growth at low concentration (testosterone), but hastens EGP closure (estrogen)	Triggers
mTOR	A protein kinase that is integral in a signalling pathway involved in major cellular functions including cell growth.(87).	Decreased secretion	-	Delays
Kisspeptin	A hormone encoded by the Kiss1 gene and responsible for the release of other hormones, some connected to puberty.(108, 109).	Decreased secretion	-	Delays
AMP-Activated Protein Kinase (AMPK)	A protein kinase that is a key regulator of body energy and homeostasis.(72).	Controls energy homeostasis	-	Delays

Bone age influences pubertal timing

One possible trigger for puberty, in spite of chronic undernutrition, is bone age. Children generally enter puberty when they achieve a particular bone age that seems to correspond with puberty stage rather than chronological age (110, 111). Conditions that impact skeletal maturation similarly impact the onset of puberty and the HPG-axis. Delayed skeletal maturation and delayed puberty onset have been observed in individuals with chronic disease, malnutrition, hypothyroidism, constitutional delay and Turner's syndrome (112). Conversely, obesity accelerates skeletal maturation and the onset of puberty – the mechanism is thought to involve insulin, leptin and the sex hormones (70, 113). Yet in boys who are adequately nourished, free from disease and without congenital abnormalities, no correlation was uncovered between skeletal maturation and age of pubertal onset (114). Because of common endocrine pathways, it remains more likely that bone age and puberty onset are regulated in parallel during states of chronic undernutrition rather than one impacting the other. Regardless, the end of puberty signals the closure of the epiphyseal growth plate and, with that, linear growth ceases.

Genetic and epigenetic regulation of height and puberty onset

Stature and puberty timing are highly heritable traits, but individually, each is governed by a delicate balance of gene expression and potential interactions. Formulas using mid-parental height are often employed in clinical settings to determine the height of offspring, while familial studies such as those focused on twins and rare monogenetic conditions have advanced our understanding of growth and height potential (115). More recently, Genome-Wide Association Studies (GWAS) identified 697 variants at 423 genomic loci associated with height; these loci explain only 20 per cent of manifested height (6). A closer examination of genes regulating the growth plate uncovers the complex interactions responsible for hormonal signalling, pancreatic endocrine signalling and cartilage proliferation.

Figure 3. LOCI Associated with Pubertal Height and their Overlap with Pubertal Timing and Adiposity (6)



GWAS reveal an overlap of genes responsible for stature potential, pubertal timing and adiposity [1]. Two of the discovered genes correlate to both adult height and pubertal timing (PXMP3 and LIN28B). In addition, one gene discovered is responsible for three known traits including adult height, pubertal timing and adiposity (ADCY3-POMC) (see Figure 3). This finding suggests the feasibility of CUG during puberty given underlying genetic pathways and elucidates the complexity which still exists.

Likewise, early familiar studies found strong associations with age at menarche (AAM) and half of the variance in the AAM has been attributed to heritability. A recent GWAS determined that 123 signals at 106 genomic loci were associated with AAM but this only explained about 15 per cent of all variance within AAM (116). The same study found that loci common to puberty timing and height – LIN28B – linked earlier puberty with an increased growth velocity and shorter adult height in boys and girls.

An alternative control mechanism is the epigenetic regulation of puberty and adult height. Epigenetic modification of gene expression allows the environment to impart alterations to phenotype without altering genotype, the DNA sequence (117). The elucidation of epigenetic pathways explaining puberty regulation is in its infancy. However, epigenetics are implicated in the hypothalamic control of the GnRH neuronal network and the Kisspeptin neurons.

In animal models, puberty was triggered when epigenetic modifications activated Kiss1 through DNA demethylation, recruitment of activating histones and loss of repressive histones (118). In the same study, Lomniczi et al. triggered puberty delay by pharmacologically inducing DNA methylation, preventing the increase of Kiss1 expression that occurs prior to puberty onset and thereby confirming the epigenetic pathway of Kiss1 expression.

In the bone plate, epigenetic and microRNA mediated mechanisms are impacted by environmental or nutritional factors like the availability of Vitamin D and stage-specific proteins that regulate the production of chondrocyte secretion factors in the chondrogenesis cascade(53). This can alter the local extracellular matrix, which imparts epigenetic mechanisms to growth patterns by slowing chondrogenesis in states of undernutrition.

DISCUSSION AND CONCLUSIONS

Research gaps

Though we have contributed to the catch-up growth debate, several limitations exist in the epidemiological literature on CUG. Methodological inconsistencies in definitions and reference populations make a comparison between studies challenging. This is particularly true in the longitudinal cohorts in LMICs. Additionally, studies lacking pubertal measures can mistakenly report later maturing adolescents with impaired linear growth.

Hormonal, nutrient and energy pathways support part of the epidemiological evidence showing an association between undernutrition, impaired linear growth and delayed puberty. However, limitations related to the current understanding of the biological mechanisms of growth during puberty also exist. Adolescents suffering from chronic undernutrition eventually enter into puberty and achieve full reproductive capability and not all stunted children become short adults. Additionally, some epigenetic mechanisms in animal models involved in linear growth and puberty have been uncovered.

Despite these discoveries, much is yet to be gleaned. Are growth trajectories epigenetically altered early in life? If so, are they malleable to further epigenetic change when favourable conditions exist? How long can undernutrition delay puberty? What triggers the inevitable puberty onset – bone age or a genetic biological clock? Do certain epigenetic factors have a stronger influence on puberty than others?

In the same light, although puberty may provide an opportunity for 'catch-up' growth, adolescent-specific mechanisms that influence linear growth remain unknown. Here as well, many questions exist. Can stunting be decreased during puberty? What is the optimal timing for increased nutrition to impact linear growth – before or after puberty onset? Would improved nutrition during puberty also cause an increase in puberty progression and precipitate early senescence at the growth plate?

Recommendations for future research

Ultimately, these lingering questions and data gaps highlight the need for collaboration amongst clinicians and CUG researchers to ensure agreement around research methodology and clinical standards and to substantiate the hypothesis of CUG in adolescence. Only then will investments in newborn and childhood interventions to prevent SGA births, precocious puberty and CUG be completely justified.

REFERENCES

1. Prentice AM, Ward KA, Goldberg GR, Jarjou LM, Moore SE, Fulford AJ, et al. Critical windows for nutritional interventions against stunting. *Am J Clin Nutr.* 2013;97(5):911-8.
2. Angood C, Khara T, Dolan C, Berkley JA, WaSt Technical Interest G. Research Priorities on the Relationship between Wasting and Stunting. *PLoS One.* 2016;11(5):e0153221.
3. Golden MH. Is complete catch-up possible for stunted malnourished children? *Eur J Clin Nutr.* 1994;48 Suppl 1:S58-70; discussion S1.
4. Prader A, Tanner JM, von HG. Catch-up growth following illness or starvation. An example of developmental canalization in man. *J Pediatr.* 1963;62:646-59.
5. Himes JH. Why study child growth and maturation? In: Hauspie RC, Cameron N, Molinari L, editors. *Methods in human growth research.* New York: Cambridge University Press; 2004. p. 3-26.
6. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet.* 2014;46(11):1173-86.
7. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. 1995. Report No.: 0512-3054 (Print).
8. Stewart CP, Iannotti L, Dewey KG, Michaelsen KF, Onyango AW. Contextualising complementary feeding in a broader framework for stunting prevention. *Maternal & child nutrition.* 2013;9 Suppl 2:27-45.
9. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Our future: a Lancet commission on adolescent health and well-being. *The Lancet.* 2016;387(10036):2423-78.
10. Lloyd RS, Oliver JL, Faigenbaum AD, Myer GD, De Ste Croix MB. Chronological age vs. biological maturation: implications for exercise programming in youth. *Journal of strength and conditioning research.* 2014;28(5):1454-64.
11. McIntyre MH. Adult stature, body proportions and age at menarche in the United States National Health and Nutrition Survey (NHANES) III. *Ann Hum Biol.* 2011;38(6):716-20.
12. Willemsen RH, Dunger DB. Normal Variation in Pubertal Timing: Genetic Determinants in Relation to Growth and Adiposity. *Endocrine development.* 2016;29:17-35.
13. Martos-Moreno GA, Chowen JA, Argente J. Metabolic signals in human puberty: effects of over and undernutrition. *Mol Cell Endocrinol.* 2010;324(1-2):70-81.
14. Tinggaard J, Mieritz MG, Sorensen K, Mouritsen A, Hagen CP, Aksglaede L, et al. The physiology and timing of male puberty. *Curr Opin Endocrinol Diabetes Obes.* 2012;19(3):197-203.
15. Yadav S, Rustogi D. Small for gestational age: growth and puberty issues. *Indian pediatrics.* 2015;52(2):135-40.
16. Hernandez MI, Mericq V. Impact of being born small for gestational age on onset and progression of puberty. *Best Pract Res Clin Endocrinol Metab.* 2008;22(3):463-76.
17. Crane RJ, Berkley JA. Progress on growth faltering. *Lancet Glob Health.* 2017;5(2):e125-e6.
18. Spear BA. Adolescent growth and development. *Journal of the American Dietetic Association.* 2002;102(3 Suppl): S23-9.
19. Hauspie R, Roelants M. Chapter 3 - Adolescent Growth A2 - Cameron, Noël. In: Bogin B, editor. *Human Growth and Development (Second Edition).* Boston: Academic Press; 2012. p. 57-79.
20. Largo RH. Catch-up growth during adolescence. *Hormone research.* 1993;39 Suppl 3(s3):41-8.
21. Luo ZC, Karlberg J. Critical growth phases for adult shortness. *American journal of epidemiology.* 2000;152(2):125-31.
22. Wit JM, Boersma B. Catch-up growth: definition, mechanisms, and models. *J Pediatr Endocrinol Metab.* 2002;15 Suppl 5:1229-41.

23. WHO Working Group on the Growth Reference Protocol, WHO Task Force on Methods for the Natural Regulation of Fertility. Growth patterns of breastfed infants in seven countries. *Acta paediatrica* (Oslo, Norway: 1992). 2000;89(2):215-22.
24. Cameron N. Chapter 1 - The Human Growth Curve, Canalization and Catch-Up Growth. *Human Growth and Development (Second Edition)*. Boston: Academic Press; 2012. p. 1-22.
25. Kay's SK, Hindmarsh PC. Catch-up growth: an overview. *Pediatric endocrinology reviews : PER*. 2006;3(4):365-78.
26. Coupe B, Grit I, Darmaun D, Parnet P. The timing of "catch-up growth" affects metabolism and appetite regulation in male rats born with intrauterine growth restriction. *Am J Physiol Regul Integr Comp Physiol*. 2009;297(3):R813-24.
27. Gat-Yablonski G, De Luca F. Effect of Nutrition on Statural Growth. *Horm Res Paediatr*. 2017;88(1):46-62.
28. Saxena A, Phadke SR, Agarwal SS. Linear catch-up growth. *Indian J Pediatr*. 2000;67(3):225-30.
29. Horak P, Valge M. Why did children grow so well at hard times? The ultimate importance of pathogen control during puberty. *Evol Med Public Health*. 2015;2015(1):167-78.
30. Svefors P, Rahman A, Ekstrom EC, Khan AI, Lindstrom E, Persson LA, et al. Stunted at 10 Years. Linear Growth Trajectories and Stunting from Birth to Pre-Adolescence in a Rural Bangladeshi Cohort. *PLoS One*. 2016;11(3):e0149700.
31. Stein AD, Lundeen EA, Martorell R, Suchdev PS, Mehta NK, Richter LM, et al. Pubertal Development and Prepubertal Height and Weight Jointly Predict Young Adult Height and Body Mass Index in a Prospective Study in South Africa. *J Nutr*. 2016;146(7):1394-401.
32. Teivaanmaki T, Cheung YB, Kortekangas E, Maleta K, Ashorn P. Transition between stunted and nonstunted status: both occur from birth to 15 years of age in Malawi children. *Acta Paediatr*. 2015;104(12):1278-85.
33. Tanner S, Leonard WR, Reyes-Garcia V, Team TBS. The consequences of linear growth stunting: influence on body composition among youth in the Bolivian Amazon. *Am J Phys Anthropol*. 2014;153(1):92-102.
34. Fink G, Rockers PC. Childhood growth, schooling, and cognitive development: further evidence from the Young Lives study. *Am J Clin Nutr*. 2014;100(1):182-8.
35. Lundeen EA, Stein AD, Adair LS, Behrman JR, Bhargava SK, Dearden KA, et al. Height-for-age z scores increase despite increasing height deficits among children in 5 developing countries. *Am J Clin Nutr*. 2014;100(3):821-5.
36. Bosch AM, Baqui AH, van Ginneken JK. Early-life determinants of stunted adolescent girls and boys in Matlab, Bangladesh. *J Health Popul Nutr*. 2008;26(2):189-99.
37. Adair LS. Filipino children exhibit catch-up growth from age 2 to 12 years. *J Nutr*. 1999;129(6):1140-8.
38. Tudehope D, Vento M, Bhutta Z, Pachi P. Nutritional requirements and feeding recommendations for small for gestational age infants. *J Pediatr*. 2013;162(3 Suppl):S81-9.
39. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health*. 2013;1(1):e26-36.
40. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res*. 1995;38(5):733-9.
41. Karlberg J, Albertsson-Wikland K, Baber FM, Low LC, Yeung CY. Born small for gestational age: consequences for growth. *Acta paediatrica* (Oslo, Norway : 1992) Supplement. 1996;417:8-13; discussion 4.
42. Katz J, Wu LA, Mullany LC, Coles CL, Lee AC, Kozuki N, et al. Prevalence of small-for-gestational-age and its mortality risk varies by choice of birth-weight-for-gestation reference population. *PLoS One*. 2014;9(3):e92074.

43. Kozuki N, Katz J, Christian P, Lee AC, Liu L, Silveira MF, et al. Comparison of US Birth Weight References and the International Fetal and Newborn Growth Consortium for the 21st Century Standard. *JAMA Pediatr.* 2015;169(7):e151438.
44. Chrestani MA, Santos IS, Horta BL, Dumith SC, de Oliveira Dode MA. Associated factors for accelerated growth in childhood: a systematic review. *Matern Child Health J.* 2013;17(3):512-9.
45. Mericq V, Martinez-Aguayo A, Uauy R, Iniguez G, Van der Steen M, Hokken-Koelega A. Long-term metabolic risk among children born premature or small for gestational age. *Nat Rev Endocrinol.* 2017;13(1):50-62.
46. Ong KK. Catch-up growth in small for gestational age babies: good or bad? *Curr Opin Endocrinol Diabetes Obes.* 2007;14(1):30-4.
47. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ.* 2000;320(7240):967-71.
48. Singhal A. Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth. *Annals of nutrition & metabolism.* 2017;70(3):236-40.
49. Boguszewski MC, Mericq V, Bergada I, Damiani D, Belgorosky A, Gunczler P, et al. Latin American consensus: children born small for gestational age. *BMC pediatrics.* 2011;11:66.
50. Ibanez L, Ferrer A, Marcos MV, Hierro FR, de Zegher F. Early puberty: rapid progression and reduced final height in girls with low birth weight. *Pediatrics.* 2000;106(5):E72.
51. Lazar L, Pollak U, Kalter-Leibovici O, Pertzalan A, Phillip M. Pubertal course of persistently short children born small for gestational age (SGA) compared with idiopathic short children born appropriate for gestational age (AGA). *European journal of endocrinology.* 2003;149(5):425-32.
52. Albertsson-Wikland K, Karlberg J. Natural growth in children born small for gestational age with and without catch-up growth. *Acta Paediatrica, International Journal of Paediatrics, Supplement.* 1994;83(399):64-71.
53. Ghirri P, Bernardini M, Vuerich M, Cuttano AM, Coccoli L, Merusi I, et al. Adrenarche, pubertal development, age at menarche and final height of full-term, born small for gestational age (SGA) girls. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology.* 2001;15(2):91-7.
54. Odberg MD, Sommerfelt K, Markestad T, Elgen IB. Growth and somatic health until adulthood of low birthweight children. *Archives of disease in childhood Fetal and neonatal edition.* 2010;95(3):F201-5.
55. Saigal S, Stoskopf BL, Streiner DL, Burrows E. Physical growth and current health status of infants who were of extremely low birth weight and controls at adolescence. *Pediatrics.* 2001;108(2):407-15.
56. Last JM, Abramson JH, Freidman GD. *A dictionary of epidemiology:* Oxford University Press New York; 2001.
57. Pak S. The growth status of North Korean refugee children and adolescents from 6 to 19 years of age. *Econ Hum Biol.* 2010;8(3):385-95.
58. Houghton LC, Cooper GD, Booth M, Chowdhury OA, Troisi R, Ziegler RG, et al. Childhood environment influences adrenarcheal timing among first-generation Bangladeshi migrant girls to the UK. *PloS one.* 2014;9(10):e109200.
59. Coly AN, Milet J, Diallo A, Ndiaye T, Benefice E, Simondon F, et al. Preschool stunting, adolescent migration, catch-up growth, and adult height in young senegalese men and women of rural origin. *J Nutr.* 2006;136(9):2412-20.
60. Viridis R, Street ME, Zampolli M, Radetti G, Pezzini B, Benelli M, et al. Precocious puberty in girls adopted from developing countries. *Arch Dis Child.* 1998;78(2):152-4.
61. Proos L, Karlberg J, Hofvander Y, Tuvemo T. Pubertal linear growth of Indian girls adopted in Sweden. *Acta Paediatrica.* 1993;82(8):641-4.
62. Le Mare L, Audet K. A longitudinal study of the physical growth and health of postinstitutionalized Romanian adoptees. *Paediatr Child Health.* 2006;11(2):85-91.

63. Zhang N, Bécares L, Chandola T. Does the timing of parental migration matter for child growth? A life course study on left-behind children in rural China. *BMC public health*. 2015;15(1):966.
64. Bogin B, Smith P, Orden AB, Varela Silva MI, Loucky J. Rapid change in height and body proportions of Maya American children. *American Journal of Human Biology*. 2002;14(6):753-61.
65. Teilmann G, Boas M, Petersen JH, Main KM, Gormsen M, Damgaard K, et al. Early pituitary-gonadal activation before clinical signs of puberty in 5- to 8-year-old adopted girls: a study of 99 foreign adopted girls and 93 controls. *J Clin Endocrinol Metab*. 2007;92(7):2538-44.
66. Teilmann G, Pedersen CB, Skakkebaek NE, Jensen TK. Increased risk of precocious puberty in internationally adopted children in Denmark. *Pediatrics*. 2006;118(2):e391-9.
67. Krstevska-Konstantinova M, Charlier C, Craen M, Du Caju M, Heinrichs C, De Beaufort C, et al. Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides. *Human Reproduction*. 2001;16(5):1020-6.
68. Bourguignon JP, Juul A. Normal female puberty in a developmental perspective. *Endocrine development*. 2012;22:11-23.
69. Lee Y, Styne D. Influences on the onset and tempo of puberty in human beings and implications for adolescent psychological development. *Horm Behav*. 2013;64(2):250-61.
70. Shalitin S, Kiess W. Putative Effects of Obesity on Linear Growth and Puberty. *Horm Res Paediatr*. 2017;88(1):101-10.
71. Castellano JM, Tena-Sempere M. Metabolic control of female puberty: potential therapeutic targets. *Expert Opin Ther Targets*. 2016;20(10):1181-93.
72. Roa J, Tena-Sempere M. Energy balance and puberty onset: emerging role of central mTOR signalling. *Trends Endocrinol Metab*. 2010;21(9):519-28.
73. Roa J, Garcia-Galiano D, Castellano JM, Gaytan F, Pinilla L, Tena-Sempere M. Metabolic control of puberty onset: new players, new mechanisms. *Mol Cell Endocrinol*. 2010;324(1-2):87-94.
74. Abreu AP, Kaiser UB. Pubertal development and regulation. *Lancet Diabetes Endocrinol*. 2016;4(3):254-64.
75. Bourguignon JP, Rasier G, Lebrethon MC, Gerard A, Naveau E, Parent AS. Neuroendocrine disruption of pubertal timing and interactions between homeostasis of reproduction and energy balance. *Mol Cell Endocrinol*. 2010;324(1-2):110-20.
76. Coutant R, Bouhours-Nouet N. Endocrine Control and Regulation of Growth Hormone: An Overview. 2012. In: *Handbook of growth and growth monitoring in health and disease* [Internet]. New York, NY: Springer Science+Business Media; [73-92].
77. Benyi E, Savendahl L. The Physiology of Childhood Growth: Hormonal Regulation. *Horm Res Paediatr*. 2017;88(1):6-14.
78. Vizmanos B, Marti-Henneberg C, Cliville R, Moreno A, Fernandez-Ballart J. Age of pubertal onset affects the intensity and duration of pubertal growth peak but not final height. *Am J Hum Biol*. 2001;13(3):409-16.
79. Ferrandez A, Carrascosa A, Audi L, Bager L, Rueda C, Bosch-Castane J, et al. Longitudinal pubertal growth according to age at pubertal growth spurt onset: data from a Spanish study including 458 children (223 boys and 235 girls). *J Pediatr Endocrinol Metab*. 2009;22(8):715-26.
80. Yousefi M, Karmaus W, Zhang H, Roberts G, Matthews S, Clayton B, et al. Relationships between age of puberty onset and height at age 18 years in girls and boys. *World J Pediatr*. 2013;9(3):230-8.
81. Limony Y, Koziel S, Friger M. Age of onset of a normally timed pubertal growth spurt affects the final height of children. *Pediatr Res*. 2015;78(3):351-5.
82. Lui JC, Nilsson O, Baron J. Growth plate senescence and catch-up growth. *Endocrine development*. 2011;21:23-9.
83. Lui JC. Nutritional Regulation of the Growth Plate. 2018. In: *The Biology of the First 1,000 Days* [Internet]. Boca Raton: CRC Press.

84. Lampl M, Schoen M. How long bones grow children: Mechanistic paths to variation in human height growth. *Am J Hum Biol.* 2017;29(2).
85. van der Eerden BC, Karperien M, Wit JM. Systemic and local regulation of the growth plate. *Endocrine reviews.* 2003;24(6):782-801.
86. Wuelling M, Vortkamp A. Molecular Control of Cartilage Differentiation. In: Grassel S, Aszodi A, editors. *Cartilage: Volume 1: Physiology and Development.* Cham: Springer International Publishing; 2016. p. 191-213.
87. Laplante M, Sabatini DM. mTOR signalling in growth control and disease. *Cell.* 2012;149(2):274-93.
88. Semba RD, Shardell M, Sakr Ashour FA, Moaddel R, Trehan I, Maleta KM, et al. Child Stunting is Associated with Low Circulating Essential Amino Acids. *EBioMedicine.* 2016;6:246-52.
89. Williams GR, Bassett JHD. Thyroid diseases and bone health. *Journal of Endocrinological Investigation.* 2017.
90. Kumar S, Nadkarni J, Dwivedi R. Thyroid hormone status in malnourished children. *Indian pediatrics.* 2009;46(3):263-4.
91. Gat-Yablonski G, Phillip M. Nutritional-Induced Longitudinal Catch-Up Growth: A Focus on the Growth Plate, Growth-Related Genes, Autophagy, mTOR, and microRNAs. 2012. In: *Handbook of growth and growth monitoring in health and disease [Internet].* [1029-43].
92. Fazeli PK, Klibanski A. Determinants of GH resistance in malnutrition. *J Endocrinol.* 2014;220(3):R57-65.
93. Biro FM, Huang B, Wasserman H, Pinney S. Pubertal Growth, IGF1, and Windows of Susceptibility. *Journal of Pediatric and Adolescent Gynecology.* 2016;29(2):160.
94. Roldan Martin MB, Witchel SF. Growth and the Insulin-Like Growth Factor-1 Receptor (IGF1R). 2012. In: *Handbook of growth and growth monitoring in health and disease [Internet].* [2711-22].
95. Rogol A, Roemmich J, Clark P. Growth at Puberty. *J Adolesc Health.* 2002;31:192-200.
96. Wu S, Levenson A, Kharitonov A, De Luca F. Fibroblast growth factor 21 (FGF21) inhibits chondrocyte function and growth hormone action directly at the growth plate. *The Journal of biological chemistry.* 2012;287(31):26060-7.
97. Yoon BS, Pogue R, Ovchinnikov DA, Yoshii I, Mishina Y, Behringer RR, et al. BMPs regulate multiple aspects of growth-plate chondrogenesis through opposing actions on FGF pathways. *Development.* 2006;133(23):4667-78.
98. Shtaf B, Dror N, Bar-Maisels M, Phillip M, Gat-Yablonski G. Growth without growth hormone: can growth and differentiation factor 5 be the mediator? *Growth factors (Chur, Switzerland).* 2015;33(4):309-18.
99. Gat-Yablonski G, Phillip M. Nutritionally-induced catch-up growth. *Nutrients.* 2015;7(1):517-51.
100. Lui JC, Baron J. Effects of glucocorticoids on the growth plate. *Endocrine development.* 2011;20:187-93.
101. Casazza K, Hanks LJ, Alvarez JA. Role of various cytokines and growth factors in pubertal development. *Medicine and sport science.* 2010;55:14-31.
102. Wu S, Yang W, De Luca F. Insulin-like growth factor-independent effects of growth hormone on growth plate chondrogenesis and longitudinal bone growth. *Endocrinology.* 2015;156(7):2541-51.
103. Shim KS. Pubertal growth and epiphyseal fusion. *Annals of pediatric endocrinology & metabolism.* 2015;20(1):8-12.
104. Nakajima R, Inada H, Koike T, Yamano T. Effects of leptin to cultured growth plate chondrocytes. *Hormone Research in Paediatrics.* 2003;60(2):91-8.
105. Zhang F, He Q, Tsang WP, Garvey WT, Chan WY, Wan C. Insulin exerts direct, IGF-1 independent actions in growth plate chondrocytes. *Bone research.* 2014;2:14012.
106. Williams GR. Thyroid hormone actions in cartilage and bone. *European thyroid journal.* 2013;2(1):3-13.

107. Chagin A, Lindberg M, Andersson N, Moverare S, Gustafsson JÅ, Säwendahl L, et al. Estrogen Receptor Inhibits Skeletal Growth and Has the Capacity to Mediate Growth Plate Fusion in Female Mice. *Journal of Bone and Mineral Research*. 2004;19(1):72-7.
108. Castellano JM, Bentsen AH, Mikkelsen JD, Tena-Sempere M. Kisspeptins: bridging energy homeostasis and reproduction. *Brain Res*. 2010;1364:129-38.
109. Sanchez-Garrido MA, Tena-Sempere M. Metabolic control of puberty: roles of leptin and kisspeptins. *Horm Behav*. 2013;64(2):187-94.
110. Bordini B, Rosenfield RL. Normal pubertal development: Part I: The endocrine basis of puberty. *Pediatrics in review*. 2011;32(6):223-9.
111. Lazar L, Lebenthal Y, Shalitin S, Phillip M. Natural history of idiopathic advanced bone age diagnosed in childhood: pattern of growth and puberty. *Horm Res Paediatr*. 2011;75(1):49-55.
112. Sedlmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. *J Clin Endocrinol Metab*. 2002;87(4):1613-20.
113. Klein KO, Newfield RS, Hassink SG. Bone maturation along the spectrum from normal weight to obesity: a complex interplay of sex, growth factors and weight gain. *J Pediatr Endocrinol Metab*. 2016;29(3):311-8.
114. Flor-Cisneros A, Roemmich JN, Rogol AD, Baron J. Bone age and onset of puberty in normal boys. *Mol Cell Endocrinol*. 2006;254-255(254-255):202-6.
115. Barstow C, Rerucha C. Evaluation of Short and Tall Stature in Children. *Am Fam Physician*. 2015;92(1):43-50.
116. Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature*. 2014;514(7520):92-7.
117. Barros SP, Offenbacher S. Epigenetics: connecting environment and genotype to phenotype and disease. *Journal of dental research*. 2009;88(5):400-8.
118. Lomniczi A, Wright H, Castellano JM, Sonmez K, Ojeda SR. A system biology approach to identify regulatory pathways underlying the neuroendocrine control of female puberty in rats and nonhuman primates. *Horm Behav*. 2013;64(2):175-86.

