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Child Growth, Puberty, Adolescent Pregnancy, and Adult Anthropometric Outcomes

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Abstract

Child Growth, Puberty, Adolescent Pregnancy, and Adult Anthropometric Outcomes

By Elizabeth Ann Lundeen

Low- and middle-income countries (LMICs) undergoing the nutrition transition face the dual burden of both stunting and rising obesity prevalence among children. Programs aimed at improving nutrition in the first 1,000 days and beyond seek to improve children's linear growth, along with the associated cognitive, schooling, and adult income benefits. The challenge is to promote nutrition that improves linear growth, while not increasing obesity among children in LMICs. Longitudinal data with numerous anthropometric measurements from birth to young adulthood are needed to better understand child growth in LMICs. We used data from nine cohorts in LMICs to explore child growth patterns, including stunting and recovery from stunting, incidence of obesity, pubertal development, and associations with adult anthropometric outcomes. We found there is substantial growth recovery among children who are stunted post-infancy. We contributed to the debate on evaluating the existence of catch-up growth in a population by showing that from age 2y to adulthood, mean height-for-age z scores increased, despite increasing absolute height deficits from the reference population. We found that in South Africa, overweight and obesity were not widely prevalent among boys; however, among girls, the combined prevalence increased throughout childhood, and by late adolescence had reached levels seen in higher income countries. Interventions to prevent overweight and obesity among girls should target the early childhood and peri-pubertal years. We found that among males and females, there was a strong positive association between both height and body mass index (BMI) in early childhood and the tempo of pubertal development. Among females, greater childhood height and BMI were also associated with earlier pubertal development. We concluded that the previously observed relationship between pubertal timing and adult risk of obesity is largely explained by the association of childhood BMI with both puberty and adult BMI. The prevention of childhood obesity is critical, due to its association with both adult obesity and early puberty. Carefully designed interventions are needed to improve linear growth among children in LMICs, while not increasing obesity. Improving child growth could impact pubertal development, and interventions are needed to mitigate the social and psychological consequences of early puberty.

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Dedication

I would like to dedicate this dissertation to the memory of Patrice Engle, a woman whose contribution to the field of child health and development needs no explanation. I first met Patrice in Kyrgyzstan in 2009. Together we collaborated with our UNICEF colleagues on a national child nutrition and early childhood development program. She was an absolute joy to work with, and her unwavering passion for bettering the lives of children was an inspiration to all with whom she worked. I had the good fortune to continue collaborating with her on the Young Lives study when I joined Emory. As a woman and a widely recognized expert in her field, Patrice embodied the type of public health practitioner I aspire to be – smart, tough, dedicated, passionate, dynamic, creative, collaborative, funny, kind. I will never forget that Patrice was sending me comments to a paper, even in the very final stages of her disease. Her dedication inspires me.

This is a dissertation about how children grow up, and Patrice is someone who made an enormous contribution to improving the way in which children grow and develop. Patrice was the type of person who reminds us what this is all for.

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Chapter 1: Introduction

Low- and middle-income countries are going through a "nutrition transition," characterized by significant changes in access to food, as well as the structure and composition of the diet (1-3). Improvements in childhood nutrition have led to a global decrease in the prevalence of growth stunting, although it remains a problem, with one in four children under the age of five stunted (4). The decline in stunting has occurred in parallel with a global increase in overweight and obesity among children (4, 5), with the majority of overweight children under five years now living in low- and middle-income (LMICs) countries (4). Nutrition and health programs that target the first 1,000 days of life aim to improve linear growth among children in LMICs in order to enable them to achieve their full growth potential, as well as the cognitive, schooling, and adult income benefits associated with maximal attained height (6). However, improvements in access to food and changes in the composition of the diet may result in more prevalent overweight and obesity among children in LMICs, similar to what is seen in higher-income countries that have gone through the nutrition transition. Ultimately, the goal should be to achieve improvements in linear growth, while promoting healthy nutritional habits and access to healthy foods, to reduce the risk of obesity in childhood and beyond.

Rich longitudinal growth data are needed to better understand trends in childhood growth in LMICs, and the possible consequences of nutrition interventions aimed at early life growth. Much of the data on child growth in LMICs comes from cross-sectional surveys,

and focuses on narrow populations such as children under five years. This dissertation models longitudinal child growth data from cohorts in eight LMICs (Ethiopia, Peru, Vietnam, India, Brazil, Guatemala, Philippines, and South Africa). The overall aim of this research is to better understand and characterize child growth patterns from birth through young adulthood. Analysis of these rich longitudinal data, with many time points from birth through young adulthood, helps to address gaps in the literature on child growth in LMICs. Additionally, the South African cohort provides rich longitudinal pubertal development data, enabling a better understanding of the role of puberty in the child and adolescent growth pathway.

Following are the specific aims of this dissertation:

Specific Aim One

- Characterize patterns of linear growth, including stunting and recovery from stunting, across numerous time points from birth to adulthood.
- Contribute to the debate on methods for assessing recovery and catch-up growth.

Chapter 3: We used data from the four Young Lives cohorts to describe growth patterns at 1, 5, and 8 years of age, and determine the incidence of stunting and recovery from stunting post-infancy. The study aimed to determine whether there is appreciable recovery from stunting post-infancy, to assess the potential usefulness of nutritional interventions targeted after infancy.

Chapter 4: We analyzed data from five birth cohorts in the Consortium of Health-orientated Research in Transitioning Societies (COHORTS) to describe the incidence of stunting and recovery from stunting during intervals spanning from birth to adulthood. This study expanded upon the research in Chapter 3 in that we were able to characterize patterns of linear growth from birth through adulthood. Additionally, in this paper, we compared two different metrics for assessing longitudinal changes in growth in a population: 1) mean height-for-age z score in a population, and 2) the distance between the mean height in the population and the median height in a reference population. We discuss the usefulness of each metric in determining catch-up growth in a longitudinal cohort.

Specific Aim Two

- Identify predictors of adolescent pregnancy in South African girls and explore the association between adolescent pregnancy and maternal attained height.

Chapter 5: We analyzed data on black girls in the South African Birth-to-Twenty cohort, to identify determinants of adolescent pregnancy, and determine whether having an adolescent pregnancy is associated with shorter maternal adult height.

Specific Aim Three

- Characterize patterns of obesity incidence among South African children from infancy to late adolescence, and determine gender differences in overweight and obesity.

Chapter 6: We used growth data spanning from infancy to late adolescence among boys and girls in the South African Birth-to-Twenty cohort to describe the prevalence of overweight and obesity, and incidence of obesity between key periods: infancy/toddlerhood, early childhood, early adolescence, mid-adolescence, and late adolescence. This paper aims to determine gender differences in overweight and obesity, and to identify key periods for intervention to prevent overweight and obesity.

Specific Aim Four

- Determine the association between childhood growth measures – height and body mass index – and the timing and tempo of pubertal development.
- Determine the association between the timing and tempo of pubertal development and adult height and body mass index.

Chapter 7: We used data on the development of secondary sexual characteristics from 9-16 years among boys and girls in the Birth-to-Twenty cohort to describe the longitudinal progression of puberty and to classify children based on unique trajectories for pubertal development. We then explored the relationship between the timing and trajectory (or tempo) of pubertal development and height and body mass index at 5 and 8 years of age.

Chapter 8: We used these same trajectories for pubertal development in the Birth-to-Twenty cohort to explore the relationship between the timing and tempo of pubertal development and adult height and body mass index.

Chapter 2: Background

The Nutrition Transition

Over the last century, countries throughout the world have gone through the "nutrition transition," a period of rapid social and economic development that profoundly changes access to food, the structure and composition of the diet, the amount of physical activity involved in labor and tasks of daily living, body size and composition, and chronic disease risk (1-3). High-income countries experienced this transition earlier, whereas many low- and middle-income countries (LMICs) are continuing to undergo this transition (1, 3). In countries going through this transition, certain segments of the population continue to suffer food insecurity, lacking access to adequate calories and micronutrients, while other segments have increased access to energy-dense, processed foods high in fat and sugar (2). In some cases, children start out life, in utero and in the early childhood years, deprived of adequate nutrition, and later consume an abundance of energy-dense foods in excess of their caloric needs. Theories of the developmental origins of health and disease suggest that early life, particularly fetal, deprivation results in adaptive mechanisms, one of which programs the body for fat deposition, and this adaptive propensity for fat deposition is exacerbated by excess caloric intake later in life (3, 7). Early life undernutrition and growth faltering, followed by caloric excess and rapid weight gain later in childhood may have a synergistic effect in predisposing one to overweight and obesity, as well as chronic disease, in adulthood (4, 6). The "dual burden" of both stunting and childhood overweight and obesity is common in countries undergoing this transition (3, 8, 9), and both stunting and childhood obesity are prevalent problems in LMICs globally. While there have been gains in linear height over the last

few decades, one in four children under the age of five remain stunted (4). Additionally there has been a global increase in overweight and obesity among children, with 13% of children in LMICs overweight or obese (4, 5). It is not completely understood whether this "dual burden" of stunting and obesity are causally related, but recent evidence suggests they could be independent phenomena, rather than having a common cause resulting in a disproportionate occurrence in the same individuals or households (10, 11). While distinct strategies may be required to address these two problems, public health leaders have called for a coordinated effort to reduce the burden of both stunting and overweight, recognizing that interventions to improve household food security and child nutrition could lead to excess energy intake (10).

The First 1,000 Days Agenda

Nutrition and health programs in LMICs have targeted interventions toward the first 1,000 days of life to maximize the growth, health, and cognitive benefits associated with improved nutrition (4). These programs aim to promote adequate linear growth and weight gain, as well as improve both the physical and cognitive development of children. A primary aim of these nutrition interventions is to enable children to achieve their linear growth potential, given the strong association between height and human capital measures such as cognitive development, school performance, and adult income (6). However, in doing so, it is important to prevent overweight and obesity, a burgeoning problem in LMICs, and a common but unintended consequence of improved access to food and changes in the structure and composition of the diet. It has been found that

faster linear growth, particularly during the first two years of life, is associated with improved educational outcomes, but that faster weight gain independent of height after the first two years is associated with greater risk of adult overweight and elevated blood pressure, without any benefit for human capital (12, 13). These findings underscore the importance of targeting interventions toward improving linear growth in the first two years, without promoting excess weight gain after two years (12, 13). It is therefore important to identify which interventions – micronutrient supplementation, breastfeeding promotion, protein supplementation – will promote optimal linear growth without increasing excess weight gain (13). For example, it has been suggested that cash transfer or food distribution programs designed to improve nutrition in micronutrient deficient, but not energy deficient, populations can have the undesired effect of increasing energy intake, raising concerns about whether these programs are increasing obesity risk (10, 14).

Global Changes in Pubertal Development

The Biology of Pubertal Development

Puberty is a complex series of physiological changes under the tight control of hormone signaling, and includes an acceleration of linear growth, changes in body composition, the development of primary and secondary sexual characteristics, and achievement of reproductive capabilities. Adrenarche, the first phase of puberty, which begins around 6-9 years of age for girls and around one year later in boys, is, is characterized by an increase in adrenal androgens (dehydroepiandrosterone and androstendione) but no visible

external signs of puberty (15). During the second phase of puberty, gonadarche, the hypothalamic-pituitary gonadal axis is activated, resulting in the secretion of lutenizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland, as well as an increase in the secretion of gonadal sex steroids (testosterone and estradiol) (15). Gonadarche begins around 9-10 years in girls and around one year later in boys. The hormonal cascade of gonadarche results in maturation of primary sexual characteristics (ovaries develop and testes increase in size), development of secondary sexual characteristics (pubic hair, breasts, and genitals), and commencement of fertility (15). In girls, ovarian estrogen secretion controls breast development (16), while adrenal and ovarian androgens bring about pubic hair development (15, 16). In boys, FSH and LH cause the increase in testicular volume, with pubic hair development under the control of adrenal and testicular androgen secretion (16). Ovulation and menarche, or the onset of menstruation in girls, occur relatively late in gonadarche, whereas spermarche, the onset of nocturnal emission in boys, occurs in early to mid-puberty. An increase in growth hormone, as well as more evenly distributed pulsatile release of growth hormone throughout the 24 hour day, result in an acceleration of linear growth during puberty (15). This pubertal growth spurt occurs on average at 12 years among girls, versus 14 years among boys, and in girls is often the first visible sign of puberty (15). Puberty is also a time of changes in body composition and sexual dimorphism, with girls gaining greater amounts of fat mass and boys gaining greater muscle and skeletal mass (16). Both leptin and estrogen, hormones produced in adipose cells, are thought to play a role in the stimulation of pubertal development (16). Estrogen plays an important role in the pubertal growth spurt, as well as the bone maturation that occurs during puberty (16).

The Epidemiology of Pubertal Development

The rapid improvements in nutrition and socioeconomic conditions in countries that have gone through the nutrition transition, as well as subsequent changes in body composition, have occurred concurrently with global shifts in the timing of pubertal development (17). In the U.S. and Western European countries, there was a marked decline in the average age of menarche (17y to 13y) from the mid-19th to the mid-20th century, and there continues to be a strong secular trend in the reduction of menarcheal age in LMICs, which have developed and gone through the nutrition transition more recently (17, 18). Studies have also shown a secular trend toward earlier development of breasts and pubic hair among girls (19-23), and some research suggests earlier genital and pubic hair development in boys (22-24).

The global shift in age at pubertal onset has been concurrent with increases in height, suggesting improved nutrition and socioeconomic conditions have contributed to both trends (25). It has been found that height in children is inversely associated with age of pubertal onset (26-29). Furthermore, secular trends in pubertal development have mirrored the increase in body mass index (BMI) among children (30, 31), and studies on the role of overweight and obesity in pubertal development have garnered much attention (20, 32-34). There is evidence of an association between higher BMI in childhood or adolescence and earlier onset of puberty among girls (20, 26, 29, 33, 35-39). Additionally, women who experience menarche at an earlier age have been found to have

a greater adult BMI and significantly increased risk of obesity in adulthood (40-46). However, generally, studies have not been able to account for the potential role of childhood BMI in this relationship. If childhood BMI is associated with pubertal timing and also tends to track into adulthood (47-49), it could confound the relationship between puberty and adult BMI.

In addition to the potential effect of puberty timing on adult risk of overweight and obesity, trends in earlier puberty are concerning due to the association between early puberty and poor psychosocial outcomes. Early puberty among girls is associated with a higher risk of depression, eating disorders, substance abuse, poor academic achievement, and risky sexual behaviors (50). Puberty also signals readiness for sexual activity, child-bearing, and marriage, and trends toward earlier puberty in LMICs could have profound social implications. Therefore, it is important to understand the potential impact on puberty of programs designed to improve child growth, as child growth may be closely linked to pubertal timing.

Understanding Child Growth and Development in LMICs

In order to have a better understanding of the potential effects of programs aimed at improving child growth, it is necessary to utilize rich longitudinal growth data from LMICS, as well as improved methods for characterizing longitudinal growth and development. It is important to better understand patterns of child growth from birth to late adolescence, including linear growth stunting and recovery from stunting, as well as

incidence of obesity and critical periods for intervention. Much of the child growth data for LMICs are cross-sectional, being derived from the Demographic and Health Surveys or the UNICEF Multiple Indicator Cluster Surveys. Rich longitudinal growth data with anthropometric measurements at multiple time points from birth through adolescence are needed to better understand how children in LMICs grow over time.

Contribution of This Dissertation

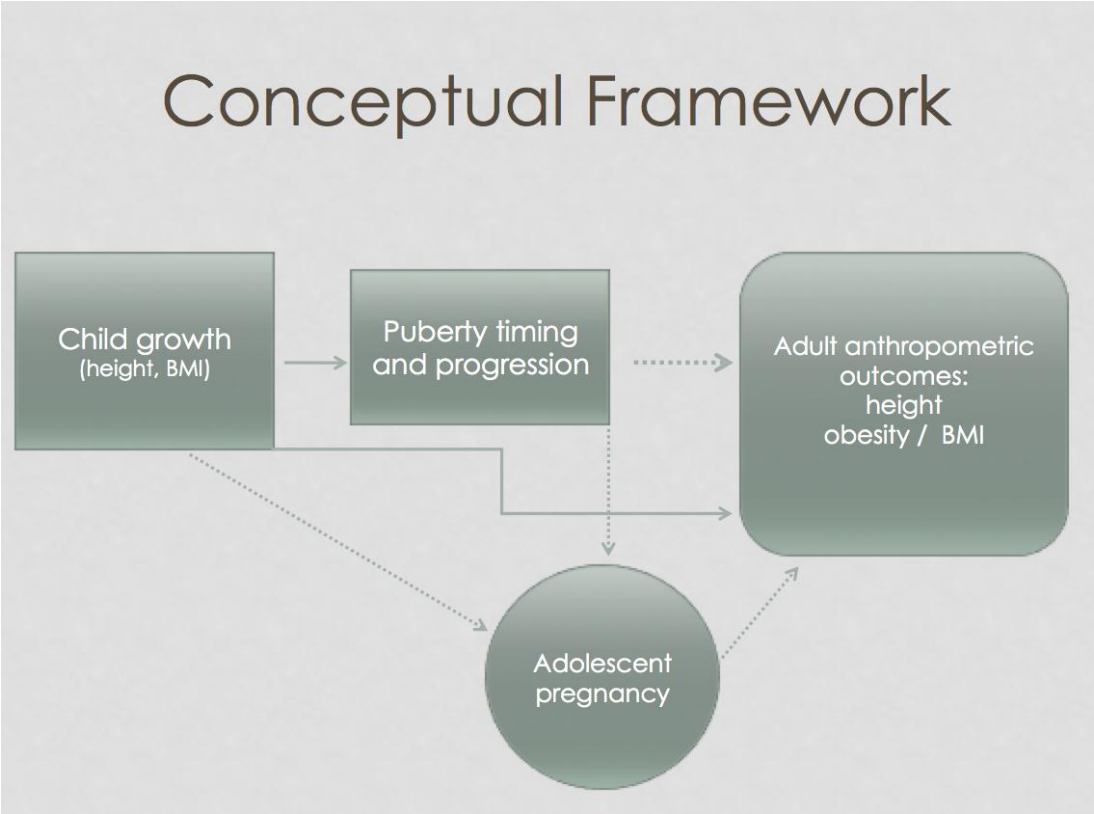
The overarching theme of this dissertation is how children in LMICs grow, from birth through young adulthood. The 1,000 day agenda, and public health and nutrition programs more generally, should strive to help children achieve their linear growth potential, while maintaining appropriate weight gain and minimizing risk of overweight and obesity throughout childhood into adulthood. Children should be able to gain the human capital benefits associated with linear growth, while not succumbing to the risk of obesity and chronic disease, which often accompanies the nutrition transition. A first step in understanding the potential consequences of the 1,000 day agenda and nutrition programs aimed at improving child growth is better understanding how children grow in LMICs.

We address gaps in the literature by using rich longitudinal growth and pubertal development data spanning many time points throughout childhood and adolescence. The data are derived from the four Young Lives cohorts in Ethiopia, India, Peru, and Vietnam, as well as the five birth cohorts in India, Brazil, Guatemala, Philippines, and

South Africa, which are a part of the Consortium of Health-orientated Research in Transitioning Societies (COHORTS). Details of these cohorts are described more fully in the chapters to follow, and the cohort profiles have been previously published (51-53).

Using these data, we explore patterns in linear growth, including stunting and recovery from stunting, as well as the nature and definitions of "catch-up growth." We also explore obesity incidence patterns, pubertal development trajectories, and the complex relationships between child growth, puberty, and adult anthropometric outcomes. This research was designed based on the following conceptual framework (**Figure 2.1**), which recognizes the relationship between childhood height and BMI and pubertal development, the association between puberty and adult anthropometric outcomes, and the tracking of childhood height and BMI into adulthood.

Figure 2.1: Conceptual framework for child growth, puberty, adolescent pregnancy and adult anthropometric outcomes



The following chapters will explore these relationships in detail.

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Chapter 3: Growth faltering and recovery in children ages 1 to 8y in four low- and middle-income countries: Young Lives

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Abbreviations used: HAZ, height-for-age z score; LMIC, low- and middle-income countries; DHS, Demographic and Health Surveys.

Abstract

Objective: We characterized post-infancy child growth patterns and determined the incidence of becoming stunted and of recovery from stunting.

Design: Data came from Young Lives, a longitudinal study of childhood poverty in four low- and middle-income countries (LMICs).

Setting: We analyzed length/height measurements for children at ages 1, 5, and 8y.

Subjects: 7,171 children in Ethiopia, India, Peru and Vietnam.

Results: Mean height-for-age z-score (HAZ) at age 1y ranged from -1.51 (Ethiopia) to -1.08 (Vietnam). From age 1 to 5y, mean HAZ increased 0.27 SD in Ethiopia ($p<0.001$) and decreased among the other cohorts (range: -0.19 (Peru) to -0.32 (India)) (all $p<0.001$). From 5 to 8y, mean HAZ increased in all cohorts (range: 0.19 (India) to 0.38 (Peru)) (all $p<0.001$). Prevalence of stunting (HAZ<-2.0) at 1y ranged from 21% (Vietnam) to 46% (Ethiopia). From age 1 to 5y, stunting prevalence decreased 15.1 percentage points (PP) in Ethiopia ($p<0.001$) and increased in the other cohorts (range: 3.0 PP (Vietnam) to 5.3 PP (India)) (all $p\leq0.001$). From 5 to 8y, stunting prevalence decreased in all cohorts (range: 5.0 PP (Vietnam) to 12.7 PP (Peru)) (all $p<0.001$). The incidence of becoming stunted between ages 1 to 5y ranged from 11% (Vietnam) to 22% (India); between ages 5 to 8y, it ranged from 3% (Peru) to 6% (India and Ethiopia). The

incidence of recovery from stunting between ages 1 and 5y ranged from 27% (Vietnam) to 53% (Ethiopia); between ages 5 and 8y, it ranged from 30% (India) to 47% (Ethiopia).

Conclusions: We found substantial recovery from early stunting among children in four LMICs.

Introduction

Characterizing child growth patterns, including the incidence of becoming stunted and of recovery from stunting, in low- and middle-income countries (LMICs) is important for understanding the determinants and consequences of childhood growth trajectories and for developing effective interventions and policies. Cross-sectional data from the Demographic and Health Surveys (DHS) show that on average children in LMICs experience rapid growth faltering during the first two years of life, with height-for-age z scores (HAZ), the preferred indicator of long-run nutritional status, declining dramatically over the first 24 months of life and increasing only slightly after then (1). These and similar findings have been used to suggest that recovery after two years of age is unlikely and therefore the "window of opportunity" for preventing undernutrition ends at two years.

Nutritional interventions are increasingly targeted toward children under two years, as it has been suggested that, similar to linear growth retardation, the cognitive and developmental deficiencies resulting from poor growth may also be largely irreversible after about two years of age (2-8). However, some evidence challenges these findings (9-17) and suggests that there is significant opportunity for both catch-up growth, as well as the associated cognitive and schooling improvements, following post-infancy growth stunting. Such evidence may support a complementary approach focused on identifying and targeting children post-infancy who are stunted or at risk for growth faltering, for further nutritional or health interventions. There are few published longitudinal studies of child growth and its consequences for health and development (Adair et al., 1999 (18)

is an exception), limiting the conclusions that can be drawn about child growth trajectories in LMICs.

Our study addresses this gap in the literature by presenting longitudinal child growth data from population-based cohorts in four LMICs. We analyzed data on growth patterns of children post-infancy (≥ 12 mo), in order to describe growth patterns and determine the incidence of becoming stunted, and of recovery from stunting.

Methods

Young Lives Study

Young Lives is a longitudinal study of the causes and consequences of childhood poverty in Peru, Vietnam, India, and Ethiopia (19). Within each country, the study follows a cohort of ~2000 children (there is also an older cohort of about half this size). The Young Lives Project used a multi-stage sampling strategy, whereby the first stage consisted of the selection of 20 sentinel sites (clusters) per country using a sampling methodology referred to as the Sentinel Site Surveillance system. In each country, the sentinel sites were selected in a semi-purposive manner based on socioeconomic, demographic, geographic, and policy variables that were relevant to the project. In Peru, Vietnam and Ethiopia, a nationwide sampling frame was used, whereas in India the sentinel sites were selected within the state of Andhra Pradesh. The sampling frame allowed for oversampling for poor areas and a mixture of urban and rural areas. In the second stage, within each sentinel site, households with a child in the target age range were enumerated

and approximately 100 index children were selected according to comparable, but country-specific, protocols that were analogous to statistical random sampling. Refusal rates among selected households were <2% in all four countries, and in the case of refusal, replacement sampling was used (19). These sampling methods resulted in a sample for each country that reflected the ethnic, geographic, and religious diversity of the population, but that was not chosen to be directly nationally representative. Further details on the sampling strategy used within each country can be found in the Preliminary National Reports accessible at http:/www.younglives.org.uk/. Data collection took place in 2002 (round 1, age 6-18 mo), in 2006-2007 (round 2, age 4.5 to 5 y), and in 2009-2010 (round 3, age 7 to 8 y). Supine length (round 1) and standing height (rounds 2 and 3) were measured with length/height boards using standardized WHO methodology (20) and measurements precise to 1mm. The length and height measurements were converted to z scores (HAZ) using WHO standards (21-23).

Data Cleaning and Analysis

Length measurements were available at recruitment for 1,946 children in Ethiopia, 1,992 children in India, 2,040 children in Peru, and 1,990 children in Vietnam. Data were excluded from analysis if the child was not in the target age range (6-17.9 months) at recruitment (0 children in Ethiopia, 39 in India, 27 in Peru, and 69 in Vietnam); was not measured at all three rounds (115 children in Ethiopia, 87 in India, 146 in Peru, and 72 in Vietnam); or had HAZ values that were implausible, defined as $|HAZ| > 5$ at any one round or an absolute value of change in HAZ between rounds > 4 (121 children in Ethiopia, 70 in India, 32 in Peru, and 19 in Vietnam). After these exclusions, data were

available for 7,171 children (1,710 in Ethiopia, 1,796 in India, 1,835 in Peru, and 1,830 in Vietnam), representing 90% of the original sample.

Children who were younger at recruitment tended to have higher HAZ scores and children who were older at recruitment tended to have lower HAZ scores (**Figure 3.1**). Failing to account for the variability in age at recruitment would distort an assessment of the incidence of becoming stunted and of recovery between rounds 1 and 2, because children who were older than 12 months at round 1 would be coded as having greater recovery than they otherwise would have had they been recruited at 12 months, while children who were younger than 12 months at round 1 would be coded as having greater incidence of stunting than they otherwise would have, assuming that over short periods of time children track along the growth trajectory that is typical of the community in which they live. Therefore, we adjusted round 1 HAZ by adding the difference between the child's observed HAZ and the site-specific mean HAZ for all children within +/- 1 month of the child's age to the site-specific mean HAZ for children ages 11-13 months. Overall, there was little difference by month of age in mean HAZ in rounds 2 and 3, and therefore we did not conduct a similar adjustment for these rounds.

Characterizing Growth

We compared the mean values for HAZ at each round and the mean within-child change in HAZ between rounds. We computed the prevalence of stunting (HAZ < -2.0) in each round as well as the incidence of becoming stunted (the proportion of children who were not stunted in an earlier round but were stunted at a later round) and of recovery (the

proportion of children who were stunted in an earlier round but were not stunted at a later round). Tests of statistical significance were carried out using linear regression analyses that accounted for both the paired nature of the data, as well as the clustering within the data due to sampling procedures; all p-values are presented as two-sided. We also determined the extent to which HAZ measurements at earlier ages predict HAZ at later ages by regressing HAZ at round 2 on the HAZ score at round 1, and by regressing HAZ at round 3 on HAZ at rounds 1 and 2. We used the Intercooled STATA 10.0 (StataCorp, College Station, Texas) statistical program for all data analyses.

Results

The average age at recruitment was 12.2 months, with some variation across cohorts (**Table 3.1**). At round 1, the Ethiopian cohort had the lowest mean HAZ (-1.51), and the Vietnamese cohort had the highest (-1.08) (**Table 3.2**). From round 1 to round 2, mean HAZ increased among Ethiopian children (0.27; $p<0.001$) and decreased among the other cohorts (range -0.19 to -0.32; all $p<0.001$). From round 2 to round 3, mean HAZ increased in all four cohorts (range 0.19 to 0.38; all $p<0.001$). At round 1, the Ethiopian cohort had the highest prevalence of stunting (46%), and the Vietnamese cohort had the lowest (21%). From round 1 to round 2, the Ethiopian cohort experienced a 15.1 percentage points [PP] reduction in the prevalence of stunting ($p<0.001$), while the prevalence of stunting increased (range 3.0 to 5.3 PP; all $p\leq0.001$) in the other three cohorts. From round 2 to round 3, the prevalence of stunting decreased (range 5.0 to 12.7 PP; all $p<0.001$) in all four cohorts. Taking the whole study period, from round 1 to round 3, there was a significant decrease in the prevalence of stunting in Ethiopia (25.4

PP; p<0.001), Peru (8.3 PP; p<0.001), and Vietnam (2.0 PP; p=0.04); however, the decrease of 0.8 PP in India was not significant (p=0.45).

From round 1 to round 2, the majority of children had a change in HAZ ≥ 0.50 (**Figure 3.2**), whereas from round 2 to round 3, the majority of children experienced a change in HAZ ≤ 0.49.

The incidence of becoming stunted from round 1 to round 2 ranged from 11% (Vietnam) to 22% (India) (**Table 3.3**), and from round 2 to round 3 ranged from 3% (Peru) to 6% (India and Ethiopia). The incidence of recovery ranged from 27% (Vietnam) to 53% (Ethiopia) between rounds 1 and 2, and from 30% (India) to 47% (Ethiopia) between rounds 2 and 3. From round 1 to round 3, the incidence of becoming stunted ranged from 8% (Peru) to 18% (India), and the incidence of recovery ranged from 45% (Vietnam) to 67% (Ethiopia).

When HAZ at round 2 was regressed on HAZ at round 1, the r-squared was 0.26 in Ethiopia, 0.33 in India, 0.47 in Peru, and 0.60 in Vietnam; therefore, between 26% to 60% of the variability in HAZ at round 2 was predicted by HAZ at round 1. When HAZ at round 3 was regressed on HAZ at rounds 1 and 2, the r-squared was 0.53 in Ethiopia, 0.65 in India, 0.71 in Peru, and 0.73 in Vietnam; therefore, between 53% to 73% of the variability in HAZ at round 3 was predicted by HAZ at rounds 1 and 2.

Discussion

We analyzed child growth patterns using HAZ scores at ages 1, 5, and 8 years for 7,171 children in four LMICs participating in the Young Lives Study. Cross-sectional data from round 1 demonstrated decreasing mean HAZ scores between ages 6-18 mo. Three of the four countries continued to experience declining HAZ scores between age 1 and age 5. Mean HAZ increased in all four countries between age 5 and age 8. While stunting status at round 1 was predictive of stunting at rounds 2 and 3, there was substantial recovery from early stunting, with recovery rates ranging from 27% to 53% between rounds 1 and 2, and from 30% to 47% between rounds 2 and 3. Intra-child height measurements over time are highly correlated, reflecting a combination of genetic predisposition and environmental influences that affect linear growth. However, a substantial proportion of the variability in HAZ at age 5 (40-74%) and HAZ at age 8 (27-47%) was not predicted by HAZ measurements at earlier time points.

The data we used were collected through a large, multi-country longitudinal study, using standardized anthropometric procedures and rigorously trained field workers, and provided four diverse country contexts with which to study child growth patterns. However, several limitations of the data merit discussion. The Young Lives study began collecting data when the children were 6-17.9 months, so length at birth is not consistently available. Round 1 data were collected during an age period in which growth faltering occurs in many LMIC settings (1), and indeed our data show this age-related decrease in length-for-age. We addressed this challenge by internally adjusting our data to age 12 mo. Length was not measured at age 2 y, the age at which HAZ generally

reaches its nadir (1). However, data from the INCAP nutrition supplementation study showed that HAZ scores at ages 6, 12, and 18 months are strongly correlated with HAZ at age 24 months ($r=0.74$, 0.83, 0.91, respectively; all $p<0.001$), suggesting that HAZ between ages 6-18 months can serve as a reasonable proxy for HAZ at age 24 months (24). Additionally, having only three length/height measurements (at ages 1, 5, and 8) limits our ability to characterize post-infancy child growth patterns.

In the present analysis, the calculation of z-scores used growth standards from two distinct populations. The child growth standards used to calculate z-scores for the Young Lives cohorts at one year of age come from the longitudinal World Health Organization Multicentre Growth Study, a population of exclusively or predominantly breastfed children. The data for these growth standards end at five years of age, so the WHO developed reference charts for children older than five years based on cross-sectional data from the 1977 U.S. National Center for Health Statistics study of child growth, where feeding type was not controlled (22). We used these WHO reference charts for older children in the calculation of z-scores at five and eight years of age. This can limit the comparability of the z-scores at the three time points, and suggests that the data should be interpreted carefully.

The results of this analysis are based on data from four diverse country contexts, and we aimed to present and interpret country-specific findings, while also discussing growth patterns that were common across the sites. We did not, however, attempt to explain sources of variation across sites in the magnitude of growth failure and the incidence of

stunting and recovery from stunting, as such an analysis would require far more sites than the four in Young Lives, and the models would quickly become saturated.

This analysis has several strengths. When compared to other longitudinal studies that have collected child growth data, such as those participating in the COHORTS collaboration (25), the Young Lives study provides unique data with which to characterize child growth patterns. The Young Lives study provides more recent data on children born at about the same time the Millennium Development Goals (MDGs) were established. The data were collected longitudinally within four diverse population-based cohorts using a study-wide standardization and training process. With its emphasis on LMICs, the Young Lives study is well-positioned to document the incidence and timing of stunting and recovery among post-infancy children in MDG-focused countries characterized by poor childhood nutrition and growth.

Our data demonstrate that while child growth trajectories throughout the preschool and early school-age years are predicted in part by size at age 1, there is significant variation in growth after age 1 y. This includes catch-up growth in some children and faltering in others. These results suggest that while prevention of early-life stunting must continue to be a top priority, program planners and implementers should consider identifying and targeting for further nutritional interventions children who nevertheless become stunted during infancy, as well as children at risk for later growth faltering. An important area for future research is identifying the factors that contribute to these later variations in growth.

Table 3.1: Baseline characteristics of children in the Young Lives cohorts

Characteristics[1]	**Ethiopia**	**India**	**Peru**	**Vietnam**
Number of children	1,710	1,796	1,835	1,830
Age at recruitment (mo) (mean (SD))	12.2 (3.6)	12.2 (3.4)	12.0 (3.5)	12.3 (3.1)
Male (%)	53.2	53.4	50.1	51.2

1 Based on children in the present analysis.

Table 3.2: HAZ measures at 1, 5 and 8 y and changes in HAZ between these ages, among children in the Young Lives study, by country
(Continued on next page)

	Ethiopia (n = 1,710)		**India** (n = 1,796)	
	Mean (SD)	Range	Mean (SD)	Range
HAZ Round 1 (age 1 y)	-1.51 (1.58)	(-4.98, 4.59)	-1.30 (1.35)	(-4.87, 4.61)
HAZ Round 2 (age 5 y)	-1.46 (1.04)	(-4.84, 2.00)	-1.63 (0.95)	(-4.71, 3.13)
HAZ Round 3 (age 8 y)	-1.21 (1.00)	(-4.87, 3.56)	-1.43 (0.99)	(-4.87, 2.21)
HAZ change Rounds 1 to 2	0.27 (1.35)	(-3.84, 3.92)	-0.32 (1.11)	(-3.99, 3.89)
HAZ change Rounds 2 to 3	0.25 (0.78)	(-2.56, 3.99)	0.19 (0.62)	(-3.23, 3.93)
Stunting (HAZ < -2.0) (%)				
Round 1 (age 1 y)	45.5	-	29.3	-
Round 2 (age 5 y)	30.4	-	34.6	-
Round 3 (age 8 y)	20.1	-	28.5	-

Note: Mean (SD) unless otherwise noted.

Table 3.2: HAZ measures at 1, 5 and 8 y and changes in HAZ between these ages, among children in the Young Lives study, by country
(Continued from previous page)

	Peru (n = 1,835)		**Vietnam** (n = 1,830)	
	Mean (SD)	Range	Mean (SD)	Range
HAZ Round 1 (age 1 y)	-1.29 (1.22)	(-4.95, 3.23)	-1.08 (1.15)	(-4.94, 3.81)
HAZ Round 2 (age 5 y)	-1.51 (1.08)	(-4.61, 2.05)	-1.33 (1.01)	(-4.65, 2.87)
HAZ Round 3 (age 8 y)	-1.13 (1.02)	(-4.29, 2.17)	-1.09 (1.03)	(-4.50, 2.88)
HAZ change Rounds 1 to 2	-0.19 (0.90)	(-3.78, 3.51)	-0.21 (0.72)	(-3.58, 3.52)
HAZ change Rounds 2 to 3	0.38 (0.62)	(-2.31, 3.62)	0.24 (0.55)	(-3.42, 3.40)
Stunting (HAZ < -2.0) (%)				
Round 1 (age 1 y)	27.9	-	21.2	-
Round 2 (age 5 y)	32.3	-	24.2	-
Round 3 (age 8 y)	19.6	-	19.2	-

Note: Mean (SD) unless otherwise noted.

Table 3.3: Incidence of stunting[1] and of recovery[2] from stunting among children in the Young Lives study, by country

Country	Round	HAZ Status	Status at Round 1 %	Status at Round 2		Status at Round 3	
				HAZ < -2.0 %	HAZ ≥ -2.0 %	HAZ < -2.0 %	HAZ ≥ -2.0 %
Ethiopia n=1,710	1	HAZ < -2.0	45.5	47.4	52.6	32.9	67.1
		HAZ ≥ -2.0	54.5	16.1	83.9	9.3	90.7
India n=1,796	1	HAZ < -2.0	29.3	65.3	34.7	54.3	45.7
		HAZ ≥ -2.0	70.7	21.9	78.1	17.7	82.3
Peru n=1,835	1	HAZ < -2.0	27.9	69.7	30.3	49.2	50.8
		HAZ ≥ -2.0	72.1	17.8	82.2	8.1	91.9
Vietnam n=1,830	1	HAZ < -2.0	21.2	72.9	27.1	54.8	45.2
		HAZ ≥ -2.0	78.8	11.2	88.8	9.6	90.4
			Status at Round 2 %				
Ethiopia n=1,710	2	HAZ < -2.0	30.4			52.6	47.4
		HAZ ≥ -2.0	69.6			5.9	94.1
India n=1,796	2	HAZ < -2.0	34.6			70.3	29.7
		HAZ ≥ -2.0	65.4			6.3	93.7
Peru n=1,835	2	HAZ < -2.0	32.3			53.9	46.1
		HAZ ≥ -2.0	67.7			3.2	96.8
Vietnam n=1,830	2	HAZ < -2.0	24.2			65.2	34.8
		HAZ ≥ -2.0	75.8			4.5	95.5

1 Incidence of stunting is the proportion of children who were not stunted at an earlier survey round but were stunted at a later survey round (stunting is defined as HAZ <-2.0)

2 Incidence of recovery is the proportion of children who were stunted at an earlier survey round but were not stunted at a later survey round

Figure 3.1: Mean round 1 HAZ scores by age at recruitment in months

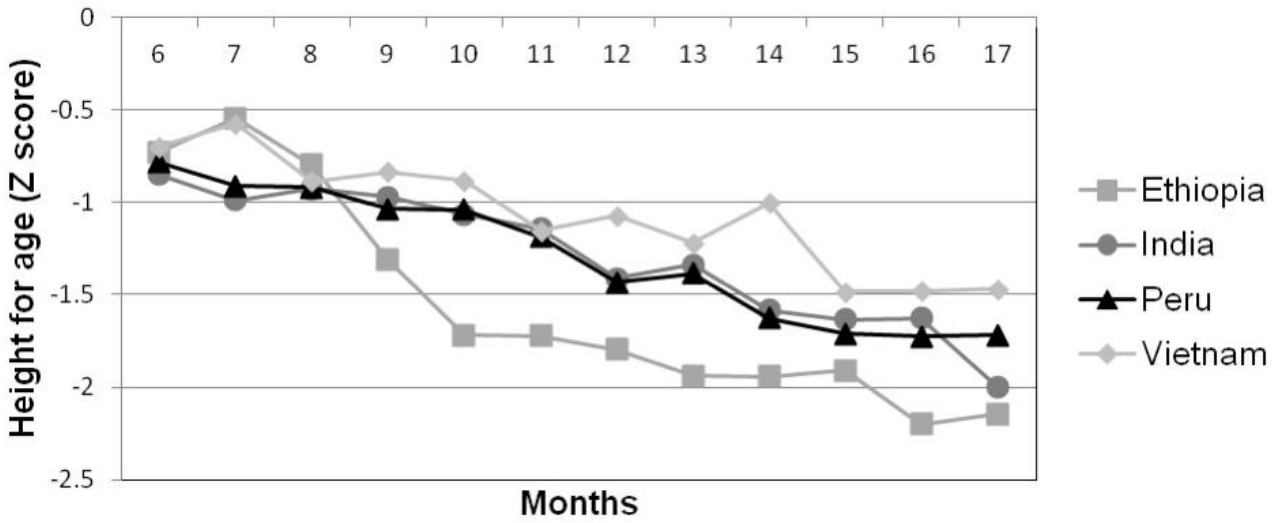
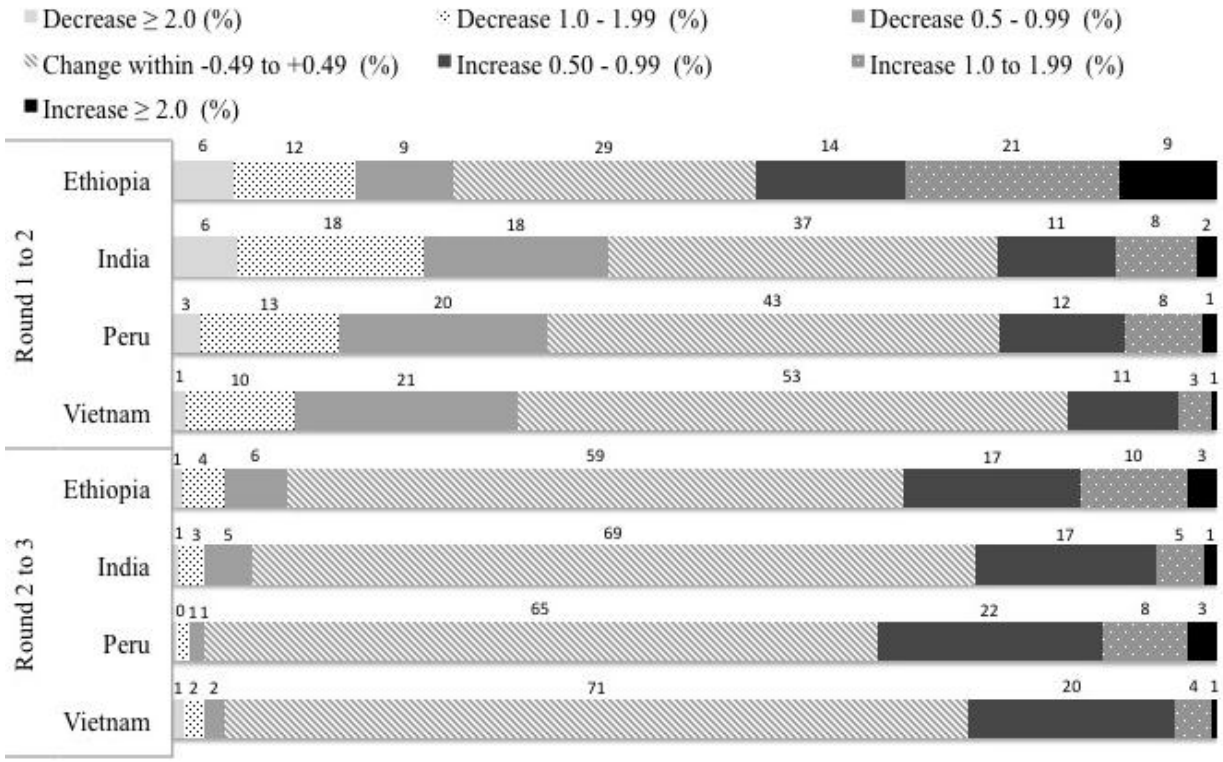


Figure 3.2: Categories of HAZ change between rounds among children in the Young Lives Study, by country



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Chapter 4: Height-for-age z scores increase despite increasing height deficits among children in five developing countries

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Abbreviations used: consortium of health-orientated research in transitioning societies (COHORTS); height-for-age z score (HAZ)

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Abstract

Background: Growth failure remains a persistent challenge in many countries, and understanding child growth patterns is critical to the development of appropriate interventions and their evaluation. Interpretation of changes in mean height-for-age z scores (HAZ) over time to define catch-up growth has been the subject of debate. Most studies of child growth have been cross-sectional or have focused on children through age 5 y.

Objective: Characterize patterns of linear growth among individuals followed from birth into adulthood.

Design: We compared HAZ and difference in height (cm) from the WHO reference median at birth, 12 mo, 24 mo, mid-childhood and adulthood for 5287 individuals from birth cohorts in Brazil, Guatemala, India, the Philippines and South Africa.

Results: Mean HAZ scores were <0 at birth in the three cohorts with data and ranged from -0.6 (Brazil) to -2.9 (Guatemala) at age 24 mo. Between 24 mo and mid-childhood, HAZ increased by 0.3 to 0.5 in South Africa, Guatemala, and the Philippines and was unchanged in Brazil and India. Between mid-childhood and adulthood, mean HAZ increased in all cohorts but remained <0 in adulthood (mean range -0.3 (Brazil) to -1.8 (Guatemala and Philippines)). However, from 24 mo to adulthood, height differences from the reference median became greater.

Conclusions: From age 2 y to adulthood, mean HAZ increased, even though height deficits relative to the reference median also increased. These two metrics may result in different interpretations of the potential for and the impact of catch-up growth in height.

Introduction

Globally, the prevalence of growth stunting in children under five years decreased from 40% in 1990 to 26% in 2011 (1). Much of this improvement can be attributed to major decreases in the prevalence of stunting in several countries in Asia, whereas stunting prevalence has stagnated in much of Africa over the last two decades (2). Growth failure still remains a persistent challenge in many low- and middle-income countries, and understanding child growth patterns is critical to the development of appropriate interventions and their evaluation.

However, research on childhood growth patterns has several limitations. Much of the data on child growth comes from cross-sectional studies, rather than longitudinal cohorts, limiting the inferences that can be made about how children grow over time. Additionally, studies tend to focus on children up to 5 years of age, and less is known about growth patterns after this age. Furthermore, the use and interpretation of indicators like height-for-age z scores (HAZ) for characterizing growth patterns has been the subject of debate (3).

We aimed to address these limitations in the child growth literature by characterizing patterns of linear growth from birth to adulthood among cohorts in five middle-income countries, and evaluating these data to further understanding of the interpretation of child growth indicators used to define catch-up growth.

Methods

We used data from the consortium of health-orientated research in transitioning societies (COHORTS), which includes birth cohorts in five middle-income countries: the 1982 Pelotas Birth Cohort (Brazil), the Institute of Nutrition of Central America and Panama Nutrition Trial Cohort (Guatemala), the New Delhi Birth Cohort (India), the Cebu Longitudinal Health and Nutrition Survey (the Philippines), and the Birth to Twenty Cohort (South Africa) (4). Each study was reviewed and approved by an appropriate ethics committee or institutional review board, and informed consent was provided by the participants or their caretakers.

The present analysis employs length and height data collected within each cohort using study-specific, but comparable, methodologies. Some aspects of the length/height data at these time points have been previously published (5, 6). With the exception of the Guatemala cohort, in all studies supine length was measured until 24 months, and standing height was measured thereafter. In Guatemala, supine length was measured through the age of 7 years, and for the purposes of comparability, supine length was converted to standing height by subtracting 1.0 cm from lengths obtained at ages 24 months and older (7). Length (cm) measurements were available at birth in India, within six days of birth in the Philippines, and within fifteen days of birth in Guatemala. Length at birth was not measured in South Africa and Brazil.

The studies varied in the timing and frequency of length/height measurements (details published previously) (5). For the present analysis, data from common child ages were used, specifically: birth (India, Philippines, Guatemala); 12 months (all 5 cohorts); 24 months (all 5 cohorts); mid-childhood (48 months in Brazil, Guatemala, India and South Africa, and 102 months in the Philippines) and adulthood (all 5 cohorts). The mean age at the time of the adult height measure was 23.1 years in Brazil, 31.3 years in Guatemala, 29.4 years in India, 21.2 years in the Philippines, and 18.2 years in South Africa.

Length and height measurements were converted to z scores (HAZ) using either the 2006 growth standards (0-59 months) (8), derived from the longitudinal World Health Organization Multicentre Growth Study, a population of exclusively or predominantly breastfed children from six countries, or the 2007 WHO reference curves (5-19 years) (9), which are based on national cross-sectional anthropometric data from the U.S. National Center for Health Statistics for 1977. Using these growth standards, for each time point we also computed the difference between the individuals' length/height (cm) and the age- and sex-specific value of the 50^{th} percentile of the reference population (referred to hereafter as the height difference).

Statistical Methods

We restricted the analysis to participants who had either a weight or a length measure at birth, a length measure at 12 months, and a height measure at 24 months, mid-childhood, and adulthood (n=5,696). We eliminated from the analysis individuals with implausible HAZ values, defined as $|HAZ| > 5$ at any one round (n= 257) or an absolute value of

change in HAZ between rounds > 4 (n=152). Following these restrictions, the final analytical sample was n = 5,287.

We computed means for the height difference and HAZ and the prevalence of stunting (HAZ < -2.0) at each time point, as well as changes in these measures between time points. We determined the incidence of stunting (the proportion of children who were not stunted at an earlier time point but were stunted at a later time point), as well as the incidence of recovery (the proportion of children who were stunted at an earlier time point but were not stunted at a later time point). We used Intercooled STATA 10.0 (StataCorp, College Station, Texas) statistical program for all data analyses.

Results

For the three cohorts with data, the prevalence of stunting at birth ranged from 5.8% (Philippines) to 9.4% (India) (**Figure 4.1**). The prevalence of stunting increased through 24 months (range of stunting prevalence at 24 mo: 13.2% (Brazil) to 81.2% (Guatemala)). The prevalence of stunting decreased from 24 mo to adulthood (range at adulthood: 3.2% (Brazil) to 41.1% (Philippines)). The majority of incident stunting had occurred by age 24 mo (**Figure 4.2**); recovery from stunting was highest after age 24 mo (**Figure 4.3**).

For the three cohorts with data, the mean HAZs at birth were all <0, and in all five cohorts, HAZ decreased through age 24 mo (**Table 4.1**). Mean HAZ at 24 mo ranged from -0.6 (Brazil) to -2.9 (Guatemala). Between 24 mo and mid-childhood, mean HAZ

increased in South Africa, Guatemala, and the Philippines, and was virtually unchanged in Brazil and India. Between mid-childhood and adulthood, mean HAZ increased (range: 0.2 (Philippines) to 0.8 (India)), but remained <0 (adult mean HAZ range: -0.3 (Brazil) to -1.8 (Guatemala and Philippines)).

As the cohorts aged, the difference between the mean height and the reference medians became greater (Table 4.1). At 24 mo the mean difference between the children's heights and the reference ranged from -1.5 cm (Brazil) to -8.9 (Guatemala). Between 24 mo and adulthood there was a further increase in this difference, so that in adulthood the difference ranged from -2.4 cm (Brazil) to -12.6 (Philippines). Thus, from 59% (Philippines) to 90% (South Africa) of the deficit in adult height was established by age 24 mo.

Discussion

Using prospectively-followed birth cohorts in five middle-income countries, we have documented that from age 2 y through adulthood, mean HAZ increased and the prevalence of stunting decreased, even though height deficits relative to the reference median became larger.

Growth is a widely-used measure to gauge the quality of a child's environment, as growth failure is related to a wide range of adverse outcomes in later life (10). HAZ scores are frequently used to compare children of the same age and sex in different locations and over time. An analysis of cross-sectional data from 54 countries, most of which were low-and middle-income settings, found that mean HAZ is <0 at birth and

decreases sharply until age 24 months, after which it increases slightly until 5 years of age (11). These and many other data support a focus on the first 1,000 days of life (conception to 24 months) for interventions aimed at improving growth. However, several studies, including an earlier paper using COHORTS data (5), demonstrate an increase in HAZ from its nadir at 24 mo. Prentice et al., (2013) (6) used those data to suggest that there may be periods beyond 24 months in which substantial catch-up growth occurs and interventions could improve growth. Lundeen et al., (2013), Crookston et al., (2013), Schott et al. (2013), and Fink and Rockers (2014) found similar results for Ethiopia, India, Peru and Vietnam (12-15).

The interpretation of within-child changes in mean HAZ over time, particularly in reference to catch-up growth, has been the subject of debate (3, 16). Leroy and Ruel argue that the interpretation of Prentice et al. is incorrect, and that the increase in mean HAZ after 24 months does not represent true catch-up growth in terms of height deficits, but instead is a result of the method for calculating z scores (3). Our data support Leroy and Ruel's argument. We show that increases in HAZ can coexist with further accumulation of deficits in height relative to the reference medians. The arithmetic explanation for this apparent paradox can be found in the calculation of HAZ as the difference between the child's measured length and that of the reference child of the same age and sex, divided by the standard deviation of the age- and sex-specific reference distribution. The standard deviation of the reference distribution varies by age, being (for males) 1.89 cm at birth, 2.38 at 12 mo, 3.06 at 24 mo, 4.19 at 48 mo and 7.30 in adulthood (8, 9). A similar pattern holds for females. Thus, for a constant absolute

difference in height from the reference, HAZ will attenuate as the standard deviation increases. This same calculation also explains at least part of the decreases in prevalence of stunting, which is defined as HAZ<-2.0. As HAZ increases, the prevalence of stunting will decrease even without any true recovery of the heights of the individuals being measured.

A limitation of these data is possible sample selection bias resulting from attrition within the cohorts. To be included in the analytical sample, participants had to have a weight or length measure at birth and length or height measures at all subsequent time periods. Among the five cohorts, Brazil and South Africa had relatively higher attrition of participants. However, an analysis of HAZ patterns in the cross sectional data showed that they were parallel to the patterns seen among those for whom we have complete longitudinal data, making selection bias unlikely.

Our findings argue for careful interpretation of the metrics used for defining catch-up growth in height in populations where growth failure is still the norm. Choosing HAZ or absolute height differences from the median as alternative metrics may result in opposite conclusions about the existence of catch-up growth from birth to adulthood. We suggest that height deficit should always be included in the evaluation, as the mathematical properties of HAZ over time will by nature result in a more optimistic assessment of catch-up growth.

Additionally, the two measures may differ in their value for evaluating associations between child growth and long-term health and development outcomes. For any given

age, HAZ is a linear transformation of the height deficit from the reference median, and thus they are perfectly correlated and equivalent in their predictive value at that time point. However, changes in HAZ and height deficits over time are not necessarily perfectly correlated, and therefore these two measures may differ in their ability to predict long-term outcomes. An important area for future research is determining which metric, changes in HAZ or changes in height deficit over time, is better at predicting different outcomes. We are aware of no such research.

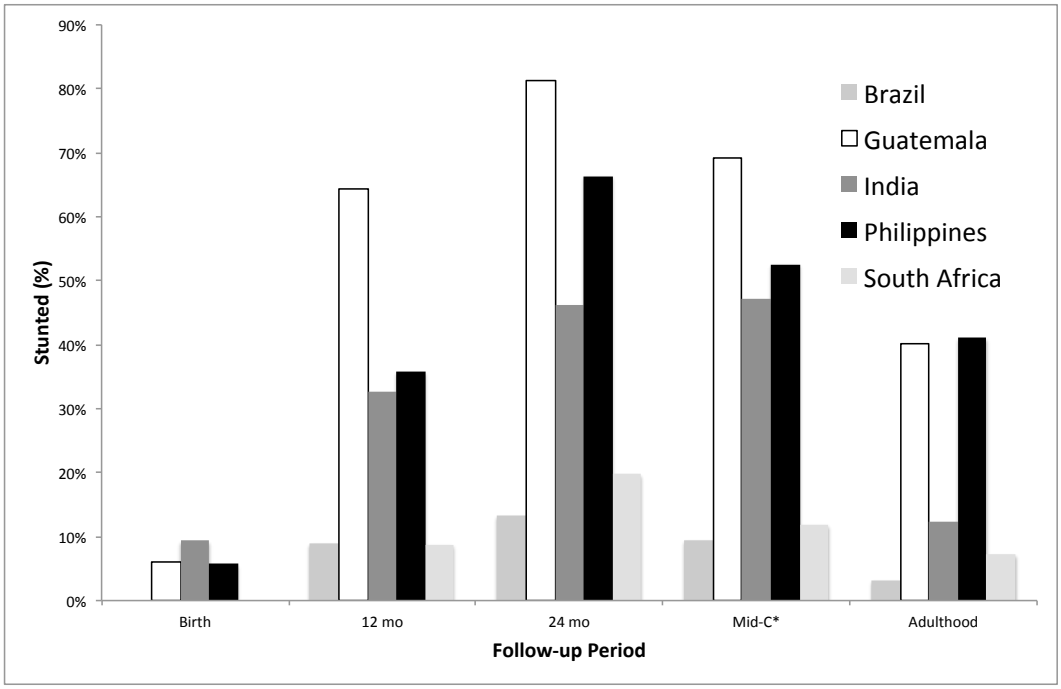
The majority of the deficit in adult height - from 59% in the Philippines to 90% in South Africa - is accrued by 24 months. Taken together with evidence on the importance of early growth for cognitive development in particular and adult human capital in general (17), we strongly endorse a continued focus on the 'first 1000 days' as a critical window for interventions to promote human capital over the life course.

Table 4.1: Measures of linear growth at selected ages in five cohorts from middle-income countries, COHORTS

	n	Height (cm) Mean (SD)	Height-for-age z scores Mean (SD)	Height deficit from reference[1] (cm) Mean (SD)
Brazil				
Birth	-	-	-	-
12 months	966	73.0 (3.3)	-0.4 (1.2)	-0.3 (2.9)
24 months	966	84.6 (3.8)	-0.6 (1.2)	-1.5 (3.7)
Mid-childhood	966	100.0 (4.7)	-0.6 (1.1)	-2.2 (4.5)
Adulthood	966	167.5 (8.6)	-0.3 (0.9)	-2.4 (6.1)
Guatemala				
Birth	197	49.3 (2.2)	-0.1 (1.1)	-0.2 (2.1)
12 months	266	69.1 (2.5)	-2.3 (0.9)	-5.6 (2.4)
24 months	266	78.1 (3.0)	-2.9 (0.9)	-8.9 (2.9)
Mid-childhood	266	93.4 (3.7)	-2.4 (0.9)	-9.6 (3.6)
Adulthood	266	157.6 (8.2)	-1.8 (0.8)	-12.3 (5.5)
India				
Birth	1,059	48.4 (2.1)	-0.6 (1.1)	-1.2 (2.0)
12 months	1,070	71.3 (2.8)	-1.5 (1.1)	-3.7 (2.7)
24 months	1,070	80.6 (3.5)	-1.9 (1.1)	-6.6 (3.4)
Mid-childhood	1,070	94.9 (4.1)	-1.9 (1.0)	-8.1 (4.1)
Adulthood	1,070	163.5 (9.2)	-1.1 (0.9)	-7.4 (5.9)
Philippines				
Birth	1,806	49.1 (2.0)	-0.2 (1.0)	-0.4 (2.0)
12 months	1,806	71.0 (2.7)	-1.6 (1.1)	-3.6 (2.6)
24 months	1,806	79.5 (3.3)	-2.5 (1.0)	-7.4 (3.2)
Mid-childhood[2]	1,806	117.9 (5.3)	-2.0 (0.9)	-11.7 (5.3)
Adulthood	1,806	157.7 (8.2)	-1.8 (0.8)	-12.6 (5.6)
South Africa				
Birth	-	-	-	-
12 months	1,179	73.4 (2.9)	-0.6 (1.1)	-1.1 (2.8)
24 months	1,179	83.2 (3.2)	-1.2 (1.0)	-3.8 (3.1)
Mid-childhood	1,179	99.0 (4.0)	-0.9 (0.9)	-3.6 (3.9)
Adulthood	1,179	165.0 (8.7)	-0.6 (0.9)	-4.2 (6.5)

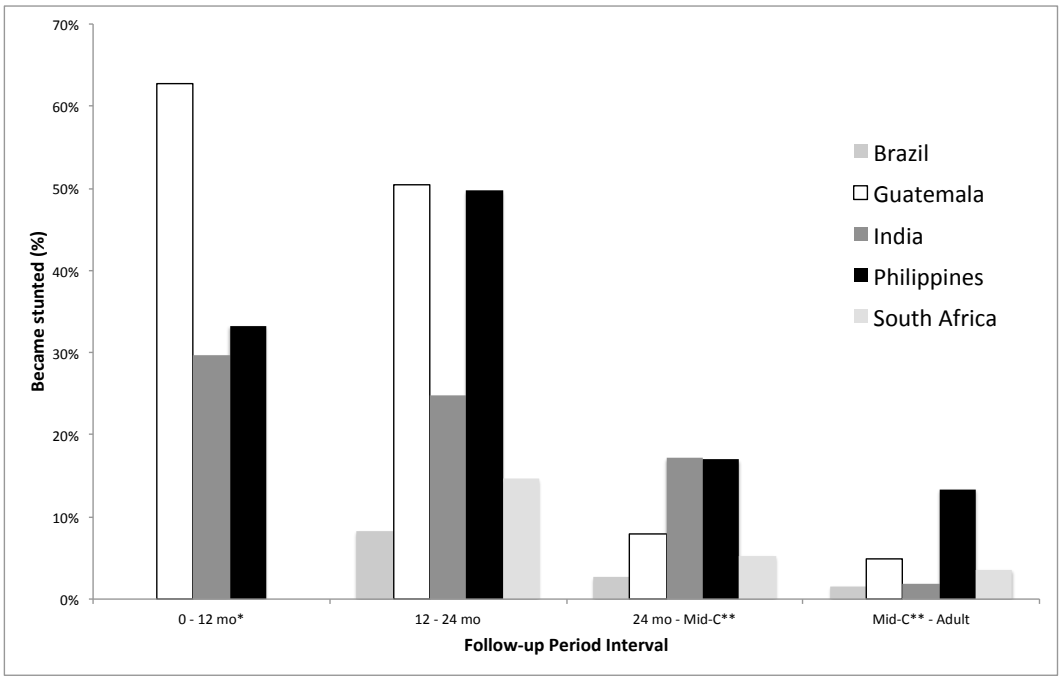
1 Reference is the 50th percentile (median) for the age- and sex-specific height (cm) based on the WHO growth standards; each individual's height difference from the reference was calculated and then the mean difference was determined for each country and time point.
2 Mid-childhood is defined as 48 mo. for all countries except Philippines, where it is defined as 102 mo.

Figure 4.1: Prevalence of stunting† among children in five birth cohorts in middle-income countries, COHORTS



Legend for Figure 4.1
† Stunting is defined as HAZ<-2.0
* Mid-childhood

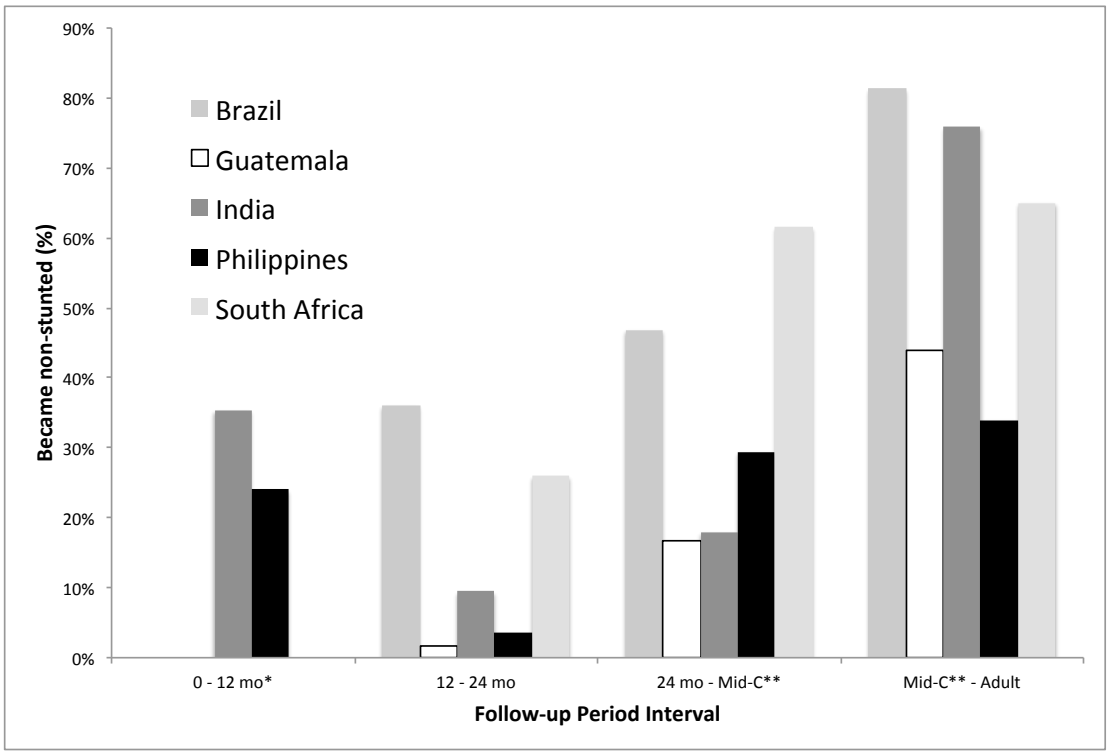
Figure 4.2: Incidence of stunting† among children in five birth cohorts in middle-income countries, COHORTS



Legend for Figure 4.2

† Incidence of stunting is the proportion of children who were not stunted at an earlier survey round but were stunted at a later survey round (stunting is defined as HAZ<-2.0)
* Height data at birth not available for Brazil and South Africa
** Mid-childhood

Figure 4.3: Incidence of recovery† among children in five birth cohorts in middle-income countries, COHORTS



Legend for Figure 4.3

† Incidence of recovery is the proportion of children who were stunted at an earlier survey round but were not stunted at a later survey round (stunting is defined as HAZ<-2.0)

* Height data at birth not available for Brazil and South Africa; incidence of recovery was 0.0% in Guatemala

** Mid-childhood

Chapter 4 References

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Chapter 5: Adolescent pregnancy and attained height among Black South African girls: matched-pair prospective study

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Abbreviations used: height-for-age z score (HAZ)

Abstract

Study objective: The impact of adolescent pregnancy on offspring birth outcomes has been widely studied, but less is known about its impact on the growth of the young mother. We aimed to help clarify conflicting evidence on the association between adolescent pregnancy and maternal attained height, by controlling for factors that increase risk of adolescent pregnancy and impact adult height.

Design: Birth-to-Twenty Plus, a prospective birth cohort.

Setting: Cohort members followed from birth to age 20y in Soweto, South Africa.

Participants: From 840 Black females with sufficient data, we identified 54 matched pairs, in which a girl who became pregnant before the age of 17y was matched with a girl who did not have a pregnancy by age 20y. Pairs were matched on age at menarche and height-for-age z scores in the year before the case became pregnant.

Main Outcome Measures: The adolescent pregnancy group was compared to matched controls and to other females in the cohort with respect to attained height, measured at mean age 18.5y.

Results: Mean age at conception was 15.9y (range: 13.7 to 16.9y). Mean height at matching was 159.4 cm in the adolescent pregnancy group and 159.3 cm in the comparison group (p=0.3). Mean attained height was 160.4 cm in the adolescent

pregnancy group, versus 160.3 cm in the comparison group (p=0.7), and 159.5 cm among all other females (p=0.3).

Conclusions: After controlling for age at menarche and pre-pregnancy height, adolescent pregnancy among Black females in Soweto, South Africa was not associated with attained height.

Introduction

About 16 million women 15–19 years old give birth each year, with ninety-five percent of these births occurring in low- and middle-income countries (1, 2). The proportion of births that occur to women 15-19 y is 18% in Latin America and the Caribbean and more than 50% in sub-Saharan Africa (1). In South Africa, 27% of girls have had at least one birth by age 19 (3). The impact of adolescent pregnancy on offspring birth outcomes has been widely studied. Adolescent pregnancy is associated with maternal and neonatal mortality (4-7), preterm delivery (4-6, 8-12), low birth weight (4-6, 8-11, 13, 14), and infants being born small for gestational age (6, 9, 10).

Less is known about the impact of early pregnancy on the growth of the young mother herself. If pregnancy occurs while a young woman is still growing, it could lead to competition between mother and fetus for nutrients, potentially reducing attained height in comparison to that which would have been achieved in the absence of pregnancy (15, 16). Longitudinal studies have demonstrated that there is potential for an appreciable degree of linear growth among girls following menarche (17-20). In the Fels Longitudinal Study, the median increase in stature following menarche was 7.4 cm, and the median age of attainment of adult stature among girls was 17.3 years (17-19). Frisch found that from menarche to 18 years, girls grew an average of 7.1 cm (20). In the Camden Adolescent Pregnancy and Nutrition Project, over 55% of adolescents continued to increase in height (21).

Evidence for an adverse impact of adolescent pregnancy on attained adult height is limited, and the findings are conflicting. Studies in Brazil, India, and the U.S. found a significant deficit in attained height (from 0.3 to 3.0 cm) (22-24) relative to women who did not experience adolescent pregnancy, while another study of a U.S. population found no difference in attained height (25). While several of these studies controlled for age at menarche, they did not control for height immediately preceding the adolescent pregnancy. Given the methodological limitations and conflicting findings of existing studies, we aim to contribute evidence by using more rigorous methods to control for factors that predict both a girl's risk of becoming pregnant and her attained height. The present analysis examines the association between adolescent pregnancy and attained height among Black females living in Soweto, South Africa.

Methods

We analyzed data from the Birth to Twenty Plus study, a birth cohort that began in 1990 in Soweto, the urban township adjacent to Johannesburg in South Africa. Detailed information on this cohort has been published elsewhere (26). The cohort enrolled 3,273 pregnant women at gestational age 26–40 weeks, who were expected to deliver during a 6-week period in early 1990. Participants were predominantly Black women with low socioeconomic status. The study was designed to track prospectively the growth, health, well-being and educational progress of their children. Weight at birth and weight and length (or height after age 2 y) were measured using standard procedures (27). Throughout the study, participants or their caregivers provided written informed consent,

and ethical approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects (approval ID #M010556).

The children's serial height data were used for this analysis. Data were restricted to Black females (n=1,329), as this group comprised eighty percent of the cohort and was at the highest risk for adolescent pregnancy and its consequences. For each round, supine length (<24 mo) and standing height (≥24 mo) measurements were converted to height-for-age z scores (HAZ) using the WHO references (28-30). We removed from the analysis heights/HAZ scores where the HAZ was implausible, defined as |HAZ| > 5 at any one round or an absolute value of change in HAZ between rounds > 4. To be eligible for matching and analysis, a girl had to have birth weight (birth length was not measured), an attained height (considered to be age 17 y or later) and at least one intermediate height. Attained height (cm) was defined based on the oldest age at which a height measurement was available (20 y, 18 y, or 17 y). There remained 840 females in the analytic sample.

Fifty-nine girls (7%) conceived prior to age 17 y. Of those, five girls experienced miscarriage or voluntary abortion of the pregnancy, the precise dates of which were not available. We matched each girl who conceived before age 17 y and went on to give birth (early pregnancy group, n=54) to one girl who did not become pregnant up to age 20y (comparison group), based on age at self-reported menarche (in integer years) and on HAZ from the year before the early pregnancy occurred (all pairs were within 0.14 SD). The onset of menarche, in addition to being a prerequisite for pregnancy, is an indicator of pubertal development, the timing of which impacts adult height in girls (31, 32).

Matching on age was not necessary, as the girls were all born within fourteen weeks of each other. The final analytical sample included 54 matched pairs. The remaining 732 females were considered as an internal reference group.

Statistical Methods

Descriptive statistics were used to present the distribution of key demographic, socioeconomic, and anthropometric characteristics. The socioeconomic variable 'assets' is a measure of the wealth of the child's caretakers, reported in quintiles (1-poorest; 5-wealthiest), and based on home type, home ownership, electricity in the home, and ownership of a car, refrigerator, washing machine, or phone. The income variable is a measure of the monthly income (in Rands) of those supporting the child. Both variables represent the child's socioeconomic status at birth.

We compared characteristics between the early pregnancy and comparison groups using paired t-tests, the Wilcoxon signed rank test, McNemar's chi-square test for paired proportions, and the Sign test. We also compared characteristics between the early pregnancy group and all other girls in the cohort (excluding the comparison group; n=732) using the two-sample t-test, the Wilcoxon rank sum test, and Fisher's exact test. Mean height and HAZ at each measurement from three months to 18 years were plotted. To determine whether there was a statistically significant difference in adult height between the early-pregnancy and comparison groups, and the early pregnancy group and all other females in the cohort, we used the paired t-test and 2-sample t-test, respectively. We calculated the within- pair difference in adult height, and used this difference as the outcome in a linear regression model, which controlled for the within-pair differences in

maternal height and pre-pregnancy HAZ, and an indicator variable representing a subsequent second pregnancy for the early pregnancy girl before the adult height measurement was taken. As maternal height was only available for both members of 26 matched pairs, we ran the regression models with and without this variable. The Intercooled STATA 10.0 (StataCorp, College Station, Texas) statistical program was used for all data analyses.

Results

Girls were matched on average at 15.0 y, and the mean age at conception for the early pregnancy group was 15.9 years (range: 13.7 to 16.9 y). There were no statistically significant differences between the early pregnancy and comparison groups for several demographic and socioeconomic factors (**Table 5.1**). There were, however, significant differences between the early pregnancy group and all other females in the cohort with respect to her mother's education ($p<0.01$), her own age at menarche ($p<0.01$), and her height at 11y ($p=0.04$) and 12y ($p<0.01$). The mean adult height, on average at 18.5 y, was 160.4 cm for the early pregnancy group, versus 160.3 cm for the comparison group ($p=0.7$), and 159.5 cm for all other females ($p=0.3$). The median change in height from matching to adulthood was 0.6 cm for the early pregnancy group and 0.8 cm for the comparison group ($p=0.9$). For both the early pregnancy and comparison groups, adult height was reached around 15 years of age, and the growth trajectories for both groups were nearly identical (**Figure 5.1**). Compared to all other girls in the cohort, the early-pregnancy and comparison groups had a higher HAZ; this difference was especially pronounced in the pre- and peri-pubescent years (**Figure 5.2**).

In the linear regression model, none of the predictor variables (within-pair differences in maternal height (p=0.5) or pre-pregnancy matched HAZ scores (p=0.4), or whether the girl in early-pregnancy group experienced a second pregnancy (p=0.7)) were significantly related to within-pair difference in attained height (**Table 5.2**). In the larger sample available when within-pair difference in maternal height was removed from the model, these inferences were unchanged.

Discussion

The adverse effects of adolescent pregnancy on birth outcomes, such as maternal and neonatal mortality (4-7), preterm delivery (4-6, 8-12), low birth weight (4-6, 8-11, 13, 14), and small for gestational age (6, 9, 10), have been well established. Teenage pregnancy has been associated with higher rates of school drop-out for young mothers and higher risk for living below the poverty line (33, 34). However, far less is known about the impact of teenage pregnancy on the growth of the young mother. We used data from the prospective Birth to Twenty Plus cohort study in Soweto, South Africa to examine the association between pregnancy before age 17 and the attained height of the young mother. We found no difference in final adult height between girls who experienced an early pregnancy and those who did not after controlling for key potential confounders.

Several studies have examined growth during and immediately following adolescent pregnancy to determine its short-term effect on the growth of the young mother. In the

Camden Adolescent Pregnancy and Nutrition Project (New Jersey, USA), 56.5% of pregnant adolescents (average age 15.6 y) made gains in height during pregnancy, as determined by knee height measurements (21). However, other studies found that adolescent pregnancy halted short-term growth. In Mexico, Casanueva et al. matched non-pregnant adolescents with girls who had a pregnancy at ≤ 17 years (average 15.3 y), based on socioeconomic status, chronological age, menarche age, and body mass index. They found that pregnant adolescents did not make gains in height during the 5-month follow-up period, whereas the non-pregnant controls grew 0.94 cm on average (35). They concluded that pregnant adolescents appear to adjust their resting energy needs by ceasing growth (35). Similarly, in Bangladesh, when adolescent primigravidae girls (average age 16.3 y) were matched with non-pregnant controls based on age and time since menarche, it was found that from the first trimester to six months postpartum, pregnant girls did not gain in stature, compared with the non-pregnant girls who grew 0.35 cm on average (36).

In contrast to these studies of the short-term associations of adolescent pregnancy with the growth of the young mother, the duration of our study (on average 3.5 years between the pre-conception and adult height measurements) allowed us to determine longer-run associations with attained height. Research exploring these longer-term impacts is sparse, especially in low- and middle-income countries, and the results have been inconsistent. In Pelotas, Brazil, girls who experienced more than one pregnancy between 15-18 y of age had a 1.6 cm deficit in stature relative to those who did not become pregnant ($p<0.01$) after adjusting for age at menarche, but there was not a significant difference in height

among girls who had only one adolescent pregnancy (22). In the 1998–1999 India National Family Health Survey women had their first child at 16.8 y, and statistically significant deficits in adult height were found among women who had one (-0.26 cm), two (-0.53 cm) and three (-0.98 cm) births before age 18 y (24). In a retrospective cohort study using U.S. National Health and Nutrition Examination Survey data from 1999 to 2004, non-Hispanic white women who had their first live birth before age 18 years were 2.97 cm shorter at adulthood (20-30 y) than women who gave birth to their first child at ≥ 18 y ($p=0.03$) (after adjusting for age at menarche), with no differences in final adult height among Mexican-American and non-Hispanic black women (23). In the U.S. National Heart, Lung and Blood Growth and Health Study, Gunderson et al. adjusted for age at menarche and height at 9-10 years of age, and found no difference in adult height between those who did and did not experience an adolescent pregnancy (25).

There are several possible reasons why our study found no effect of adolescent pregnancy on adult height. Two important factors could be the timing of conception in relation to reaching adult height, as well as nutritional status before and at the time of pregnancy. Chronic undernutrition has been found to cause a delay in growth and development, which shifts the growth period from primarily occurring during early adolescence to continuing through late adolescence (37). When chronic undernutrition is combined with adolescent pregnancy, it often results in a young woman's growth period overlapping with her pregnancy, thus creating competition between mother and fetus for nutrients to fuel growth (15). South Africa is a middle-income country where undernutrition is not as widespread as in other countries in the region. On average, in our matched pairs, as well

as those in the Birth to Twenty cohort who were not included in our study, adult height was reached around 15 years of age. We had previously found that the median age at skeletal maturity for black girls was 15.0 years (unpublished observations). Therefore, presumably due to adequate nutrition, these girls had reached adult height by the time of conception. The few girls who were still growing at the time of pregnancy may have entered pregnancy sufficiently nourished to fuel both their growth and the growth of the fetus. From a public health perspective, there may be value in focusing attention on delaying pregnancy until adult height is reached, and these efforts may be particularly important in countries where nutritional status is poor, and thus skeletal maturation may be delayed.

A limitation of our study was the relative infrequency of adolescent pregnancy in this population, resulting in a small number of matched pairs for analysis. However, the strengths of the study design enabled us to make a significant methodological contribution to the literature on adolescent pregnancy and adult height. The use of data from a prospective birth cohort allowed us to match on factors collected prior to conception, and to carefully control for proximate predictors of adolescent pregnancy risk. Several of the previous studies controlled for age at menarche, however, to our knowledge, this is the only study to control for height immediately preceding the adolescent pregnancy. We found that girls who had an early pregnancy experienced menarche onset at an earlier age and were taller at 11y and 12y of age, meaning they matured more quickly, than the other females in this cohort. These factors increase risk of adolescent pregnancy and impact adult height, however, by controlling for them through

our matched-pair design, we found no association between adolescent pregnancy and adult height.

Conclusion

After controlling for age at menarche and pre-pregnancy height, adolescent pregnancy among Black females in Soweto, South Africa was not associated with attained height.

Table 5.1: Selected Demographic, Socioeconomic, and Anthropometric Characteristics of the Early Pregnancy Group, the Comparison Group and All other Females in the Birth-to-Twenty Plus Cohort

Characteristics	Early Pregnancy[a] (n=54)	Comparison (n=54)	All other females in the cohort (n=732)
Demographic and socioeconomic factors			
Maternal height, cm[b]	158.7 ± 6.1	159.5 ± 6.4	158.5 ± 6.0
Maternal schooling, y[c]	8.3 ± 3.2	9.7 ± 2.4	9.7 ± 2.7**
Maternal parity[c]	2.4 ± 1.7	2.3 ± 1.3	2.1 ± 1.3
Caretaker monthly income, rands[d]	9900 ± 9200	11300 ± 8700	9400 ± 7800
Assets / wealth quintiles, %[e]			
1 (lowest)	18.8	18.8	15.8
2	18.8	18.8	18.1
3	33.3	22.9	36.0
4	20.8	20.8	19.2
5 (highest)	8.3	18.8	10.9
Age at menarche, y[f]	12.2 ± 1.0	12.2 ± 1.0	12.8 ± 1.2**
Age at conception, y	15.9 ± 0.8	-	-
Height at ages prior to matching, cm			
11y[g]	149.0 ± 5.4	148.8 ± 6.3	145.9 ± 7.5**
12y[h]	155.0 ± 5.6	154.1 ± 6.1	151.3 ± 6.8**
Height at matching, cm[i]	159.4 ± 5.5	159.3 ± 5.5	-
HAZ at matching[i]	-0.3 ± 0.8	-0.3 ± 0.8	-
Stunted at matching, %[j]	3.7	3.7	-
Adult height, cm[k]	160.4 ± 5.5	160.3 ± 5.8	159.5 ± 6.1
Height change, cm[l, m]	0.6 (0.1, 1.7)	0.8 (0.03, 1.9)	-

Mean ± SD unless otherwise specified; tests of statistical significance performed on early pregnancy vs. comparison groups, as well as the early pregnancy group vs. all other girls in the cohort.

a. Early pregnancy defined as conception prior to age 17. b. Paired t-test (early pregnancy vs. comparison); Wilcoxon rank sum test (early pregnancy vs. all others). c. Friedman test (for paired ordinal variables) (early pregnancy vs. comparison); Wilcoxon rank sum test (early pregnancy vs. all others). d. Signed-rank test (early pregnancy vs. comparison); Wilcoxon rank sum test (early pregnancy vs. all others). e. Friedman test (for paired ordinal variables) (early pregnancy vs. comparison); Fisher's exact test (chi-square) (early pregnancy vs. all others). f. Signed-rank test (early pregnancy vs. comparison); 2-sample t-test (early pregnancy vs. all others). g. Paired t-test (early pregnancy vs. comparison) (data available for 24 cases and 36 controls; sig. test performed on 16 matched pairs); 2-sample t-test (early pregnancy vs. all others). h. Paired t-test (early pregnancy vs. comparison) (data available for 40 cases and 47 controls; sig. test performed on 35 matched pairs); 2-sample t-test (early pregnancy vs. all others). i. Paired t-test (early pregnancy vs. comparison).

j. McNemar's chi-square test for paired proportions (early pregnancy vs. comparison). k. Paired t-test (early pregnancy vs. comparison); 2-sample t-test (early pregnancy vs. all others). l. Median (interquartile range). m. Sign test (median presented due to non-normality) (early pregnancy vs. comparison)

* Significant difference between early pregnancy and comparison group (at the $\alpha = 0.05$ level)

** Significant difference between early pregnancy group and all other girls in the cohort (at the $\alpha = 0.05$ level)

Table 5.2: Multiple regression analysis of within-pair differences in attained height among 54 women who conceived prior to age 17 y and matched pairs, Birth to Twenty Plus Cohort

	β	SE	95% CI	p-value
Model 1[a]				
Intercept	0.1	0.4	(-0.6, 0.9)	0.69
Maternal height difference	0.0	0.1	(-0.1, 0.2)	0.45
Matching HAZ difference	-12.9	13.9	(-41.8, 15.9)	0.36
Second pregnancy – case	-0.5	1.3	(-3.1, 2.2)	0.73
Model 2[b]				
Intercept	0.0	0.3	(-0.6, 0.5)	0.92
Matching HAZ difference	14.7	8.6	(-2.6, 32.0)	0.09
Second pregnancy – case	0.6	0.9	(-1.2, 2.3)	0.52

a Within-pair difference in maternal height, difference in matching HAZ, and a subsequent second pregnancy in the case before the adult height measurement was taken; n=26 pairs because only 26 pairs had maternal height information

b Difference in matching HAZ and a subsequent second pregnancy in the case before the adult height measurement was taken; n=54 pairs

Figure 5.1: Mean height (cm) by age, girls in the Birth-to-Twenty Plus Study

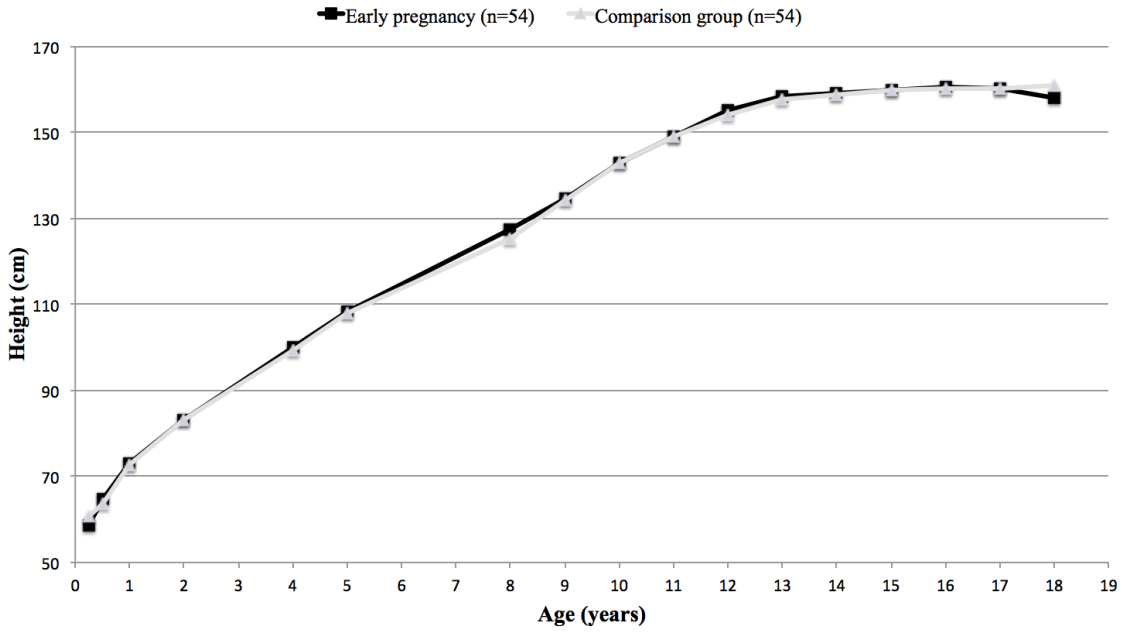
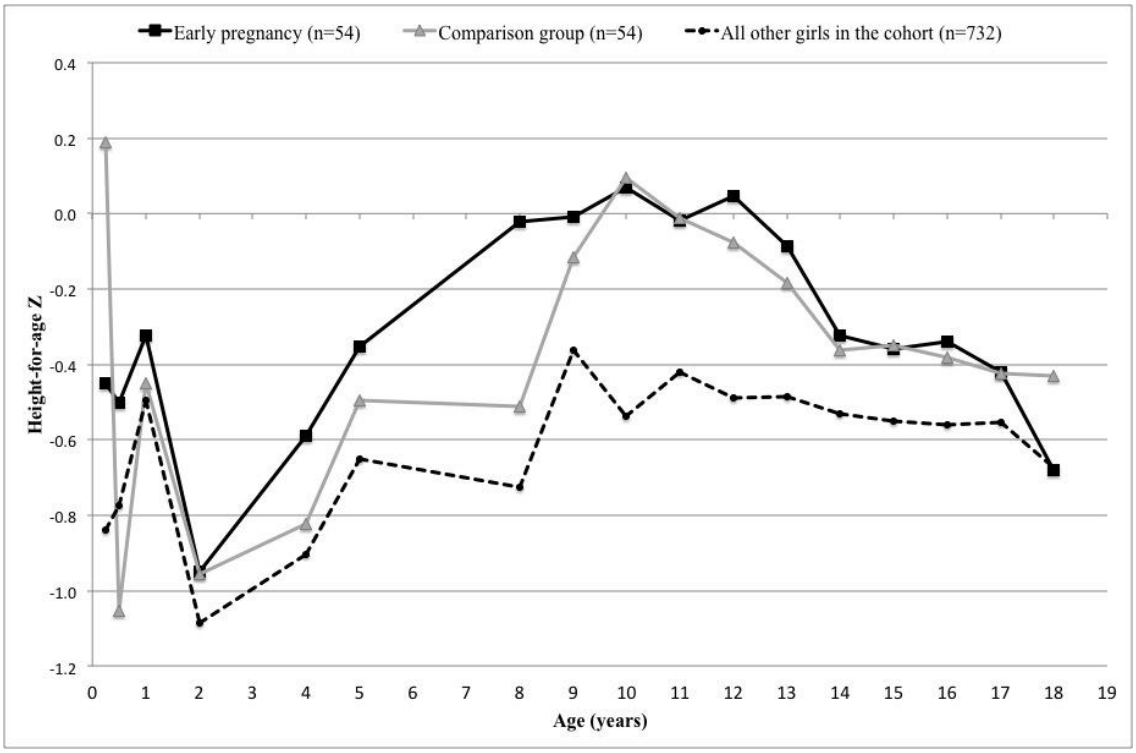


Figure 5.2: Mean Height-for-age Z score by age, girls in the Birth-to-Twenty Plus study



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Chapter 6: Sex differences in obesity incidence: 20-year prospective cohort in South Africa

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Abbreviations used: Body mass index (BMI); body mass index z score (BMIZ); low- and middle-income countries (LMICs); Centers for Disease Control and Prevention (CDC); International Obesity Task Force (IOTF); World Health Organization (WHO)

What is already known about this subject
• Childhood overweight and obesity is a growing problem in both high-income and low- and middle-income countries. • Overweight and obesity track from childhood to adulthood, and greatly increase risk of chronic disease later in life. • Low- and middle-income countries, particularly in sub-Saharan Africa, lack incidence data to better understand childhood obesity trends and identify key periods for intervention.
What this study adds
• In this South African cohort, overweight and obesity increased throughout childhood among girls, and by late adolescence, levels were close to those in high-income countries; overweight and obesity were not prevalent among boys. • Particularly among girls, there was evidence of early tracking, as overweight and obesity in early childhood greatly increased the risk of obesity in late adolescence. These findings highlight the importance of early childhood intervention. • Among girls, the post-pubertal years are also an opportune time for intervention.

Abstract

Background: Prospective data spanning childhood and adolescence are needed to better understand obesity incidence among children, and to identify important periods for intervention.

Objective: Describe gender differences in overweight and obesity from infancy to late adolescence in a South African cohort.

Methods: We analyzed body mass index at 1-2y, 4-8y, 11-12y, 13-15y and 16-18y among 1172 participants in the South African Birth-to-Twenty cohort.

Results: Among boys, overweight and obesity prevalence declined from age 1-2y to 16-18y. Among girls, overweight and obesity prevalence increased from 4-8y to 16-18y. Obesity incidence was highest from 4-8y to 11-12y in boys (6.8 cases/1,000 person-years) and from 11-12y to 13-15y in girls (11.2 cases/1,000 person-years). Among girls, obesity at 16-18y was associated with overweight (OR=3.6; 95% confidence interval (CI) 1.8-7.2) or obesity (OR=8.0; 95% CI 3.7-17.6) at 1-2y, and overweight (OR=6.8; 95% CI 3.3-13.9) or obesity (OR=42.3; 95% CI 15.0-118.8) at 4-8y; for boys, obesity at 16-18y was associated with overweight at 1-2y (OR=5.6; 95% CI 1.7-18.0) and obesity at 4-8y (OR=19.7; 95% CI 5.1-75.9).

Conclusions: Among girls, overweight and obesity increased throughout childhood. Overweight and obesity were not widely prevalent among boys. Early childhood and post-puberty may be important periods for intervention among girls.

Introduction

The increasing prevalence of overweight and obesity is a growing concern in most regions of the world. Recent estimates have shown that the combined prevalence of overweight and obesity among adults globally has risen by 28% in the last three decades, with 37% of men and 38% of women having a body mass index (BMI) of 25 kg/m^2 or greater (1). Obese adults have a greatly increased risk of chronic diseases such as diabetes and cardiovascular disease (2). This disease pathway may have its origins early in life, as childhood overweight and obesity have been shown to track into adulthood (3-5). Therefore, the increasing prevalence of overweight and obesity among children is a major public health concern (6).

From 2008 to 2013, the global prevalence of overweight and obesity among children 2-19 years increased by 47% (1). By 2013, the combined prevalence of overweight and obesity was 24% among boys and 23% among girls in high-income countries, and 13% among both boys and girls in low- and middle-income countries (1). For many countries in Africa, childhood malnutrition is characterized primarily by undernutrition, and this region has a lower prevalence of overweight and obesity than other regions of the world. However, over the past 20 years, South Africa has undergone dramatic and rapid social and economic transitions. Recent figures show that in sub-Saharan Africa, South Africa has one of the highest prevalence rates of childhood (<20 years) overweight and obesity — 19% of boys and 26% of girls — rivaling that of many high-income countries (1).

Understanding childhood obesity trends and important periods for intervention requires data not only on the prevalence, but also the incidence of obesity during key stages of childhood and adolescence. Few high-income countries have population-based data on the incidence of obesity throughout childhood, and these data are essentially absent in low- and middle-income country settings, where prevalence estimates are typically derived from cross-sectional surveys and focus on children under five years. Longitudinal data spanning childhood and adolescence are needed. Such data are particularly sparse in sub-Saharan Africa (7). We address this research gap by investigating the incidence of overweight and obesity among children in a birth cohort in Soweto, South Africa.

Methods

We analyzed data from the Birth-to-Twenty study, a birth cohort initiated in 1990 in Soweto, an urban township in South Africa. Detailed information on this cohort has been published elsewhere (8). The cohort enrolled 3273 pregnant women at gestational age 26–40 weeks, who were expected to deliver during a six-week period in early 1990. Participants were predominantly Black women with a low socioeconomic status. The study was designed to track the growth, health, well-being and educational progress of their children, who have been studied prospectively. Weight at birth and weight and length/height at subsequent rounds were measured using standard procedures (9). Throughout the study, participants or their caregivers provided written informed consent and ethical approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects (approval ID #M010556).

Using weight, length, and height measurements at each survey round, body mass index (BMI) values were calculated as weight (kg) divided by height squared (m^2), and these values were then converted to z scores (BMIZ) using the World Health Organization (WHO) references (10-12). As not all children had BMI values for every year of measurement, to maximize data availability we grouped survey rounds as follows: infant/toddler (1y and 2y); early childhood (4y, 5y, and 8y); early adolescence (11y and 12y); mid-adolescence (13y, 14y, 15y); and late adolescence (16y, 17y, and 18y). When more than one BMIZ value was available within a period, one was selected at random. We included in the analysis all participants who had a BMIZ for all five time periods, (n=1172). The large majority (88%) of participants were Black, with other represented groups including white (2%), Indian (1%) and coloured or mixed-ancestral (9%) children.

We defined overweight and obesity for all five time periods using the WHO cut-off points for children 5-19 years: overweight was defined as a BMIZ > 1.0 and ≤ 2.0 SD from the reference median; obese was a BMIZ > 2.0 SD from the reference median (12). To enable comparisons with other studies, we also used definitions from the U.S. Centers for Disease Control and Prevention (13) and the International Obesity Task Force (14). We computed the prevalence of overweight and obesity at each time period. Incidence of obesity was calculated as the percentage of children who were not obese in the earlier time period who became obese by the subsequent time period. To account for the different durations of the intervals between periods, for each interval, we also computed the incidence density rate as the number of incident cases per 1000 person-years, where

person-years was computed by summing the number of years of follow-up contributed by each child at risk of becoming obese during that period.

We computed a measure of the persistence of obesity by calculating the proportion of children who became obese at any point during the 1-2y to 13-15y periods, who remained obese in the 16-18y period. We used logistic regression to model the risk of being obese at 16-18y, based on status at the 1-2y or 4-8y periods, with the referent category being those who were classified as normal BMI (not overweight or obese) at that time period. We also calculated the proportion of children who were obese in the earlier time period who became non-obese by the subsequent time period.

A sensitivity analysis was performed using two methods to determine whether there was a systematic difference between the cohort of children who had data at all five time periods and those who did not. We calculated overweight and obesity prevalence figures using all available cross sectional data at each of the time points, and compared them to prevalence figures for children who had complete longitudinal data. Additionally, we compared overweight and obesity prevalence figures for children with complete longitudinal data versus those who were not included in the analysis. We used STATA 10.0 (StataCorp, College Station, Texas) statistical program for all data analyses.

Results

For both boys and girls, mean BMI was around 16.8 kg/m^2 at 1-2y, decreased slightly by 4-8y and then increased steadily through 16-18y (**Table 6.1**). At 16-18y, mean BMI was

22.8 kg/m^2 in girls and 20.3 kg/m^2 in boys. Using the WHO reference, mean BMIZ at 1-2y was 0.3 and 0.4 in boys and girls, respectively, and decreased to -0.2 in boys and -0.03 in girls at 11-12y. Thereafter, mean BMIZ continued to decline in boys, dropping to -0.6 at 16-18y, but rose among girls, reaching 0.3 at 16-18y.

Among boys, the prevalence of overweight was highest through 4-8y and declined thereafter, while obesity was highest at ages 1-2y and 11-12y, but decreased to < 3% by 16-18y. Among girls, the prevalence of overweight increased steadily after 4-8y, reaching 19% by 16-18y. The prevalence of obesity in girls also continued to rise after 4-8y, reaching 8% by 16-18y. While the absolute numbers differ, similar patterns were seen when the IOTF and CDC definitions of overweight and obesity were used.

For both boys and girls, the period incidence of obesity was highest from 4-8y to 11-12y (**Table 6.2**). This pattern held true for boys when the incidence density rate was compared. However, among girls, the incidence density rate was highest in the periods from 11-12y to 13-15y and from 13-15y to 16-18y. In some periods, for example from 1-2y to 4-8y, incident obesity is observed, however there was an overall decreasing prevalence of obesity due to the majority of transition in that period being reversion from obese to non-obese (Table 6.2).

Girls who were overweight at 1-2y had 3.6 times increased odds of being obese from 16-18y ($p<0.001$), while those who were obese had 8.0 times greater odds ($p<0.001$) **(Table 6.3)**. Girls who were overweight at 4-8y had 6.8 times increased odds of being obese

from 16-18y ($p<0.001$), while those who were obese had 42.3 times greater odds ($p<0.001$). Among females who became obese from the 1-2y to 13-15y periods (n=97), obesity was persistent, or present during 16-18y, in 36.1% (data not shown).

Boys who were overweight at 1-2y had 5.6 times increased odds of being obese from 16-18y ($p<0.01$), while the increased odds conferred by obesity in this period were not significant (OR=3.4; p=0.15) (Table 3). Boys who were obese at 4-8y had 19.7 times increased odds of being obese from 16-18y ($p<0.001$), while overweight in this period did not result in significantly increased odds (OR=2.1; p=0.28). Among males who became obese from the 1-2y to 13-15y periods (n=83), obesity was persistent, or present during 16-18y, in 16.9% (data not shown).

Discussion

A key finding of our study is that in this cohort of South African children residing in a relatively poor but highly transitioned urban setting, boys and girls have very different patterns of incidence of overweight and obesity. A major strength of our analysis is that it was based on longitudinal data that spanned childhood. This is particularly important in low- and middle-income countries, especially African countries, where such data are sparse.

The prevalence of overweight and obesity among boys does not represent a significant public health concern. In boys, the combined prevalence of overweight and obesity (BMIZ > 1.0) steadily declined, and by late adolescence it was less than the 16% that

would be expected to be >1 SD from the reference (based on the percentage of observations in the tails of a normal distribution). However, among girls, the prevalence of combined overweight and obesity continued to rise, reaching 11 percentage points greater than the 16% expected for a normal distribution by late adolescence.

We found that among girls, the highest obesity incidence density rates occurred from the 11-12y to 13-15y and 13-15y to 16-18y periods. These periods typically follow the onset of puberty in girls, which is a time of rapid growth and development. However, among girls, there was evidence of development of obesity early in life and obesity tracking into adulthood. There was an appreciable degree of persistence of obesity following its onset, and both overweight and obese girls in the 1-2y and 4-8y periods had greatly increased odds of being obese by 16-18y.

The prevalence of obesity among both boys and girls in this South African cohort is lower than their counterparts in high-income countries. In a contemporary cohort of U.S. children, Cunningham et al found a much higher prevalence of obesity: around 12-13% at age 5-7 years; 22% at age 11 years; and 21% at age 14 years (15). That study did not extend to late adolescence. Obesity prevalence in our sample is lower than that of 12-19 year old African American boys (21%) and girls (23%) (16).

Our estimates for overweight and obesity by 16-18y were similar to those found in the 2012 South Africa National Health and Nutrition Examination Survey (SANHANES): 8.0% obese and 19.3% overweight among females 15-17y; 1.5% obese and 7.3%

overweight among males 15-17y (17), and the prevalence of overweight and obesity among South African high-school age adolescents is rising (18). While the overweight and obesity prevalence figures for South African children, particularly boys, are still lower than those of higher-income countries, the latest adult obesity prevalence figures for South Africa are comparable to those seen in higher-income countries, and are the highest among all countries in Africa (1). Among South African men > 20 years of age, 39% are overweight or obese, as are 69% of women (1). Thus overweight and obesity continue to accrue in the adult years, and the majority of adult obesity is occurring after late adolescence (17). These statistics underscore the urgency to find effective interventions to prevent the development of obesity in the adult years, in addition to preventing its early onset in childhood.

We chose to apply to all time periods the WHO overweight and obesity thresholds for children 5-19 years. This allowed for consistency in definitions across the study, but may have overestimated the prevalence of overweight and obesity in the age 1-2y period, compared to using the WHO thresholds for children 0-5 years. Additionally, the analytical sample was limited to the 1172 children who had a BMI value for each of the five time periods. However, we found that the overweight and obesity prevalence figures based on all available cross-sectional data at each of the time points did not differ appreciably from the figures based on those who had complete longitudinal data (**Table 6.4**), and there were no statistically significant differences in any of the time periods between the overweight and obesity prevalence figures for children with complete longitudinal data versus those who were not included in the analysis (**Table 6.5**).

Therefore, selection bias is unlikely. The cohort is representative of the population of Soweto and is overwhelmingly Black, with too few non-Black participants to permit meaningful stratified analysis. Restriction of the analysis to the Black participants resulted in estimates very close to those presented.

Our results suggest the need for further research into gender differences in overweight and obesity. Future studies should explore dietary and lifestyle factors that may contribute to the differences found between South African boys and girls. Feeley et al assessed the relationship between dietary habits and BMIZ and fat mass in the Birth-to-Twenty cohort, finding an association between soft drink consumption and increased BMIZ and fat mass, but only in boys (19). Kruger et al found that South African girls had lower levels of physical activity than boys and, in both genders, low activity levels were associated with overweight and obesity (20). Another important area for future research is to explore gender differences in the interpretation of body mass index to characterize overweight and obesity.

Conclusion

Our findings have important implications not only for South Africa, but for other African countries that are rapidly transitioning. Understanding periods of high risk for the development of childhood obesity will enable program planners and policy makers in low- and middle-income countries to more appropriately target interventions. Our findings are important for addressing obesity risk across the life course. By late adolescence, overweight and obesity were not widely prevalent among boys in this South

African cohort, whereas overweight and obesity among girls increased throughout childhood and adolescence. The years following puberty appear to be a high risk period for the development of obesity in girls, and future research should further explore ways in which puberty timing and duration impact this risk. The early establishment of tracking of overweight and obesity suggests the need and potential for early intervention. Finding effective and appropriately timed interventions to promote healthy nutrition and weight among female African children is critical.

Table 6.1: Measures of overweight and obesity among South African boys (n=566) and girls (n=606) from 1-2y to 16-18y[1], Birth-to-Twenty Cohort
(Continued on next page)

	1-2y[12]	4-8y	11-12y	13-15y	16-18y
BMI[2, 4]					
Boys	16.9 (16.7, 17.0)	15.8 (15.6, 15.9)	17.8 (17.5, 18.0)	19.2 (18.9, 19.5)	20.3 (20.0, 20.6)
Girls	16.7 (16.5, 16.8)	15.7 (15.6, 15.8)	18.8 (18.5, 19.2)	21.3 (21.0, 21.7)	22.8 (22.5, 23.2)
BMIZ[3, 4]					
Boys	0.3 (0.2, 0.4)	0.2 (0.1, 0.2)	-0.2 (-0.3, -0.1)	-0.4 (-0.5, -0.3)	-0.6 (-0.7, -0.5)
Girls	0.4 (0.3, 0.5)	0.1 (0.0, 0.2)	-0.03 (-0.1, 0.1)	0.2 (0.1, 0.3)	0.3 (0.2, 0.4)
Obesity[5]					
WHO definition[6]					
Boys	8.8 (6.5, 11.2)	3.0 (1.6, 4.4)	6.0 (4.0, 8.0)	4.4 (2.7, 6.1)	2.5 (1.2, 3.8)
Girls	8.1 (5.9, 10.3)	3.1 (1.7, 4.5)	6.4 (4.5, 8.4)	7.3 (5.2, 9.3)	7.9 (5.8, 10.1)
IOTF definition[7]					
Boys	4.8 (3.0, 6.5)	0.9 (0.1, 1.7)	3.2 (1.7, 4.6)	3.2 (1.7, 4.6)	1.9 (0.8, 3.1)
Girls	4.8 (3.1, 6.5)	2.3 (1.1, 3.5)	5.1 (3.4, 6.9)	6.1 (4.2, 8.0)	7.4 (5.3, 9.5)
CDC definition[8]					
Boys	13.8 (10.9, 16.6)	6.0 (4.0, 8.0)	9.0 (6.6, 11.4)	6.2 (4.2, 8.2)	3.5 (2.0, 5.1)
Girls	12.4 (9.7, 15.0)	5.3 (3.5, 7.1)	9.9 (7.5, 12.3)	12.5 (9.9, 15.2)	12.7 (10.0, 15.4)

1. Infant/toddler – 1y or 2y; early childhood – 4y, 5y, or 8y; early adolescence – 11y or 12y; mid-adolescence – 13y, 14y, 15y; late adolescence – 16y, 17y, 18y. 2. Body mass index. 3. Body mass index z score. 4. Mean (95% confidence interval). 5. % (95% confidence interval).
6. World Health Organization (WHO) defines obesity as BMI z score > 2.0 SD from the reference median. 7. International Obesity Task Force (IOTF) defines obesity and overweight using age- and sex-specific cut-off points for children 2-18 y, which were based on models that adapted the adult cut-off points for overweight (25≤BMI<30) and obese (BMI≥30). 8. Centers for Disease Control (CDC) define obesity as BMI ≥ 95th percentile based on the reference population. 9. Overweight, but not obese. 10. World Health Organization defines overweight as BMI z score > 1.0 and ≤ 2.0 SD from the reference median. 11. Centers for Disease Control define overweight as BMI ≥ the 85th and < 95th percentile based on the reference population. 12. The IOTF and CDC definitions for overweight/obesity are for children 2-18 years and 2-19 years, respectively. IOTF and CDC prevalence figures for the infancy/toddlerhood period should be interpreted with caution, as this period contains BMI measurements at 1y and 2y of age. IOTF and CDC cut-off points for 2y were applied to the measurements at 1y.

Table 6.1: Measures of overweight and obesity among South African boys (n=566) and girls (n=606) from 1-2y to 16-18y[1], Birth-to-Twenty Cohort

(Continued from previous page)

	1-2y[12]	4-8y	11-12y	13-15y	16-18y
Overweight[5, 9]					
WHO definition[10]					
Boys	19.1 (15.8, 22.3)	16.4 (13.4, 19.5)	9.9 (7.4, 12.4)	7.8 (5.6, 10.0)	5.7 (3.7, 7.6)
Girls	19.0 (15.8, 22.1)	12.2 (9.6, 14.8)	14.7 (11.9, 17.5)	17.8 (14.8, 20.9)	19.1 (16.0, 22.3)
IOTF definition[7]					
Boys	12.7 (10.0, 15.5)	6.5 (4.5, 8.6)	9.0 (6.6, 11.4)	7.4 (5.3, 9.6)	6.9 (4.8, 9.0)
Girls	14.5 (11.7, 17.3)	7.6 (5.5, 9.7)	12.5 (9.9, 15.2)	16.0 (13.1, 18.9)	19.0 (15.8, 22.1)
CDC definition[11]					
Boys	12.4 (9.6, 15.1)	12.4 (9.6, 15.1)	6.7 (4.6, 8.8)	5.7 (3.7, 7.6)	4.6 (2.9, 6.3)
Girls	13.5 (10.8, 16.3)	9.2 (6.9, 11.6)	11.1 (8.6, 13.6)	12.0 (9.4, 14.6)	13.7 (11.0, 16.4)

1. Infant/toddler – 1y or 2y; early childhood – 4y, 5y, or 8y; early adolescence – 11y or 12y; mid-adolescence – 13y, 14y, 15y; late adolescence – 16y, 17y, 18y. 2. Body mass index. 3. Body mass index z score. 4. Mean (95% confidence interval). 5. % (95% confidence interval).
6. World Health Organization (WHO) defines obesity as BMI z score > 2.0 SD from the reference median. 7. International Obesity Task Force (IOTF) defines obesity and overweight using age- and sex-specific cut-off points for children 2-18 y, which were based on models that adapted the adult cut-off points for overweight (25≤BMI<30) and obese (BMI≥30). 8. Centers for Disease Control (CDC) define obesity as BMI ≥ 95th percentile based on the reference population. 9. Overweight, but not obese. 10. World Health Organization defines overweight as BMI z score > 1.0 and ≤ 2.0 SD from the reference median. 11. Centers for Disease Control define overweight as BMI ≥ the 85th and < 95th percentile based on the reference population. 12. The IOTF and CDC definitions for overweight/obesity are for children 2-18 years and 2-19 years, respectively. IOTF and CDC prevalence figures for the infancy/toddlerhood period should be interpreted with caution, as this period contains BMI measurements at 1y and 2y of age. IOTF and CDC cut-off points for 2y were applied to the measurements at 1y.

Table 6.2: Incidence of obesity among South African boys (n=566) and girls (n=606) from 1-2y to 16-18y[1], Birth-to-Twenty Cohort

	1-2y to 4-8y	4-8y to 11-12y	11-12y to 13-15y	13-15y to 16-18y
Obesity[2] incidence				
Period incidence[3]				
Boys	2.1 (0.9, 3.4)	4.4 (2.7, 6.1)	0.9 (0.1, 1.8)	0.4 (-0.1, 0.9)
Girls	2.0 (0.8, 3.1)	4.9 (3.2, 6.7)	2.8 (1.5, 4.2)	3.0 (1.6, 4.4)
Incidence density rate[4]				
Boys	5.1 (2.8, 9.1)	6.8 (4.6, 10.2)	3.7 (1.5, 8.8)	1.3 (0.3, 5.3)
Girls	5.0 (2.8, 9.0)	7.4 (5.2, 10.7)	11.2 (6.9, 18.3)	11.0 (6.8, 17.7)
Reversion incidence				
Period incidence[5]				
Boys	88.0 (78.7, 97.3)	41.2 (15.1, 67.3)	41.2 (23.7, 58.6)	52.0 (31.0, 73.0)
Girls	83.7 (72.9, 94.4)	47.4 (22.6, 72.1)	28.2 (13.4, 43.0)	29.5 (15.5, 43.6)

1 Infant/toddler – 1y or 2y; early childhood – 4y, 5y, or 8y; early adolescence – 11y or 12y; mid-adolescence – 13y, 14y, 15y; late adolescence – 16y, 17y, 18y

2 World Health Organization defines obesity as BMI z score > 2.0 SD from the reference median

3 Incident obesity cases during the period among those who were at risk for obesity at the beginning of the period; % (95% CI)

4 Number of incident obesity cases during the period per 1,000 person-years

5 Incident cases of reverting from obese to non-obese during the period among those who were obese at the beginning of the period; % (95% CI)

Table 6.3: Modeling risk of obesity from 16-18y based on BMI status at 1-2y and 4-8y among South African boys (n=566) and girls (n=606), Birth-to-Twenty Cohort [1]

	Odds Ratio	95% CI
Girls		
Infancy/toddlerhood (1-2y)		
Overweight	3.6***	1.8, 7.2
Obese	8.0***	3.7, 17.6
Early childhood (4-8y)		
Overweight	6.8***	3.3, 13.9
Obese	42.3***	15.0, 118.8
Boys		
Infancy/toddlerhood (1-2y)		
Overweight	5.6**	1.7, 18.0
Obese	3.4	0.6, 17.8
Early childhood (4-8y)		
Overweight	2.1	0.5, 8.4
Obese	19.7***	5.1, 75.9

1 Models the risk of being obese at late adolescence (16y, 17y, 18y) based on status at the infant/toddler (1y or 2y) or early childhood periods (4y, 5y, or 8y), with the referent category being those who were classified as normal BMI (not overweight or obese) at that time period.

* P-value <0.05

** P-value <0.01

*** P-value <0.001

Table 6.4 Measures of overweight and obesity among South African boys and girls from 1-2y to 16-18y[1], Birth-to-Twenty Cohort (Sensitivity analysis: presenting figures based on cross-sectional, or all available, data at each time period)

	1-2y[9] (n=2,163)	4-8y (n=2,162)	11-12y (n=1,839)	13-15y (n=2,192)	16-18y (n=2,113)
Obesity[2]					
WHO definition[3]					
Boys	9.4 (7.6, 11.1)	3.4 (2.3, 4.5)	5.5 (4.0, 7.0)	4.5 (3.2, 5.7)	3.0 (1.9, 4.0)
Girls	9.1 (7.5, 10.8)	2.9 (1.9, 3.9)	6.7 (5.2, 8.3)	7.9 (6.3, 9.4)	8.7 (7.1, 10.4)
IOTF definition[4]					
Boys	5.0 (3.6, 6.3)	1.5 (0.8, 2.3)	3.2 (2.0, 4.4)	3.6 (2.5, 4.8)	2.6 (1.6, 3.5)
Girls	5.7 (4.4, 7.1)	2.0 (1.1, 2.8)	5.3 (3.9, 6.7)	6.6 (5.1, 8.0)	8.1 (6.5, 9.7)
CDC definition[5]					
Boys	15.0 (12.8, 17.1)	6.9 (5.4, 8.5)	8.7 (6.8, 10.5)	6.2 (4.7, 7.7)	4.1 (2.9, 5.4)
Girls	14.0 (12.0, 16.0)	5.5 (4.2, 6.8)	10.6 (8.6, 12.5)	12.4 (10.5, 14.3)	13.0 (11.0, 15.0)
Overweight[2, 6]					
WHO definition[7]					
Boys	18.8 (16.4, 21.2)	15.7 (13.5, 17.9)	9.8 (7.8, 11.8)	7.1 (5.6, 8.7)	5.3 (3.9, 6.7)
Girls	18.7 (16.5, 21.0)	12.3 (10.3, 14.2)	15.1 (12.8, 17.3)	15.8 (13.7, 18.0)	17.7 (15.4, 19.9)
IOTF definition[4]					
Boys	14.6 (12.5, 16.7)	6.4 (4.9, 7.9)	8.2 (6.4, 10.0)	6.8 (5.2, 8.3)	6.1 (4.6, 7.6)
Girls	15.6 (13.5, 17.7)	8.1 (6.5, 9.7)	13.2 (11.0, 15.3)	14.6 (12.6, 16.7)	17.7 (15.4, 19.9)
CDC definition[8]					
Boys	11.6 (9.6, 13.5)	11.3 (9.4, 13.2)	6.5 (4.9, 8.1)	5.1 (3.8, 6.5)	4.1 (2.9, 5.4)
Girls	12.7 (10.8, 14.7)	9.1 (7.4, 10.7)	10.9 (8.9, 12.9)	10.8 (9.0, 12.6)	12.7 (10.7, 14.6)

1. Infant/toddler – 1y or 2y; early childhood – 4y, 5y, or 8y; early adolescence – 11y or 12y; mid-adolescence – 13y, 14y, 15y; late adolescence – 16y, 17y, 18y. 2. % (95% confidence interval). 3. World Health Organization (WHO) defines obesity as BMI z score > 2.0 SD from the reference median
4. International Obesity Task Force (IOTF) defines obesity and overweight using age- and sex-specific cut-off points for children 2-18 y, which were based on models that adapted the adult cut-off points for overweight (25≤BMI<30) and obese (BMI≥30). 5. Centers for Disease Control (CDC) define obesity as BMI ≥ 95th percentile based on the reference population. 6. Overweight, but not obese. 7. World Health Organization defines overweight as BMI z score > 1.0 and ≤ 2.0 SD from the reference median. 8. Centers for Disease Control define overweight as BMI ≥ the 85th and < 95th percentile based on the reference population. 9. The IOTF and CDC definitions for overweight/obesity are for children 2-18 years and 2-19 years, respectively. IOTF and CDC prevalence figures for the infancy/toddlerhood period should be interpreted with caution, as this period contains BMI measurements at 1y and 2y of age. IOTF and CDC cut-off points for 2y were applied to the measurements at 1y.

Table 6.5: Measures of overweight and obesity among South African boys and girls from 1-2y to 16-18y[1], Birth-to-Twenty Cohort (Sensitivity analysis: presenting figures based on individuals who were lost-to-follow-up and not in the main analysis)

	1-2y[9] (n=991)	4-8y (n=990)	11-12y (n=667)	13-15y (n=1,020)	16-18y (n=941)
Obesity[2]					
WHO definition[3]					
Boys	10.0 (7.3, 12.6)	3.8 (2.1, 5.6)	4.5 (2.2, 6.8)	4.6 (2.7, 6.4)	3.6 (1.8, 5.3)
Girls	10.4 (7.8, 13.1)	2.7 (1.3, 4.1)	7.3 (4.6, 10.0)	8.6 (6.2, 10.9)	9.8 (7.1, 12.4)
IOTF definition[4]					
Boys	5.2 (3.2, 7.2)	2.3 (1.0, 3.7)	3.2 (1.2, 5.2)	4.1 (2.4, 5.9)	3.3 (1.7, 5.0)
Girls	6.9 (4.7, 9.1)	1.5 (0.5, 2.6)	5.6 (3.2, 8.0)	7.1 (4.9, 9.3)	8.9 (6.4, 11.5)
CDC definition[5]					
Boys	16.4 (13.1, 19.7)	8.1 (5.6, 10.5)	8.1 (5.0, 11.1)	6.2 (4.1, 8.4)	4.9 (2.9, 6.9)
Girls	15.9 (12.7, 19.1)	5.8 (3.8, 7.8)	11.8 (8.4, 15.1)	12.3 (9.5, 15.1)	13.4 (10.4, 16.4)
Overweight[2, 6]					
WHO definition[7]					
Boys	18.5 (15.0, 21.9)	14.9 (11.6, 18.1)	9.7 (6.4, 13.0)	6.4 (4.2, 8.6)	4.9 (2.9, 6.9)
Girls	18.5 (15.1, 21.8)	12.3 (9.5, 15.2)	15.7 (11.9, 19.5)	13.6 (10.7, 16.5)	15.9 (12.6, 19.1)
IOTF definition[4]					
Boys	16.8 (13.5, 20.2)	6.2 (4.0, 8.3)	6.8 (4.0, 9.6)	6.0 (3.9, 8.1)	5.1 (3.1, 7.2)
Girls	16.9 (13.6, 20.2)	8.7 (6.2, 11.1)	14.3 (10.6, 17.9)	13.0 (10.2, 15.9)	16.1 (12.8, 19.3)
CDC definition[8]					
Boys	10.6 (7.8, 13.3)	10.0 (7.3, 12.7)	6.1 (3.4, 8.8)	4.6 (2.7, 6.4)	3.6 (1.8, 5.3)
Girls	11.8 (9.0, 14.6)	8.9 (6.4, 11.3)	10.6 (7.4, 13.9)	9.3 (6.8, 11.8)	11.4 (8.6, 14.2)

1. Infant/toddler – 1y or 2y; early childhood – 4y, 5y, or 8y; early adolescence – 11y or 12y; mid-adolescence – 13y, 14y, 15y; late adolescence – 16y, 17y, 18y. 2. % (95% confidence interval). 3. World Health Organization (WHO) defines obesity as BMI z score > 2.0 SD from the reference median. 4. International Obesity Task Force (IOTF) defines obesity and overweight using age- and sex-specific cut-off points for children 2-18 y, which were based on models that adapted the adult cut-off points for overweight (25≤BMI<30) and obese (BMI≥30). 5. Centers for Disease Control (CDC) define obesity as BMI ≥ 95th percentile based on the reference population. 6. Overweight, but not obese. 7. World Health Organization defines overweight as BMI z score > 1.0 and ≤ 2.0 SD from the reference median. 8. Centers for Disease Control define overweight as BMI ≥ the 85th and < 95th percentile based on the reference population. 9. The IOTF and CDC definitions for overweight/obesity are for children 2-18 years and 2-19 years, respectively. IOTF and CDC prevalence figures for the infancy/toddlerhood period should be interpreted with caution, as this period contains BMI measurements at 1y and 2y of age. IOTF and CDC cut-off points for 2y were applied to the measurements at 1y.

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Chapter 7: Early Life Determinants of Pubertal Development in South African Adolescents

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Abbreviations used: body mass index (BMI); height-for-age z score (HAZ); body mass index z score (BMIZ); Tanner Sexual Maturation Scale (SMS); Latent Class Growth Analysis (LCGA); Relative risk ratio (RRR)

Abstract

Background/Objective: Early puberty increases an adolescent's risk for adverse psychosocial outcomes. Given global trends toward earlier onset of puberty, it is important to understand childhood predictors of pubertal timing and tempo. We describe the longitudinal progression of puberty, and its relation to earlier height and body mass index, among primarily black male and female adolescents in South Africa.

Methods: We analyzed data from 1,060 males and 1,135 females participating in the Birth-to-Twenty study in Soweto, South Africa. Height-for-age z scores (HAZ) and body mass index z scores (BMIZ) were calculated based on height (cm) and body mass index (kg/m^2) data at 5y and 8y. The development of genitals, breasts, and pubic hair was recorded from ages 9y to 16y using the five stages of the Tanner Sexual Maturation Scale (SMS). We used Latent Class Growth Analysis to identify trajectory classes (puberty tempo) for the development of genitals, breasts, and pubic hair, and characterized children as earlier, medium, or later developers (puberty timing) based on the median Tanner SMS score at 12y. Multinomial logistic regression was used to determine whether HAZ and BMIZ at ages 5y and 8y were associated with puberty timing and tempo.

Results: Among females, risk of being in the class with the fastest vs. slowest tempo for pubic hair development was increased with greater HAZ at 5y (relative risk ratio (RRR)=1.57; $p<0.001$) and BMIZ at 5y (RRR=1.51; $p<0.01$) and 8y (RRR=2.06; $p=0.03$); the same was true for the development of breasts and HAZ at 5y (RRR=1.78; $p<0.001$) and BMIZ at 5y (RRR=1.65; $p<0.001$) and 8y (RRR=3.35; $p<0.001$). Among

females, risk of earlier pubic hair development was increased by greater HAZ at 5y (RRR=1.40; $p<0.01$) or 8y (RRR=2.33; $p<0.01$), and greater BMIZ at 5y (RRR=1.32; $p=0.04$). Among males, risk of being in the class with the fastest vs. slowest tempo for pubic hair development was increased with greater HAZ at 5y (RRR=1.78; $p<0.001$) and BMIZ at 5y (RRR=1.43; $p<0.01$); the same was true for the development of genitals and HAZ at 5y (RRR=2.19; $p<0.01$).

Conclusions

Among both males and females, there was a positive association between both height and body mass index in early childhood and the tempo of pubertal development. This relationship emerged by age 5y. Among females, greater childhood height and body mass index were associated with earlier pubertal development, but there was no association among males.

Introduction

Puberty is an important developmental process, involving not only physical changes, but also social and emotional development, that together indicate a transition from childhood into adulthood. Pubertal development can have profound social implications, especially for females, as it signifies the beginning of reproductive capabilities, one's potential readiness for sexual activity and marriage, and the possibility for childbearing and motherhood (1-3). The timing of puberty is linked to numerous psychosocial outcomes, with early puberty among girls leading to a higher risk of depression, eating disorders, substance abuse, poor academic achievement, and risky sexual behaviors (2). Given the importance of puberty for adolescent social and emotional development, much attention has been paid to global trends indicating an earlier onset of puberty, particularly among girls.

In the U.S. and Western European countries, there was a marked decline in the age of menarche from the mid-19th to the mid-20th century, a period of rapid improvements in nutrition and socioeconomic conditions (4). The rate of decline in age at menarche in these countries has slowed over the past few decades, however in low- and middle-income countries, which have developed more recently than the U.S. and Europe, there continues to be a strong secular trend in the reduction of menarcheal age (4, 5). Studies have also shown a secular trend toward earlier development of breasts and pubic hair among girls (6-10). There is some research to suggest earlier genital and pubic hair development in boys, although there are far fewer data for males and the evidence has generally been insufficient to determine secular trends (9-11).

The shift in age at pubertal onset has been concurrent with increases in height in many populations, suggesting improved nutrition and socioeconomic conditions have contributed to both trends (12). Height in children has been found to have an inverse association with age of pubertal onset (13-16). Furthermore, the secular trends in pubertal development have been accompanied by an increase in body mass index (BMI) among children (17, 18), and studies on the role of overweight and obesity in pubertal development have garnered much attention (7, 19-21). There is evidence of an association between higher BMI in childhood or adolescence and earlier onset of puberty among girls (7, 13, 16, 20, 22-26). This relationship has been far less studied in boys, but two studies concluded that higher BMI may instead be associated with delayed puberty in males (23, 24).

Given the focus on improving nutrition and child growth in low- and middle-income countries, it is important to better understand the relationship between child growth measures and both the timing and trajectory of pubertal development among males and females. This relationship has primarily been studied in females. Additionally, most studies have focused on the relationship between childhood anthropometric measures and pubertal timing, rather than the tempo or overall trajectory of pubertal development. As both the timing and tempo of puberty may be influential in predicting later health and psychosocial outcomes, it is important to use longitudinal data to better characterize both the onset and trajectory of pubertal development, and understand their relationship with child growth measures. Lastly, studies on child growth measures and puberty have

mainly focused on Caucasian children in high-income countries, with limited evidence in other populations.

We address these gaps in the literature by using data on the development of secondary sexual characteristics from 9-16y to describe the longitudinal progression of puberty, and its relation to earlier height and body mass index, among primarily black male and female adolescents in South Africa.

Methods

We analyzed data from the Birth-to-Twenty study, a birth cohort initiated in 1990 in Soweto, an urban township in South Africa. Detailed information on this cohort has been published elsewhere (27). The cohort enrolled 3273 children who were born during a six-week period in early 1990. Participants were predominantly black, and from families with a low socioeconomic status. The study was designed to track the growth, health, well-being and educational progress of the children, who have been studied prospectively. Throughout the study, participants or their caregivers provided written informed consent and ethical approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects (approval ID #M010556).

Weight at birth and weight and length/height at subsequent rounds were measured using standard procedures (28). At birth and in the months immediately following birth, data on demographic and socioeconomic variables, such as the child's ethnicity and caretaker monthly income (in Rands), were collected. At ages 9 through 16 years, pubertal

development was assessed with the Tanner Sexual Maturation Scale (SMS), the most commonly used standard for evaluating pubertal stage in both clinical and research settings (29). The Tanner SMS consists of drawings of five progressive stages in the development of secondary sexual characteristics—breasts in females, genitals in males, and pubic hair in both genders (30, 31). The drawings are accompanied by written descriptions of each stage. The stages range from 1 (pre-pubertal) to 5 (post-pubertal), with stage 2 representing the onset of puberty. From ages 9-11 years, the Tanner SMS was administered by a trained health care provider among a subset of Birth-to-Twenty participants. Among a comparable group of South African adolescents, self-assessment using the Tanner SMS was validated against expert Tanner ratings, and a significant degree of concordance was found between the two ratings (32). Therefore, self-rating using Tanner SMS was determined to be valid, and was carried out at years 12-16 among the entire cohort of Birth-to-Twenty participants.

Participants were included in the analysis if they had a least one Tanner SMS measurement between 9-16 years, which resulted in an analytical sample of 2,195 participants. Missing data were accounted for using the Full Information Maximum Likelihood technique in Mplus (33).

Data Management

Using weight and height measurements at ages 5 and 8 years, body mass index (BMI) values were calculated as weight (kg) divided by height squared (m^2). Height and body mass index measures were converted to height-for-age z scores (HAZ) and body mass

index z scores (BMIZ) using the World Health Organization standards (34, 35). Caretaker monthly income was categorized into quintiles. We used Mplus to perform Latent Class Growth Analysis (LCGA) in order to group participants into distinct classes based on a common developmental trajectory for the Tanner SMS indicators of pubertal status (**Figure 7.1**). LCGA is a novel method of modeling trajectories for longitudinal data on growth and development. It is an extension of latent growth curve modeling, a method which estimates a latent intercept (initial level of the outcome variable) and latent slope (rate of outcome change over time) for the entire population. However, instead of assuming that one growth trajectory adequately describes the entire population, LCGA identifies numerous growth trajectories and groups observations into distinct classes based on similarities in their growth patterns. We conducted separate pubertal development trajectory analyses for females (breast and pubic hair development), and for males (genital and pubic hair development). We determined the optimal model in terms of the number of classes based on model fit statistics, with a focus on minimizing the value for the Bayesian Information Criteria, as well as parsimony of the model and identifying classes that had distinct differences in their developmental trajectories (33).

We used the ANOVA test to determine whether there was a significant difference in height and BMI at ages 5 and 8 years among classes. We also used multinomial logistic regression to determine whether height and BMI at ages 5 and 8 years are associated with group membership for the Tanner developmental trajectory classes. Height and BMI are included in these regression models as HAZ and BMIZ to ensure that the regression output for these two measures would be on the same scale, thereby enabling comparisons.

Because of the strong correlation between repeated measures in the same individuals, we used conditional growth modeling to identify the effects of HAZ and BMIZ at 8y, independent of the effect of HAZ and BMIZ at 5y (thereby producing a measure representing the change from 5y to 8y in these measures). Conditional HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). Conditional BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). HAZ at 5y is included in the model without any adjustments. BMIZ at 5y is adjusted by controlling for HAZ at 5y.

The results of the regression analyses are presented as relative risk ratios (RRR). The RRR produced by multinomial logistic regression is similar to the odds ratio generated in logistic regression on a binary outcome. The RRRs are presented as unadjusted estimates, as well as adjusted for ethnicity and quintiles of caretaker monthly income. It is known that pubertal development is influenced by ethnicity (6, 13, 16, 22, 26) and socioeconomic status (36, 37).

The LCGA analysis illustrates the different trajectories for pubertal development in this population. However, in order to make more direct comparisons with the existing literature, we conducted a separate analysis of the timing of pubertal development. We created an indicator to represent the timing of pubertal development, by comparing the children's level of development in early adolescence to that of their peers in the cohort.

Tanner scores at age 12y were used to compute this indicator, as the full cohort began providing pubertal data at this wave. Children who were at the median score (which was also the modal score) for Tanner pubic hair, breast, and genital development at 12y, were categorized as being at a medium level of development, and therefore became the reference category. Those with a lower score were considered later developers, and those with a higher score were considered earlier developers. Using these three categories of pubertal development at 12y, we repeated the multinomial logistic regression to determine whether HAZ and BMIZ at ages 5 and 8 years are associated with being at an earlier stage of development at early adolescence.

Some participants reported a lower Tanner score one year than they had in a previous wave. Therefore, we performed a sensitivity analysis to determine whether such reversion affected the conclusions of the analysis. We developed two alternative datasets. First, we assumed that once a certain level of development on the Tanner scale was reported, the child had to stay at that level of development until they reported a higher Tanner score, in effect assuming that the earlier reported value was true. For the second approach, we assigned the lower value to the previous value, assuming that the later value was true. We repeated the regression models using these alternative datasets and compared the results. We used Mplus 7.3 (Muthén & Muthén, Los Angeles, California) to perform the Latent Class Growth Analysis, and STATA 13.0 (StataCorp, College Station, Texas) for all other analyses.

Results

The study sample was 52% female (n=1,135) and 48% male (n=1,060) (**Table 7.1**). The large majority (81%) of participants were Black, with other represented groups including white (4%), Indian (2%) and coloured or mixed-ancestral (13%) children. Those who were not included in the analysis were similar with respect to ethnicity, caretaker income, and height and BMI at ages 5 and 8y. At 5y, girls were on average 106.9 cm and boys were 107.6 cm, both with HAZ scores of -0.7 SD. At 8y girls were on average 123.9 cm and boys were 124.7 cm, both with HAZ scores of -0.7 SD. At 5y, girls had a mean BMI of 15.6 (BMIZ 0.1), and boys had a mean BMI of 15.7 (BMIZ 0.2). At 8y, both girls and boys had a mean BMI of 15.8 (BMIZ -0.1).

At 9y, when collection of pubertal data began, most children were at Tanner stage 1 for pubic hair, breasts, and genitals (**Table 7.2**). Over half were still at stage 1 at 10y of age, however, by age 11y, the majority had reached Tanner stage 2 or greater, indicating the onset of puberty. At ages 12 and 13y, females were at a higher level of pubertal development than males. By age 16y, around half of the adolescents were at Tanner stage 4, and around one-fourth had reached stage 5 (post-pubertal).

Among females, LCGA resulted in 3 trajectory classes for the development of pubic hair (**Figure 7.2**) and 4 classes for breast development (**Figure 7.3**) (**Table 7.3**). Among males, 3 trajectory classes were identified for the development of pubic hair (**Figure 7.4**) and 4 classes for genital development (**Figure 7.5**). In the development of pubic hair among females, for example, class 3 represents children who started at a slightly higher

level of pubertal maturation at 9y, had a faster tempo of progression through the Tanner stages, and were at a higher stage of development at 16y (**Figure 7.2**). This growth pattern is distinct from that of individuals in classes 1 and 2, who had a slower pace of pubic hair development and had not reached post-pubertal status by 16y.

Mean height (cm) and body mass index (kg/m^2) at 5y and 8y generally increased across growth trajectory classes 1-3 for pubic hair and 1-4 for breast and genital development, meaning classes with faster tempos had higher means for height and BMI (**Table 7.4**). ANOVA tests confirmed that at least one class had a statistically significant difference in the mean height and BMI, with the exception of height at 8y and female pubic hair development classes, and BMI at 5y and male genital development classes.

When the trajectory classes for pubic hair development in females were regressed on HAZ at 5y, we found a relative risk ratio (RRR) of 1.57 for class 3 vs. 1 ($p<0.001$) and 1.34 for class 2 vs. 1 ($p<0.01$) (**Table 7.5**). Therefore, a 1 SD increase in HAZ at 5y is associated with a 57% increase in the risk of being in class 3 compared to class 1, and a 34% increase in the risk of being in class 2 vs. 1. Similarly, for breast development, HAZ at 5y was associated with a significantly increased RRR for class 4 vs. 1 and 3 vs. 1. Among females, conditional HAZ at 8y was not significant in predicting group membership for either pubic hair or breast development in the adjusted models. When trajectory classes for pubic hair development were regressed on BMIZ at 5y, there was a significantly increased RRR for class 3 vs. 1. For pubic hair and conditional BMIZ at 8y, significant relative risk ratios were found for classes 3 vs. 1 and 2 vs. 1. Similarly, for breast development, BMIZ at 5y and conditional BMIZ at 8y were associated with

significantly increased relative risk ratios, particularly for being in class 4 vs. 1 and 3 vs. 1.

Among males, when the trajectory classes for pubic hair development were regressed on HAZ at 5y, we found significantly increased RRRs for classes 3 vs. 1 and 2 vs. 1 (**Table 7.6**). Similarly, when the growth trajectory classes for genital development in males were regressed on HAZ at 5y, the RRR was increased for classes 4 vs. 1 and 3 vs. 1. In the adjusted models, BMIZ at 5y was the other significant association found among males, with an increased RRR for being in class 3 vs. 1 for pubic hair development.

Among females, the median (and modal) Tanner score for pubic hair and breast development at 12y was 3. Therefore, a score of 3 was considered medium development, and became the reference. Scores of 1 or 2 were categorized as later developers, and scores of 4 and 5 were considered earlier developers. For pubic hair development at 12y, 38% were at the medium level of development, with 19% earlier developers and 43% later developers (data not shown). For breast development, 40% were at the medium level of development, with 23% earlier developers and 37% later developers (data not shown). Having a greater HAZ at 5y significantly increased the RRR of being in the earlier development group for pubic hair, and significantly decreased the risk of being in the later group for both pubic hair and breast development (**Table 7.7**). There was a positive association between conditional HAZ at 8y and risk of being in the earlier pubic hair development group. There was also a positive association between BMIZ at 5y and risk of being in the earlier pubic hair development group.

Among males, the median (and modal) Tanner score for pubic hair and genital development at 12y was 2. Therefore, a score of 2 was considered medium development, and became the reference. A score of 1 was categorized as later developers, and scores of 3, 4, and 5 were considered earlier developers. For pubic hair development at 12y, 44% were at the medium level of development, with 33% earlier developers and 23% later developers (data not shown). For genital development, 44% were at the medium level of development, with 34% earlier developers and 22% later developers (data not shown). For males, the adjusted regression models did not produce any significant associations between HAZ and BMIZ at 5y and 8y and risk of being in the earlier development groups (**Table 7.8**). However, a greater HAZ at 5y did significantly decrease the risk of being in the later development group for genitals.

Discussion

For the tempo of pubertal development, we found that among females, greater HAZ at 5y, BMIZ at 5y, and conditional BMIZ at 8y were associated with an increased risk of being in a class with a faster tempo for pubic hair and breast development. In terms of the timing of pubertal development, we found that among females, having a greater HAZ at 5y, conditional HAZ at 8y, or BMIZ at 5y increases the risk of having earlier pubic hair development, as compared to the reference peers at 12y. The associations found between BMIZ and pubertal timing and tempo were independent of HAZ.

Among males, greater HAZ at 5y was associated with an increased risk of being in a class with a faster tempo for pubic hair and genital development. BMIZ at 5y, independent of height, was also associated with an increased risk of being in the class with the fastest tempo for pubic hair development. For males, there was little evidence of an association between HAZ and BMIZ at 5y and 8y and being in the earlier development group for pubic hair and genitals at 12y.

The associations found in both males and females indicate that linear growth in early childhood is positively associated with being in a faster pubertal development trajectory. This relationship appears to have emerged by age 5y, and linear growth by 5y seems to account for the association, as height at 8y conditioned on prior height at 5y was not significant in the models. Among females, greater childhood height and BMI may also be associated with earlier pubertal development, but there does not seem to be an association among males. While a causal relationship between childhood growth measures and puberty cannot be established with these data, if such a relationship exists, it suggests that earlier puberty or faster progression through puberty could be a possible consequence of programs aimed at improving child nutrition and linear growth. The results also suggest that earlier and faster pubertal development may be a consequence of the childhood overweight and obesity epidemic, particularly among females. The possible impact of trends in child growth on pubertal timing and tempo is a concern, given that early puberty among girls can lead to a higher risk of depression, eating disorders, substance abuse, poor academic achievement, and risky sexual behaviors (2). Furthermore, obesity has been linked to poor psychosocial outcomes like depression in adolescence (38), which

may lead to a possible synergistic effect of obesity and early puberty on adolescent mental health.

Our results are fairly consistent with other studies on the relationship between child growth and puberty. However, the literature is primarily devoted to studying this relationship among females, and focuses on the timing of puberty rather than the tempo or overall trajectory. Other studies have found a similar inverse relationship between childhood height and age of puberty onset in girls (13, 16). Several cross-sectional studies have found that a higher BMI is associated with earlier puberty among females, as defined by breast development (22, 23), pubic hair (13, 22) and age at menarche (16, 22, 24).

Longitudinal studies have helped clarify the direction of these associations. One study followed white females from age 5y to 9y, and found that girls with greater body fat at 5y and 7y were more likely to have earlier pubertal development at 9y, assessed by breast development, estradiol levels and the Pubertal Development Scale (25). This study helped to establish that weight status precedes pubertal timing (25). Another study enrolled girls at 6-8 years and followed them longitudinally to examine the association between BMI and age at onset of breast maturation. They found that girls with a greater BMI reached Tanner breast stage 2 at younger ages (7). Lee et al found that the association between high BMI and earlier breast development begins as early as 36 months (26). These relationships have been far less studied in boys, but two studies have found that higher BMI may instead be associated with delayed puberty in males (23, 24).

Limitations

A limitation of this study is that the Tanner SMS ratings were self-reported by the adolescents from ages 12-16y. The gold standard for pubertal staging is typically physical examination by a trained clinician using Tanner criteria (29). However, self-assessment using the Tanner SMS has been validated in many populations, including a highly comparable population of South African adolescents (32). Therefore, self-rating of pubertal stage can be considered reasonably valid in this study. Also, while measurement error associated with self-assessment could impact conclusions drawn about the level of pubertal development at any one cross-section within the study, the consistent use of self-rating from 12-16y means that interpretation of trends across time would be unlikely to be biased, as measurement error is equally likely at all ages.

The associations we found between BMI and breast development in females should be interpreted with caution, as it has been suggested that using the Tanner SMS to characterize breast development, in the absence of physical examination by a clinician, may result in measurement error for overweight or obese girls (29). The Tanner SMS is most accurately used to describe female breast development when a trained clinician uses palpation to distinguish between actual breast tissue and adipose tissue. Overweight or obese females using Tanner self-assessment may be prone to overestimate their level of breast development, since adipose tissue can be easily mistaken for breast tissue (29).

In our analysis of pubertal progression, characterization of trajectory groups for pubertal development could have been influenced by the existence of reversion (i.e. reporting a lower Tanner SMS score than that of an earlier round of data collection). However, the sensitivity analysis, using two methods that corrected this reversion in the data, found similar conclusions regarding the association between childhood height and BMI and pubertal trajectory group membership (**Tables 7.9-7.12**).

Our longitudinal data on pubertal development are limited by the fact that only a subset of the overall cohort provided data at ages 9-11y. This subset of the Birth-to-Twenty cohort was a group of children who were selected for a separate study on bone development. The two groups, those with pubertal data at 9-11y and those who only began providing data at 12y, were compared with respect to Tanner scores at 12y, as well as height and BMI at 5y and 8y. Among girls, there were no significant differences between the two groups. Boys who provided pubertal data at 9-11y were slightly different from those who began providing data at 12y in that they were taller at 5y, had a higher BMI at 8y, and reported more pubic hair development at 12y. These differences among the males could have impacted the group assignments for pubic hair progression, as well as regression analyses involving these groups, and these results should therefore be interpreted with caution.

Lastly, direct comparisons between the results of our study and previous research may be difficult, as our population consisted primarily of black adolescents. Some research suggests black females experience earlier pubertal development (6, 13, 16, 22, 26). While

ethnicity was not significant when controlled for in our models, we had little variation in ethnicity among our sample.

While many studies have found an association between child growth parameters and pubertal development, our study helps to clarify this relationship by examining both boys and girls, exploring the association for height as well as BMI, and using longitudinal data to describe this relationship for both pubertal timing and overall trajectory (or tempo). The collection of height and BMI measurements at two time points before the onset of secondary sexual characteristics helps to establish the timing of this association. Lastly, our study explores these associations in the context of a primarily black population in a middle-income country, while most other studies have been carried out in Caucasian populations in the U.S. and Europe.

Conclusion

Among both males and females, there was a positive association between both height and BMI in early childhood and the tempo of pubertal development. This relationship emerged by age 5y. Among females, greater childhood height and BMI were associated with earlier pubertal development, but there was no association among males.

Table 7.1: Selected Characteristics of the Study Population, Birth-to-Twenty

	Females n=1,135	Males n=1,060
Ethnicity, %		
Black	81.3	81.2
White	3.4	4.0
Coloured	13.0	12.5
Indian	2.4	2.4
Caretaker monthly income quintiles (Rands)[a], %		
1 (0 - 2,400 Rands)	23.9	21.9
2 (2,401 - 7,800 Rands)	28.6	32.4
3 (7,801 - 10,800 Rands)	16.2	13.4
4 (10,801 - 19,200 Rands)	21.0	20.2
5 (19,201 - 48,000 Rands)	10.3	12.2
Height (cm), mean ± SD		
5y	106.9 ± 4.7	107.6 ± 4.5
8y	123.9 ± 6.0	124.7 ± 6.0
Height-for-age z score, mean ± SD		
5y	-0.7 ± 0.9	-0.7 ± 0.9
8y	-0.7 ± 1.0	-0.7 ± 1.0
Body mass index (kg/m^2), mean ± SD		
5y	15.6 ±1.5	15.7 ± 1.4
8y	15.8 ± 2.0	15.8 ± 1.7
Body mass index z score, mean ± SD		
5y	0.1 ± 0.9	0.2 ± 1.0
8y	-0.1 ± 1.0	-0.1 ± 1.0

a. 623 females and 575 males had information on caretaker monthly income. In analyses using this variable, a sixth category for missing is included to preserve the sample size. In 1990, the South African Rand (ZAR) to U.S. Dollar (USD) conversion rate was 0.38956. Therefore, the ranges of ZAR in this table correspond to the following USD:
0 - 2,400 ZAR = 0 - 934.94 USD
2,401 - 7,800 ZAR = 935.33 - 3,038.57 USD
7,801 - 10,800 ZAR = 3,038.96 - 4,207.25 USD
10,801 - 19,200 ZAR = 4,207.64 - 7,479.55 USD
19,201 - 48,000 ZAR = 7,479.94 - 18,698.9 USD

Table 7.2: Distribution of Tanner Scores for Development of Pubic Hair, Female Breasts, and Male Genitals

(Continued on next page)

	Females (n=1,135)				Males (n=1,060)			
	Pubic Hair		Breast		Pubic Hair		Genital	
	N	%	n	%	n	%	N	%
Year 9,								
Mean ± SD	144	1.1 ± 0.3	144	1.2 ± 0.4	167	1.0 ± 0.2	167	1.2 ± 0.4
Stage 1, %		86.1		79.2		95.2		84.4
Stage 2		13.9		20.8		4.8		15.6
Stage 3		0.0		0.0		0.0		0.0
Stage 4		0.0		0.0		0.0		0.0
Stage 5		0.0		0.0		0.0		0.0
Year 10								
Mean ± SD	169	1.4 ± 0.5	169	1.5 ± 0.6	197	1.4 ± 0.5	197	1.5 ± 0.6
Stage 1, %		59.8		52.7		60.9		52.8
Stage 2		38.5		44.4		38.1		40.1
Stage 3		1.8		3.0		1.0		7.1
Stage 4		0.0		0.0		0.0		0.0
Stage 5		0.0		0.0		0.0		0.0
Year 11								
Mean ± SD	172	1.9 ± 0.7	172	2.0 ± 0.7	206	1.7 ± 0.5	206	1.9 ± 0.6
Stage 1, %		32.0		25.0		32.5		26.2
Stage 2		51.2		50.6		66.0		60.7
Stage 3		15.7		23.3		1.5		12.6
Stage 4		1.2		1.2		0.0		0.5
Stage 5		0.0		0.0		0.0		0.0
Year 12								
Mean ± SD	783	2.7 ± 0.9	787	2.8 ± 0.9	714	2.1 ± 0.8	712	2.2 ± 0.9
Stage 1, %		10.6		7.4		23.1		22.2
Stage 2		32.4		29.5		44.0		43.7
Stage 3		37.9		40.2		28.2		27.3
Stage 4		17.5		20.6		4.6		6.3
Stage 5		1.5		2.4		0.1		0.6

Table 7.2: Distribution of Tanner Scores for Development of Pubic Hair, Female Breasts, and Male Genitals
(Continued from previous page)

	Females (n=1,135)				Males (n=1,060)			
	Pubic Hair		Breast		Pubic Hair		Genital	
	N	%	n	%	n	%	N	%
Year 13								
Mean ± SD	847	3.3 ± 0.8	845	3.4 ± 0.8	780	2.9 ± 1.0	778	2.8 ± 0.9
Stage 1, %		1.9		1.1		10.1		6.8
Stage 2		12.9		11.7		19.1		27.1
Stage 3		46.4		40.8		43.5		42.7
Stage 4		34.5		39.9		25.8		22.2
Stage 5		4.4		6.5		1.5		1.2
Year 14								
Mean ± SD	930	3.6 ± 0.7	931	3.7 ± 0.8	865	3.5 ± 0.8	858	3.4 ± 0.9
Stage 1, %		0.5		0.0		3.1		3.2
Stage 2		4.6		4.1		7.1		11.2
Stage 3		39.1		33.1		36.4		36.8
Stage 4		47.9		48.1		47.9		44.1
Stage 5		7.9		14.7		5.6		4.8
Year 15								
Mean ± SD	979	3.8 ± 0.8	969	3.9 ± 0.8	919	3.8 ± 0.8	901	3.7 ± 0.8
Stage 1, %		0.4		0.4		1.4		1.3
Stage 2		2.7		3.1		3.5		5.2
Stage 3		28.8		21.1		22.0		27.2
Stage 4		51.4		53.2		58.0		54.7
Stage 5		16.8		22.3		15.1		11.5
Year 16								
Mean ± SD	996	4.0 ± 0.7	995	4.1 ± 0.7	930	4.1 ± 0.7	926	4.0 ± 0.8
Stage 1, %		0.1		0.0		0.3		0.8
Stage 2		2.7		2.5		1.1		2.9
Stage 3		20.2		17.3		11.9		16.9
Stage 4		53.1		51.5		61.6		58.2
Stage 5		23.9		28.7		25.1		21.3

Table 7.3: Distribution of Participants, Intercept, and Slope for the Pubertal Growth Trajectory Classes, Females and Males

	Females (n=1,135)			Males (n=1,060)		
	%	Intercept	Slope	%	Intercept	Slope
Pubic Hair						
Class 1	32.9	0.000	0.969	26.4	-0.626	1.197
Class 2	54.5	0.792	1.322	59.8	0.000	1.611
Class 3	12.7	1.162	1.976	13.8	-0.724	2.377
Breast (females)						
Class 1	23.3	0.000	0.942			
Class 2	25.8	-0.916	1.557			
Class 3	36.6	2.580	1.167			
Class 4	14.3	0.844	2.238			
Genital (males)						
Class 1				5.6	-3.410	1.227
Class 2				35.3	-0.535	1.147
Class 3				51.3	0.329	1.377
Class 4				7.8	0.000	1.942

Table 7.4: Height and BMI at 5 and 8 Years of Age by Pubertal Growth Trajectory Class and Gender

	Height (cm)				BMI (kg/m^2)			
	Year 5		Year 8		Year 5		Year 8	
	n	p-value mean ± SD	n	p-value mean ± SD	n	p-value mean ± SD	n	p-value mean ± SD
Females								
Pubic Hair	808	<0.001	615	0.1090	808	0.0016	615	<0.001[b]
Class 1		106.0 ± 4.8		123.2 ± 5.8		15.4 ± 1.5		15.5 ± 1.7
Class 2		107.2 ± 4.5		124.1 ± 6.0		15.6 ± 1.5		16.0 ± 2.2
Class 3		108.0 ± 4.9		124.8 ± 6.3		16.0 ± 1.4		16.5 ± 1.9
Breast	809	<0.001	615	<0.001	809	<0.001[b]	615	<0.001[b]
Class 1		106.0 ± 4.7		123.2 ± 5.9		15.3 ± 1.6		15.2 ± 1.6
Class 2		106.1 ± 4.5		122.4 ± 5.7		15.3 ± 1.2		15.4 ± 1.3
Class 3		107.5 ± 4.7		124.9 ± 5.9		15.7 ± 1.6		16.2 ± 2.4
Class 4		108.3 ± 4.4		125.5 ± 5.9		16.1 ± 1.5		17.0 ± 2.5
Males								
Pubic Hair	734	<0.001	603	0.0023	734	0.0194	603	0.0100[b]
Class 1		106.6 ± 4.3		123.7 ± 5.8		15.5 ± 1.3		15.6 ± 1.5
Class 2		107.8 ± 4.5		124.8 ± 6.1		15.7 ± 1.5		15.8 ± 1.8
Class 3		109.0 ± 4.6		126.5 ± 5.7		16.0 ± 1.4		16.2 ± 1.4
Genital	734	<0.001	603	<0.001	734	0.1050[b]	603	0.0094[b]
Class 1		106.0 ± 3.5		123.2 ± 5.0		15.4 ± 1.4		15.2 ± 1.1
Class 2		106.9 ± 4.7		123.8 ± 6.2		15.7 ± 1.5		16.0 ± 1.9
Class 3		108.1 ± 4.4		125.2 ± 5.8		15.6 ± 1.3		15.7 ± 1.6
Class 4		109.2 ± 4.3		127.4 ± 6.0		16.0 ± 1.2		16.2 ± 1.4

a ANOVA test to determine whether there was a significant difference in mean height and BMI between groups
b Simulated ANOVA test used because the equal variances assumption was not met

Table 7.5: Regression to Predict Pubertal Development Trajectory Group Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Females

	Age 5 years				Age 8 years			
	Unadjusted (n=808)		Adjusted[a] (n=808)		Unadjusted (n=615)		Adjusted[b] (n=526)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[c]								
3 vs. 1	1.60	(1.25, 2.04)	1.57	(1.22, 2.03)	1.26	(0.94, 1.67)	1.03	(0.57, 1.86)
2 vs. 1	1.34	(1.13, 1.58)	1.34	(1.13, 1.59)	1.14	(0.95, 1.35)	0.93	(0.65, 1.34)
Breast[d]								
4 vs. 1	1.77	(1.36, 2.30)	1.78	(1.37, 2.33)	1.58	(1.18, 2.10)	0.95	(0.52, 1.74)
3 vs. 1	1.43	(1.16, 1.76)	1.39	(1.13, 1.72)	1.33	(1.06, 1.66)	0.83	(0.52, 1.32)
2 vs. 1	1.01	(0.81, 1.27)	0.97	(0.77, 1.22)	0.93	(0.74, 1.17)	0.74	(0.46, 1.20)
BMIZ								
Pubic hair[c]								
3 vs. 1	1.58	(1.24, 2.02)	1.51	(1.17, 1.96)	1.79	(1.35, 2.39)	2.06	(1.10, 3.87)
2 vs. 1	1.13	(0.95, 1.33)	1.09	(0.91, 1.30)	1.31	(1.09, 1.58)	1.58	(1.06, 2.34)
Breast[d]								
4 vs. 1	1.77	(1.36, 2.30)	1.65	(1.25, 2.17)	2.86	(2.08, 3.92)	3.35	(1.74, 6.46)
3 vs. 1	1.35	(1.09, 1.66)	1.25	(1.01, 1.55)	1.88	(1.46, 2.42)	2.56	(1.52, 4.33)
2 vs. 1	1.01	(0.81, 1.27)	1.00	(0.79, 1.27)	1.30	(1.01, 1.68)	1.75	(1.03, 2.97)

a. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). c. Multinomial logistic regression with the outcome being the 3 growth trajectory groups for pubic hair development. d. Multinomial logistic regression with the outcome being the 4 growth trajectory groups for breast development.

Table 7.6: Regression to Predict Pubertal Development Trajectory Group Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Males

	Age 5 years				Age 8 years			
	Unadjusted (n=734)		Adjusted[a] (n=734)		Unadjusted (n=603)		Adjusted[b] (n=500)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[c]								
3 vs. 1	1.89	(1.45, 2.47)	1.78	(1.35, 2.34)	1.81	(1.37, 2.39)	1.57	(0.80, 3.07)
2 vs. 1	1.36	(1.13, 1.63)	1.32	(1.10, 1.60)	1.21	(1.00, 1.45)	1.07	(0.68, 1.67)
Genital[d]								
4 vs. 1	2.34	(1.51, 3.61)	2.19	(1.41, 3.40)	2.01	(1.27, 3.18)	1.99	(0.62, 6.37)
3 vs. 1	1.74	(1.24, 2.45)	1.68	(1.19, 2.38)	1.40	(0.99, 1.99)	1.24	(0.51, 3.05)
2 vs. 1	1.28	(0.91, 1.81)	1.28	(0.90, 1.81)	1.05	(0.74, 1.50)	0.68	(0.28, 1.66)
BMIZ								
Pubic hair[c]								
3 vs. 1	1.42	(1.12, 1.80)	1.43	(1.11, 1.85)	1.57	(1.20, 2.07)	1.00	(0.56, 1.79)
2 vs. 1	1.11	(0.94, 1.32)	1.15	(0.96, 1.37)	1.14	(0.94, 1.38)	0.70	(0.46, 1.05)
Genital[d]								
4 vs. 1	1.53	(1.03, 2.26)	1.49	(0.99, 2.26)	1.98	(1.25, 3.14)	1.40	(0.50, 3.94)
3 vs. 1	1.13	(0.83, 1.55)	1.19	(0.85, 1.66)	1.46	(1.01, 2.11)	1.56	(0.68, 3.56)
2 vs. 1	1.23	(0.89, 1.70)	1.31	(0.93, 1.85)	1.62	(1.11, 2.36)	1.48	(0.64, 3.41)

a. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). c. Multinomial logistic regression with the outcome being the 3 growth trajectory groups for pubic hair development. D. Multinomial logistic regression with the outcome being the 4 growth trajectory groups for genital development.

Table 7.7: Regression to Predict Pubertal Development Group at 12 Years Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Females

	Age 5 years				Age 8 years			
	Unadjusted (n=808)		Adjusted[a] (n=808)		Unadjusted (n=615)		Adjusted[b] (n=526)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[c]								
Earlier vs. medium	1.37	(1.07, 1.76)	1.40	(1.09, 1.81)	1.49	(1.12, 2.00)	2.33	(1.25, 4.35)
Later vs. medium	0.72	(0.59, 0.89)	0.72	(0.59, 0.89)	0.75	(0.60, 0.93)	1.06	(0.68, 1.66)
Missing vs. medium	0.77	(0.62, 0.94)	0.85	(0.68, 1.06)	0.76	(0.61, 0.95)	1.13	(0.69, 1.87)
Breast[d]								
Earlier vs. medium	1.12	(0.89, 1.41)	1.12	(0.88, 1.43)	1.14	(0.88, 1.48)	1.10	(0.63, 1.92)
Later vs. medium	0.66	(0.53, 0.81)	0.65	(0.52, 0.80)	0.74	(0.59, 0.92)	0.96	(0.61, 1.51)
Missing vs. medium	0.73	(0.60, 0.89)	0.80	(0.64, 0.99)	0.75	(0.60, 0.93)	1.01	(0.63, 1.64)
BMIZ								
Pubic hair[c]								
Earlier vs. medium	1.35	(1.06, 1.73)	1.32	(1.02, 1.70)	1.27	(0.97, 1.67)	1.25	(0.68, 2.28)
Later vs. medium	0.91	(0.74, 1.12)	0.96	(0.78, 1.19)	0.83	(0.67, 1.03)	0.73	(0.46, 1.17)
Missing vs. medium	0.88	(0.72, 1.08)	1.11	(0.88, 1.39)	0.81	(0.65, 1.02)	0.85	(0.50, 1.44)
Breast[d]								
Earlier vs. medium	1.18	(0.94, 1.49)	1.16	(0.92, 1.48)	1.35	(1.05, 1.74)	1.68	(0.97, 2.91)
Later vs. medium	0.81	(0.66, 1.00)	0.86	(0.69, 1.07)	0.73	(0.58, 0.92)	0.62	(0.38, 1.01)
Missing vs. medium	0.84	(0.69, 1.03)	1.06	(0.85, 1.32)	0.81	(0.64, 1.01)	0.88	(0.52, 1.48)

a. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). c. Multinomial logistic regression with the outcome being the 3 groups for pubic hair development: earlier, medium (ref.), later. d. Multinomial logistic regression with the outcome being the 3 groups for breast development: earlier, medium (ref.), later.

Table 7.8: Regression to Predict Pubertal Development Group at 12 Years Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Males

	Age 5 years				Age 8 years			
	Unadjusted (n=734)		Adjusted[a] (n=734)		Unadjusted (n=603)		Adjusted[b] (n=500)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
Height								
Pubic hair[c]								
Earlier vs. medium	1.30	(1.05, 1.61)	1.24	(1.00, 1.55)	1.25	(1.00, 1.55)	0.91	(0.55, 1.52)
Later vs. medium	0.78	(0.61, 0.99)	0.78	(0.61, 1.00)	0.87	(0.69, 1.11)	1.02	(0.56, 1.87)
Missing vs. medium	0.97	(0.80, 1.19)	1.02	(0.82, 1.28)	0.85	(0.69, 1.04)	0.64	(0.37, 1.11)
Genital[d]								
Earlier vs. medium	1.21	(0.98, 1.50)	1.18	(0.95, 1.47)	1.18	(0.95, 1.47)	0.82	(0.49, 1.36)
Later vs. medium	0.76	(0.60, 0.97)	0.77	(0.60, 0.98)	0.84	(0.66, 1.06)	1.05	(0.57, 1.92)
Missing vs. medium	0.97	(0.80, 1.19)	1.05	(0.84, 1.31)	0.81	(0.66, 1.00)	0.63	(0.36, 1.10)
BMIZ								
Pubic hair[c]								
Earlier vs. medium	1.05	(0.87, 1.28)	1.01	(0.82, 1.24)	1.29	(1.04, 1.61)	1.43	(0.88, 2.30)
Later vs. medium	0.78	(0.62, 0.98)	0.80	(0.63, 1.01)	0.94	(0.73, 1.21)	1.68	(1.00, 2.84)
Missing vs. medium	0.79	(0.65, 0.95)	0.96	(0.77, 1.18)	0.80	(0.64, 0.99)	1.07	(0.63, 1.82)
Genital[d]								
Earlier vs. medium	0.96	(0.79, 1.16)	0.92	(0.75, 1.13)	1.04	(0.83, 1.29)	0.95	(0.59, 1.53)
Later vs. medium	0.92	(0.74, 1.15)	0.93	(0.74, 1.18)	0.93	(0.73, 1.19)	0.85	(0.51, 1.42)
Missing vs. medium	0.79	(0.65, 0.95)	0.95	(0.77, 1.18)	0.74	(0.59, 0.92)	0.79	(0.47, 1.34)

a. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). c. Multinomial logistic regression with the outcome being the 3 groups for pubic hair development: earlier, medium (ref.), later. d. Multinomial logistic regression with the outcome being the 3 groups for genital development: earlier, medium (ref.), later.

Table 7.9: Sensitivity Analysis (METHOD 1[a]): Regression to Predict Pubertal Development Trajectory Group Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Females

	Age 5 years				Age 8 years			
	Unadjusted (n=808)		Adjusted[b] (n=808)		Unadjusted (n=615)		Adjusted[c] (n=526)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[d]								
3 vs. 1	1.54	(1.22, 1.94)	1.54	(1.21, 1.97)	1.31	(0.99, 1.72)	1.16	(0.66, 2.03)
2 vs. 1	1.31	(1.09, 1.57)	1.33	(1.10, 1.60)	1.14	(0.94, 1.38)	0.98	(0.66, 1.45)
Breast[e]								
4 vs. 1	1.76	(1.37, 2.26)	1.75	(1.36, 2.26)	1.52	(1.16, 1.99)	0.98	(0.55, 1.74)
3 vs. 1	1.34	(1.06, 1.69)	1.29	(1.02, 1.63)	1.29	(1.00, 1.65)	0.79	(0.47, 1.34)
2 vs. 1	1.03	(0.81, 1.30)	0.97	(0.76, 1.24)	0.97	(0.75, 1.24)	0.75	(0.44, 1.26)
BMIZ								
Pubic hair[d]								
3 vs. 1	1.40	(1.11, 1.76)	1.33	(1.04, 1.69)	1.74	(1.32, 2.31)	2.95	(1.60, 5.43)
2 vs. 1	1.04	(0.87, 1.25)	1.00	(0.82, 1.20)	1.25	(1.02, 1.53)	1.67	(1.07, 2.59)
Breast[e]								
4 vs. 1	1.63	(1.27, 2.10)	1.49	(1.14, 1.93)	2.95	(2.16, 4.03)	6.00	(3.05, 11.81)
3 vs. 1	1.26	(0.99, 1.59)	1.15	(0.90, 1.48)	1.90	(1.43, 2.52)	2.83	(1.53, 5.26)
2 vs. 1	1.02	(0.80, 1.30)	0.99	(0.77, 1.27)	1.54	(1.16, 2.03)	2.52	(1.36, 4.65)

a. A sensitivity analysis was performed to determine whether reversion in the data affected the conclusions of the analysis. Reversion occurred when a participant reported a lower Tanner score one year than they had in a previous wave. The regression analysis presented in this table was carried out using an alternative dataset, which assumed that once a certain level of development on the Tanner scale was reported, the child had to stay at that level of development until they reported a higher Tanner score, in effect assuming that the earlier reported value was true. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. c. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). d. Multinomial logistic regression with the outcome being the 3 growth trajectory groups for pubic hair development. e. Multinomial logistic regression with the outcome being the 4 growth trajectory groups for breast development.

Table 7.10: Sensitivity Analysis (METHOD 2[a]): Regression to Predict Pubertal Development Trajectory Group Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Females

	Age 5 years				Age 8 years			
	Unadjusted (n=808)		Adjusted[b] (n=808)		Unadjusted (n=615)		Adjusted[c] (n=526)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[d]								
3 vs. 1	1.49	(1.17, 1.89)	1.45	(1.13, 1.86)	1.26	(0.94, 1.70)	0.89	(0.49, 1.63)
2 vs. 1	1.20	(1.02, 1.41)	1.20	(1.02, 1.42)	1.03	(0.87, 1.23)	0.77	(0.54, 1.10)
Breast[e]								
4 vs. 1	1.69	(1.33, 2.15)	1.71	(1.34, 2.19)	1.48	(1.13, 1.93)	0.85	(0.48, 1.52)
3 vs. 1	1.39	(1.15, 1.70)	1.36	(1.12, 1.67)	1.29	(1.04, 1.58)	0.76	(0.49, 1.18)
2 vs. 1	1.10	(0.88, 1.38)	1.03	(0.82, 1.29)	0.98	(0.77, 1.23)	0.61	(0.37, 1.00)
BMIZ								
Pubic hair[d]								
3 vs. 1	1.51	(1.19, 1.91)	1.45	(1.13, 1.87)	1.77	(1.33, 2.37)	2.17	(1.14, 4.12)
2 vs. 1	1.04	(0.88, 1.22)	1.02	(0.86, 1.21)	1.20	(1.00, 1.44)	1.60	(1.08, 2.37)
Breast[e]								
4 vs. 1	1.81	(1.42, 2.31)	1.76	(1.36, 2.27)	2.80	(2.08, 3.77)	2.53	(1.38, 4.63)
3 vs. 1	1.34	(1.10, 1.64)	1.27	(1.03, 1.56)	1.84	(1.45, 2.33)	1.81	(1.13, 2.90)
2 vs. 1	1.16	(0.92, 1.46)	1.13	(0.89, 1.43)	1.53	(1.18, 1.98)	1.38	(0.82, 2.32)

a. A sensitivity analysis was performed to determine whether reversion in the data affected the conclusions of the analysis. Reversion occurred when a participant reported a lower Tanner score one year than they had in a previous wave. The regression analysis presented in this table was carried out using an alternative dataset, in which reversion was corrected by assigning the lower value to the previous value, thereby assuming that the later value was true. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. c. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). d. Multinomial logistic regression with the outcome being the 3 growth trajectory groups for pubic hair development. e. Multinomial logistic regression with the outcome being the 4 growth trajectory groups for breast development.

Table 7.11: Sensitivity Analysis (METHOD 1[a]): Regression to Predict Pubertal Development Trajectory Group Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Males

	Age 5 years				Age 8 years			
	Unadjusted (n=734)		Adjusted[b] (n=734)		Unadjusted (n=603)		Adjusted[c] (n=500)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[d]								
3 vs. 1	1.97	(1.52, 2.56)	1.87	(1.43, 2.44)	1.91	(1.46, 2.50)	1.63	(0.85, 3.11)
2 vs. 1	1.46	(1.21, 1.76)	1.43	(1.18, 1.73)	1.32	(1.09, 1.59)	1.05	(0.67, 1.65)
Genital[e]								
4 vs. 1	2.03	(1.52, 2.71)	1.90	(1.41, 2.54)	1.86	(1.38, 2.51)	1.27	(0.63, 2.58)
3 vs. 1	1.74	(1.39, 2.19)	1.64	(1.30, 2.07)	1.40	(1.11, 1.76)	0.98	(0.56, 1.70)
2 vs. 1	1.34	(1.09, 1.64)	1.29	(1.05, 1.60)	1.13	(0.92, 1.38)	0.76	(0.46, 1.25)
BMIZ								
Pubic hair[d]								
3 vs. 1	1.35	(1.07, 1.70)	1.38	(1.08, 1.77)	1.55	(1.19, 2.01)	1.26	(0.72, 2.21)
2 vs. 1	1.11	(0.93, 1.32)	1.13	(0.94, 1.35)	1.17	(0.96,1.42)	0.84	(0.56, 1.28)
Genital[e]								
4 vs. 1	1.08	(0.84, 1.39)	1.01	(0.77, 1.32)	1.17	(0.87, 1.56)	1.12	(0.58, 2.15)
3 vs. 1	1.14	(0.93, 1.39)	1.08	(0.87, 1.34)	1.18	(0.94, 1.48)	1.09	(0.66, 1.81)
2 vs. 1	1.10	(0.91, 1.33)	1.09	(0.89, 1.33)	1.15	(0.93, 1.42)	1.25	(0.80, 1.97)

a. A sensitivity analysis was performed to determine whether reversion in the data affected the conclusions of the analysis. Reversion occurred when a participant reported a lower Tanner score one year than they had in a previous wave. The regression analysis presented in this table was carried out using an alternative dataset, which assumed that once a certain level of development on the Tanner scale was reported, the child had to stay at that level of development until they reported a higher Tanner score, in effect assuming that the earlier reported value was true. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. c. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). d. Multinomial logistic regression with the outcome being the 3 growth trajectory groups for pubic hair development. e. Multinomial logistic regression with the outcome being the 4 growth trajectory groups for genital development.

Table 7.12: Sensitivity Analysis (METHOD 2[a]): Regression to Predict Pubertal Development Trajectory Group Based on Height-for-Age Z Score and Body Mass Index Z Score at Age 5 Years and 8 Years, Males

	Age 5 years				Age 8 years			
	Unadjusted (n=734)		Adjusted[b] (n=734)		Unadjusted (n=603)		Adjusted[c] (n=500)	
	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI	Relative Risk Ratio	95% CI
HAZ								
Pubic hair[d]								
3 vs. 1	1.67	(1.28, 2.18)	1.58	(1.19, 2.08)	1.59	(1.21, 2.11)	1.19	(0.61, 2.32)
2 vs. 1	1.42	(1.19, 1.71)	1.39	(1.16, 1.67)	1.30	(1.08, 1.55)	1.08	(0.70, 1.68)
Genital[e]								
4 vs. 1	2.09	(1.56, 2.80)	2.03	(1.50, 2.75)	1.83	(1.35, 2.47)	1.20	(0.56, 2.57)
3 vs. 1	1.46	(1.10, 1.94)	1.50	(1.12, 2.01)	1.26	(0.95, 1.68)	0.91	(0.43, 1.92)
2 vs. 1	1.25	(0.94, 1.67)	1.28	(0.95, 1.72)	1.12	(0.84, 1.50)	0.79	(0.38, 1.67)
BMIZ								
Pubic hair[d]								
3 vs. 1	1.26	(0.99, 1.60)	1.29	(1.00, 1.67)	1.38	(1.04, 1.81)	0.99	(0.54, 1.80)
2 vs. 1	1.10	(0.93, 1.29)	1.12	(0.93, 1.33)	1.14	(0.94, 1.37)	0.79	(0.53, 1.18)
Genital[e]								
4 vs. 1	0.95	(0.73, 1.23)	0.92	(0.69, 1.23)	1.22	(0.91, 1.66)	0.96	(0.49, 1.85)
3 vs. 1	0.83	(0.64, 1.08)	0.89	(0.67, 1.18)	1.08	(0.80, 1.45)	1.14	(0.60, 2.16)
2 vs. 1	0.93	(0.71, 1.21)	0.98	(0.74, 1.30)	1.19	(0.88, 1.61)	1.00	(0.52, 1.91)

a. A sensitivity analysis was performed to determine whether reversion in the data affected the conclusions of the analysis. Reversion occurred when a participant reported a lower Tanner score one year than they had in a previous wave. The regression analysis presented in this table was carried out using an alternative dataset, in which reversion was corrected by assigning the lower value to the previous value, thereby assuming that the later value was true. b. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). Height-for-age z score (HAZ) at 5y is included in the model without any adjustments. Body mass index z score (BMIZ) at 5y is adjusted by controlling for HAZ at 5y. c. Adjusted for ethnicity and quintiles of caretaker monthly income (in Rands). HAZ at 8y is included in the model as the residual produced when HAZ at 8y is regressed on HAZ at 5y (HAZ and BMIZ at 5y are controlled for in this model). BMIZ at 8y is included in the model as the residual produced when BMIZ at 8y is regressed on BMIZ at 5y (HAZ and BMIZ at 5y and HAZ at 8y are controlled for in this model). d. Multinomial logistic regression with the outcome being the 3 growth trajectory groups for pubic hair development. e. Multinomial logistic regression with the outcome being the 4 growth trajectory groups for genital development.

Figure 7.1: Latent Class Growth Analysis and Latent Growth Curve Modeling of Pubertal Development Trajectories

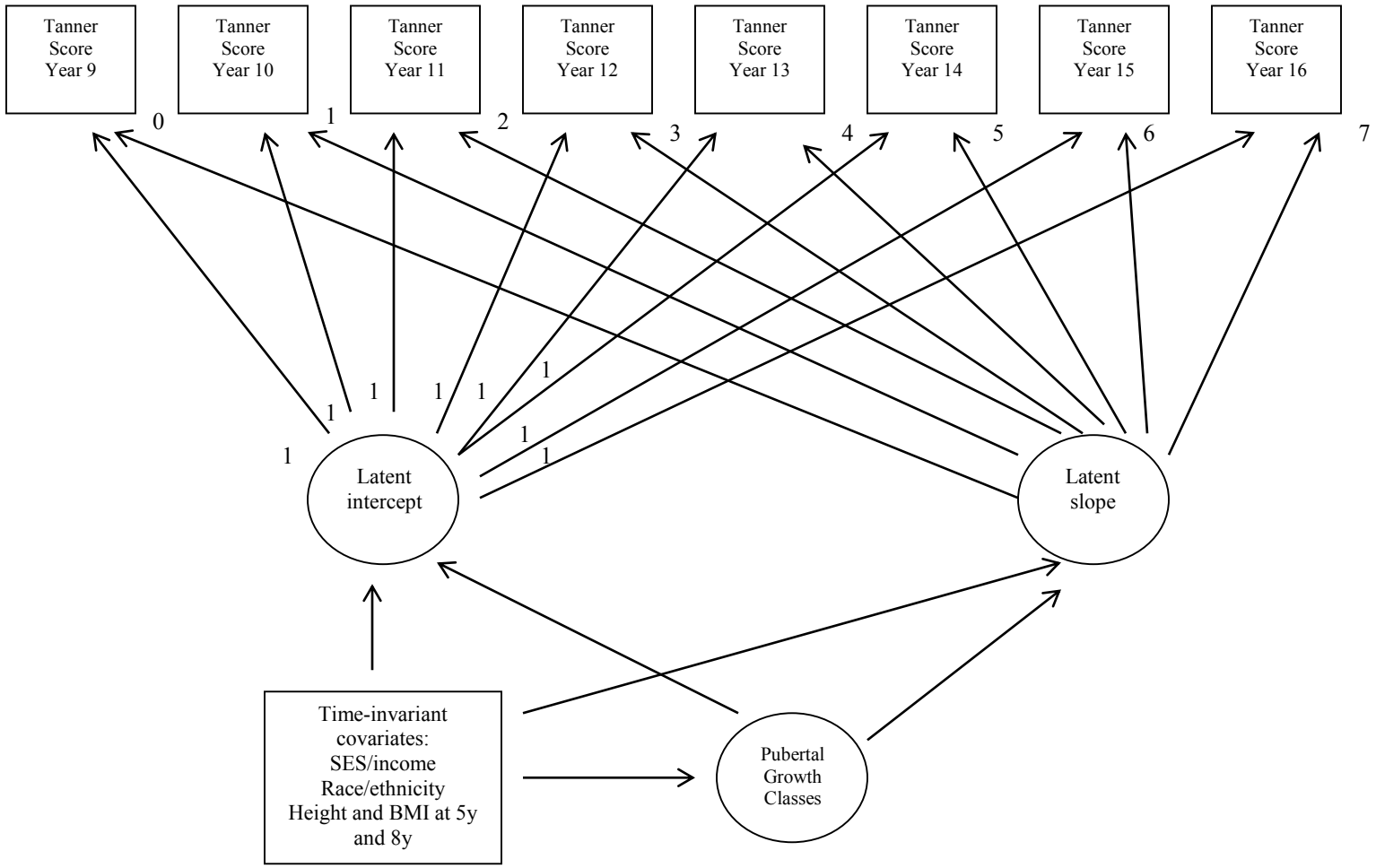


Fig. 1. Distinct growth trajectory classes with different latent intercepts and slopes are identified based on common patterns in Tanner score development from 9-16 years of age. Time-invariant covariates such as income, ethnicity, and height and BMI at 5y and 8y can be used to predict group membership. The factor loadings on the intercept growth factor are all fixed at 1.0, and the factor loadings on the slope growth factor, or time scores, are set at 0 through 7 to allow for a linear growth trajectory and equal time intervals between observation time points.

Figure 7.2: Tanner Score for Pubic Hair Development, by Growth Trajectory Class and Age, Females

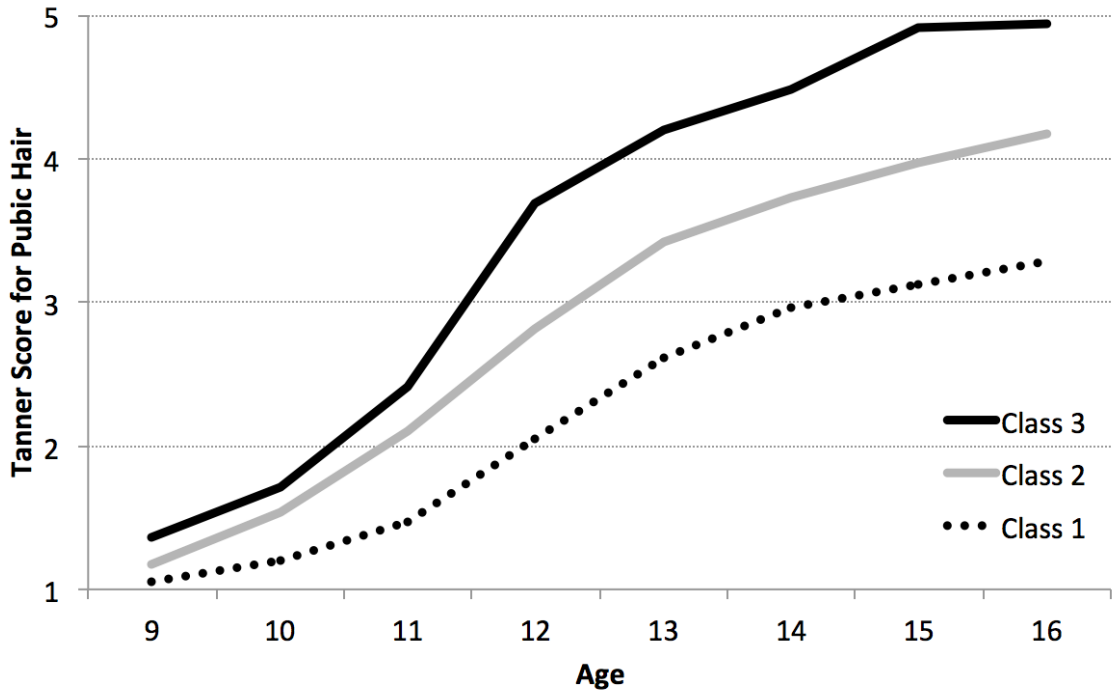


Figure 7.3: Tanner Score for Breast Development, by Growth Trajectory Class and Age, Females

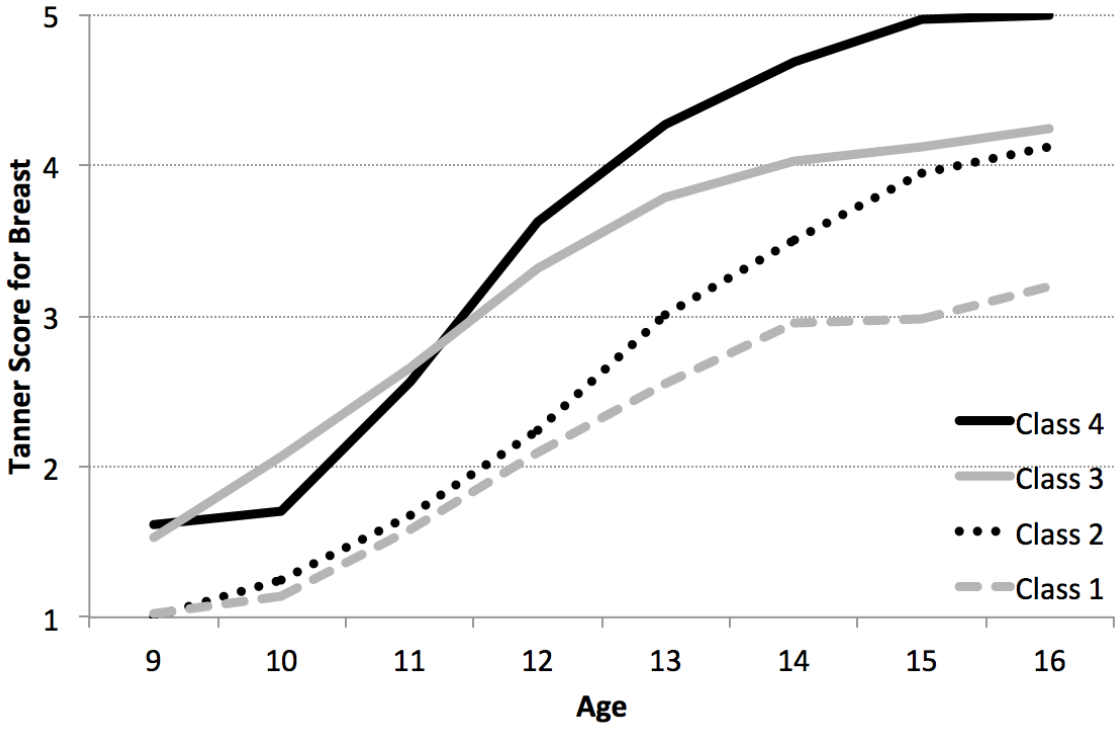


Figure 7.4: Tanner Score for Pubic Hair Development, by Growth Trajectory Class and Age, Males

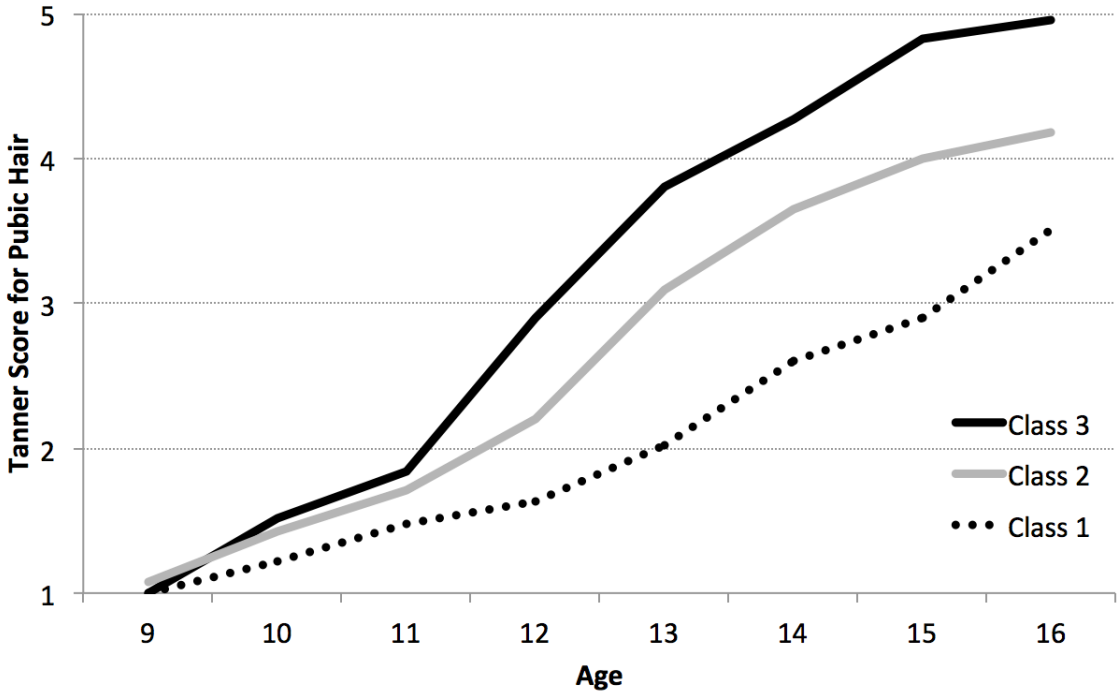
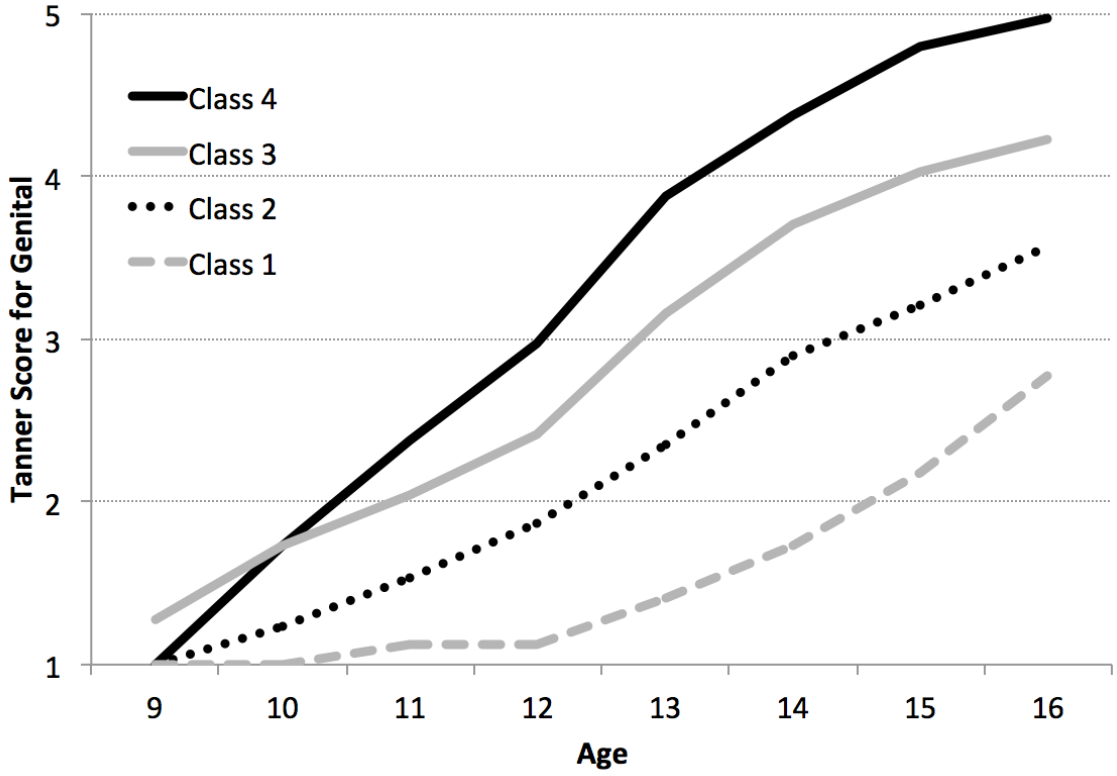


Figure 7.5: Tanner Score for Genital Development, by Growth Trajectory Class and Age, Males



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Chapter 8: Association of Pubertal Timing and Trajectory with Adult Height and Body Mass Index in South African Adolescents

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Abbreviations used: body mass index (BMI); Tanner Sexual Maturation Scale (SMS); Latent Class Growth Analysis (LCGA); Relative risk ratio (RRR); Odds ratio (OR)

Abstract

Background/Objective: Early puberty has been linked to greater risk of overweight and obesity in adulthood, particularly among females. However, childhood body mass index may confound this relationship. Better understanding the relationship between pubertal timing and tempo and adult anthropometric outcomes is important, given global trends toward earlier onset of puberty. We explored the relationship between adult height and body mass index and measures of pubertal development in a South African birth cohort.

Methods: We analyzed data from 928 males and 990 females participating in the Birth-to-Twenty cohort in Soweto, South Africa. Body mass index (BMI) at young adulthood (17-18y) was calculated as weight (kg) divided by height squared (m^2). World Health Organization cut-off points for BMI were used to classify adults as normal or underweight (BMI<25.0; abbrv. NU), overweight but not obese (BMI 25.0-29.9; ONO), obese (BMI≥30.0; OB), and overweight or obese (BMI≥25.0; OO). Females self-reported age at menarche. The development of genitals, breasts, and pubic hair was recorded from ages 9y to 16y using the five stages of the Tanner Sexual Maturation Scale (SMS). We used Latent Class Growth Analysis to identify trajectory classes (puberty tempo) for the development of genitals, breasts, and pubic hair, and characterized children as earlier, medium, or later developers (puberty timing) based on the median Tanner SMS score at 12y. Linear, logistic, and multinomial logistic regression were used to determine whether puberty timing and tempo were associated with adult height and BMI. In separate models, we controlled for height and BMI at 8y.

Results: When childhood BMI was not controlled for, the timing and tempo of pubertal development among girls was significantly associated with adult risk of OO. Risk of being OO in adulthood was increased among girls in the fastest class for the tempo of pubic hair (odds ratio (OR)=2.1; $p<0.01$) and breast (OR=6.1; $p<0.001$) development. Girls at a higher stage of pubic hair development at 12y had an increased risk of OB (relative risk ratio (RRR)=2.2; $p=0.02$), while those at a lower stage of breast development had a decreased risk of OO (OR=0.5; $p<0.01$). Each additional year in the age at menarche significantly decreased the risk of OO (OR=0.8; $p<0.001$). However, these relationships mostly disappeared when childhood BMI was included as a confounder in the models. Controlling for height at 8y, the timing and tempo of puberty in girls were significantly associated with adult height. Shorter adult stature was found in girls with earlier breast development at 12y (-2.2 cm; $p<0.001$), and among girls with the fastest tempo for breast development (-2.2 cm; $p<0.01$) and pubic hair development (-1.8 cm; $p<0.01$). Each additional year in the age at menarche was associated with a 1.0 cm increase in adult height ($p<0.001$). Among males, controlling for BMI at 8y, the risk of being overweight or obese at adulthood was significantly increased among those in the fastest class for the tempo of pubic hair development (OR=3.7; $p=0.04$); the timing and tempo of male genital development had no association. Males in the fastest class for tempo of genital development were significantly shorter at adulthood (-2.3 cm; $p=0.04$), but the tempo for pubic hair development was not associated with adult height. Timing of male pubertal development, as determined by pubic hair and genital stage at 12y, was unrelated to adult height.

Conclusion: When childhood body mass index is controlled for, the timing and tempo of breast and pubic hair development in girls are not associated with adult risk of overweight or obesity. Controlling for childhood height, girls with earlier pubertal development and faster pubertal development have a reduced adult height. Males with faster pubic hair development have an increased risk of adult overweight or obesity, and those with faster genital development are shorter at adulthood.

Introduction

Puberty is a period of rapid changes in stature and body composition. During puberty, both males and females experience acceleration in linear growth velocity (1). Puberty leads to sexual dimorphism, with males gaining greater amounts of muscle and skeletal mass, and females acquiring more fat mass (1). Research has shown that the timing of pubertal onset and associated physical changes may have implications for adult body composition.

Early menarche has been linked to shorter adult stature (2-5). Linear growth slows considerably after puberty, and girls who experience earlier menarche may lose out on several years of rapid pre-pubertal growth, resulting in a reduced adult height (3). Additionally, women who experience menarche at an earlier age have been found to have a greater adult body mass index (BMI) and significantly increased risk of obesity in adulthood (3-9).

Given rising obesity prevalence globally (10), the potential influence of puberty has garnered much attention. However, few studies linking early puberty to higher adult BMI have been able to address the potential causal nature of this relationship, and the nature of this relationship is the subject of debate (8). Research has also shown there is an association between higher BMI in childhood or adolescence and earlier onset of puberty among girls (11-19). Childhood BMI tends to track into adulthood (20-22), and studies have attempted to determine whether the inverse association between age at menarche and adult body mass index is due to the influence of childhood BMI (8, 15, 23). One

study found that the relationship between age at menarche and adult BMI was not explained by childhood BMI (8), while two other studies found that this relationship was strongly attenuated by childhood BMI (9, 23).

It is important to better understand the relationship between pubertal development and adult anthropometric outcomes, given secular trends in the reduction of menarcheal age (24, 25), and trends toward earlier development of breasts and pubic hair among girls (18, 26-29). Some data also suggest boys are experiencing earlier genital and pubic hair development (28-30). These trends have occurred concurrently with a global rise in overweight and obesity in adults (10), giving rise to speculation that the two could be linked (8).

The relationship between pubertal development and adult anthropometric outcomes has been primarily studied among girls, and has focused on the timing of pubertal onset, defined narrowly as age at menarche. This relationship has been less studied among boys, and much less is known about this relationship in the context of other indicators of puberty, such as the development of secondary sexual characteristics like breasts, genitals, and pubic hair. Additionally, few studies have explored the association between the tempo or overall trajectory of pubertal development and adult anthropometric outcomes, and few studies have had the longitudinal data necessary to account for the role of childhood anthropometric measures.

We address these gaps by using longitudinal data from a South African cohort of males and females to explore the relationship between adult anthropometric outcomes – height and body mass index – and several indicators of pubertal development, including age at menarche and the timing and tempo of the development of secondary sexual characteristics.

Methods

We analyzed data from the Birth-to-Twenty study, a birth cohort initiated in 1990 in Soweto, an urban township in South Africa. Detailed information on this cohort has been published elsewhere (31). The cohort enrolled 3273 children who were born during a six-week period in early 1990. Participants were predominantly black, from families with a low socioeconomic status. The prospective study was designed to track the growth, health, well-being and educational achievement of the children. Throughout the study, participants or their caregivers provided written informed consent and ethical approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects (approval ID #M010556).

Weight at birth and weight and length/height at subsequent rounds were measured using standard procedures (32). At birth and in the months immediately following birth, data on demographic and socioeconomic variables, such as the child's ethnicity and caretaker monthly income (in Rands), were collected. At ages 9 through 16 years, pubertal development was assessed with the Tanner Sexual Maturation Scale (SMS), the most commonly used standard for evaluating pubertal stage in both clinical and research

settings (33). The Tanner SMS consists of drawings of five progressive stages in the development of secondary sexual characteristics—breasts in females, genitals in males, and pubic hair in both genders (34, 35). The drawings are accompanied by written descriptions of each stage. The stages range from 1 (pre-pubertal) to 5 (post-pubertal), with stage 2 representing the onset of puberty. From ages 9-11 years, a trained health care professional administered the Tanner SMS. Participants self-rated their pubertal development using Tanner SMS from ages 12-16 years, after self-assessment using the Tanner SMS was validated against expert Tanner ratings in a comparable group of South African adolescents (36). Girls self-reported their age at menarche.

Data Management

Participants were included in the analysis if they had a least one Tanner SMS measurement between 9-16 years, as well as valid height and weight measurements at young adulthood (17-18 years of age). This resulted in an analytical sample of 1,918 participants. (Analyses that controlled for childhood measures reduced the sample size to 1,085). Using weight and height measurements at 5 years, 8 years, and adulthood, body mass index (BMI) values were calculated as weight (kg) divided by height squared (m^2). At adulthood, participants with a BMI<25.0 were classified as normal or underweight (hereafter abbreviated as NU), those with a BMI 25.0-29.9 were overweight but not obese (ONO), and those with BMI≥30.0 were classified as obese (OB) (37-39). The analyses with males were run with one category for overweight or obese (OO) (BMI≥25.0), as overweight and obesity were less prevalent among males, so the categories were

combined to enhance sample size. Caretaker monthly income was categorized into quintiles.

We used Mplus to perform Latent Class Growth Analysis (LCGA) in order to group participants into distinct classes based on a common developmental trajectory for the Tanner SMS indicators of pubertal status. We conducted separate pubertal development trajectory analyses for females (breast and pubic hair development), and for males (genital and pubic hair development). Details of this analysis were described in **Chapter 7**. Among females, LCGA resulted in 3 trajectory classes for the development of pubic hair and 4 classes for breast development. Among males, 3 trajectory classes were identified for the development of pubic hair and 4 classes for genital development. The classes were numbered 1-3 and 1-4, with 1 representing the slowest tempo of progression through the Tanner stages and the lowest mean Tanner score at 16 years; higher classes have progressively faster tempos for pubertal development and higher mean Tanner scores at 16 years.

Using an extension of the Wilcoxon rank-sum test, we tested for linear trend to determine if mean adult height and BMI systematically increase or decrease across classes. We used the chi-square test to determine differences between classes in the proportion of those who were NU, ONO, and OB. For females, we used multinomial logistic regression to determine the association between the Tanner pubertal trajectory classes and the three adult BMI categories: NU, ONO, and OB. Logistic regression was used to determine the association between the pubertal trajectory classes and BMI status as a dichotomous

outcome: NU vs. OO. For males, this relationship was only modeled as a dichotomous outcome. Relative risk ratios (RRR) are presented for the multinomial logistic regression models and odds ratios are presented for the logistic regression models. The RRRs produced by multinomial logistic regression are nearly identical to odds ratios generated in logistic regression. The relationship between adult height and pubertal trajectory classes was modeled using linear regression, with corresponding β coefficients presented. For females, we also ran these models separately to explore the relationship between age at menarche and adult height and BMI status. The RRRs, ORs, and βs are presented as unadjusted estimates, as well as adjusted for ethnicity and quintiles of caretaker monthly income. It is known that pubertal development is influenced by ethnicity (12, 14, 15, 19, 26) and socioeconomic status (40, 41). In the models predicting BMI category, we controlled for adult height to separate the relationship between pubertal development and BMI from its relationship with height. Additionally, we present separately the results of models that control for these covariates, as well as the effect of childhood anthropometric measures. In models predicting adult BMI status, we controlled for BMI at 8 years of age, and in models predicting adult height, we controlled for height at 8 years.

The LCGA analysis illustrates the overall trajectory and tempo for pubertal development in this population. However, in order to make more direct comparisons with the existing literature, we conducted a separate analysis of the timing of pubertal development. We created an indicator to represent the timing of pubertal development, by comparing the children's Tanner scores at 12 years of age to that of their peers in the cohort. Children who were at the median score (which was also the modal score) for Tanner pubic hair,

breast, and genital development at 12y, were categorized as being at a medium level of development, and therefore became the reference category. Those with a lower score were considered later developers, and those with a higher score were considered earlier developers. Details of the creation of this indicator were described in **Chapter 7**. Using the three categories of pubertal development at 12y, we repeated the regression analyses to determine whether being at an earlier stage of development at 12 years was associated with adult height and BMI status.

Lastly, to better understand whether puberty is a mediator on the pathway between childhood and adult anthropometric measures, we performed a mediation analysis. We regressed adult BMI on child BMI and presented this unadjusted coefficient. We then adjusted this estimate by running separate models that controlled for each of our measures of the timing and tempo of puberty. An attenuation of the relationship between adult and childhood BMI when puberty is included in the model would indicate that puberty may be a mediator on this pathway. We performed the same mediation analysis with adult and childhood height. This method was used previously in a study that sought to elucidate these pathways (8).

We used Mplus 7.3 (Muthén & Muthén, Los Angeles, California) to perform the Latent Class Growth Analysis, and STATA 13.0 (StataCorp, College Station, Texas) for all other analyses.

Results

The study sample was 52% female (n=990) and 48% male (n=928) (**Table 8.1**). The large majority (85%) of participants were Black, with other represented groups including white (3%), Indian (1%) and coloured or mixed-ancestral (11%) children. Those who were not included in the analysis were similar with respect to ethnicity, caretaker income, and height and BMI at adulthood. Mean adult height was 159.6 cm among females and 171.2 cm among males, and mean BMI was 23.1 kg/m^2 among females and 20.6 kg/m^2 among males. Seventy-two percent of females were NU, while 19% were ONO, and 9% were OB at adulthood. Among males, 92% were NU, with 6% ONO and 3% OB at adulthood. The average age of menarche was 12.7 years.

Among females, there was no trend toward increasing or decreasing mean adult height across classes of pubic hair development ($p=0.8$); there was, however, a significant trend across classes of breast development, as classes with a slower tempo for breast development had a higher mean adult height ($p=0.04$) (**Table 8.2**). Mean adult BMI increased across pubic hair trajectory classes 1-3, meaning classes with a faster tempo for pubic hair development had a higher adult BMI ($p<0.001$). The same was true across classes of breast development ($p<0.001$). The faster pubertal tempo classes also had greater proportions of females who were ONO or OB ($p<0.001$). There was no trend toward increasing or decreasing mean adult height across stages of pubic hair ($p=0.9$) or breast ($p=0.08$) development at 12 years. However, mean adult BMI increased as stage of pubic hair ($p<0.01$) and breast ($p<0.001$) development increased at 12 years.

Among males, mean adult height increased across pubic hair development classes 1-3 ($p<0.001$), and those in classes 3 and 4 for genital development were taller as adults ($p<0.001$) (**Table 8.3**). Mean adult BMI also increased across classes of male pubic hair ($p<0.001$), and genital development ($p=<0.001$). The OO status was more prevalent in males in the faster tempo classes for pubic hair development ($p<0.001$), but not genital development ($p=0.5$). There was no trend toward increasing or decreasing mean adult height across stages of pubic hair ($p=0.06$) or genital ($p=0.1$) development at 12 years. However, mean adult BMI increased as stage of pubic hair ($p<0.001$) and genital ($p=0.02$) development increased at 12 years.

For females, when the regression models were run without BMI at 8y, several significant associations were found between the timing and tempo of puberty and adult BMI. Females in the fastest class for the tempo of pubic hair development had a significantly increased odds ratio (OR) for being OO vs. NU (**Table 8.4**). The same was true for being in the two fastest classes for breast development. When the risk of overweight and obesity were modeled separately, being in a faster class for pubic hair development significantly increased the relative risk ratio (RRR) for being OB vs. NU, but was not associated with the risk of being ONO vs. NU. Being in the two fastest classes for breast development significantly increased the risk of being OB and the risk of being ONO vs. NU. Girls who were at a higher stage of pubic hair development at 12 years had an increased RRR for being OB, while girls who were at a lower stage of breast development had a significantly decreased risk for being ONO and OB, and decreased odds of being OO. As age at menarche increased, the RRR for being ONO and OB

decreased, as did the odds ratio for being OO. However, when BMI at 8y was included in the model, only one significant association remained. Controlling for BMI at 8y, girls in the fastest class for the tempo of breast development had a significantly increased OR for being OO vs. NU and increased RRR for being ONO vs. NU.

Among males, the genital development classes and stage of genital development at 12 years were not associated with the odds of being OO vs. NU (**Table 8.5**). Being at a higher stage of pubic hair development at 12 years and being in the fastest class for the tempo of pubic hair development significantly increased the odds ratio for being OO vs. NU. However, when BMI at 8y was included in the model, only the trajectory class for pubic hair development (3 vs. 1) remained significant (OR=3.7; p=0.04).

Among girls, the relationship between the timing and tempo of puberty and adult height was strengthened when height at 8 years was included in the model. Controlling for height at 8 years, girls in the fastest class for tempo of pubic hair development and in the two fastest classes for breast development had significantly decreased adult height (**Table 8.6**). Being at a higher stage of breast development at 12 years was associated with a significant decrease in adult height, and being at a lower stage of pubic hair or breast development at 12 years was associated with an increase in adult height. For each additional year in the age at menarche, adult height increased by 1.00 cm ($p< 0.001$).

When height at 8 years was included in the regression, males in the fastest class for the tempo of genital development were significantly shorter at adulthood, whereas the classes

for pubic hair development were not associated with adult height (**Table 8.7**). Pubic hair and genital stage at 12 years were unrelated to adult height among males.

Among females, we regressed adult BMI on BMI at 5 years and 8 years and found β coefficients of 1.77 ($p<0.001$) and 1.48 ($p<0.001$), respectively (**Table 8.8**). In general, these associations were not attenuated when we controlled for age at menarche and indicators of the timing and tempo of development of secondary sexual characteristics. However, the coefficients were slightly attenuated to 1.69 ($p<0.001$) and 1.42 ($p<0.001$), respectively, when we controlled for breast development trajectory classes. The relationship between adult BMI and childhood BMI was not attenuated in males when we controlled for pubertal development. In both genders, the relationship between adult height and child height was not attenuated by controlling for pubertal development.

Discussion

In a South African cohort of males and females, we explored the relationship between adult height and body mass index at 17-18 years and several indicators of pubertal development, including age at menarche and the timing and tempo of the development of secondary sexual characteristics. In analyses that did not control for body mass index at 8 years, we found that both the timing and tempo of pubertal development in girls were associated with adult risk of overweight or obesity. However, when we controlled for BMI at 8 years, we found that only one significant association remained. Girls in the fastest class for the tempo of breast development had increased odds of being overweight or obese in early adulthood.

Controlling for height at 8 years, the timing and tempo of pubertal development in girls were both significantly associated with adult height. Girls in the faster classes for tempo of pubic hair and breast development had significantly decreased adult height. Additionally, shorter adult stature was associated with being at a higher stage of breast development at 12 years, whereas taller adult stature was associated with being at a lower stage of pubic hair or breast development at 12 years. There was a strong, positive association between the age at menarche and adult height.

The relationship between the timing and tempo of puberty and adult BMI was not as strong among males, and controlling for childhood BMI had less of an impact on this relationship, as compared to females. After controlling for BMI at 8 years, we found that males in the fastest class for the tempo of pubic hair development had significantly increased odds of being overweight or obese at adulthood, whereas the timing and tempo of male genital development were not associated with overweight or obesity risk. Males with a faster tempo for genital development were significantly shorter at adulthood, but the tempo for pubic hair development was not associated with adult height. The timing of male pubertal development, as determined by pubic hair and genital stage at 12 years, was unrelated to adult height.

Our results are generally consistent with the literature on pubertal development and adult anthropometric outcomes. However, this relationship has primarily been studied among females, with a focus on the timing of puberty, defined as age at menarche. Several

studies have shown that early menarche is associated with shorter adult stature (2-4, 42). The pace of linear growth declines significantly after puberty, and girls who experience earlier menarche may miss out on several years of rapid pre-pubertal growth, resulting in a reduced adult height (3). Therefore, later onset of puberty may give girls additional time to accumulate increases in stature.

Additionally, several studies have found that women who experience menarche at an earlier age have a greater adult body mass index and significantly increased risk of obesity in adulthood (3, 4, 6-9, 23, 42-44). It has been hypothesized that this could be due to an earlier shift toward positive energy balance among early-maturing girls, who have met their growth needs (6). This relationship may also be explained by the fact that girls with early menarche have higher levels of circulating estrogen, a hormone that promotes the accumulation of body fat (4). The shorter adult stature in those with early puberty could also play a role in this association, since body mass index is a ratio of weight for height.

However, the potential causal nature of this relationship is not clear. We also know from numerous studies that there is an association between higher BMI in childhood or adolescence and earlier onset of puberty among girls (11-19). Childhood BMI tends to track into adulthood (20-22), and a few studies have attempted to determine whether the inverse association between age at menarche and adult body mass index is due to the influence of childhood BMI (8, 15, 23). In one study, researchers controlled for childhood BMI, and found that the relationship between age at menarche and adult BMI

was not confounded by childhood BMI (8). However, two other studies, one of which also adjusted for childhood BMI as a confounder (9), found that this relationship was strongly influenced by childhood BMI (9, 23). Freedman et al concluded that the importance of early menarche in adult obesity has been overestimated, based on their finding that 60-75% of the effect of menarcheal age on adult obesity could be attributed to the influence of childhood obesity on both age at menarche and adult obesity (9). Similar to two of these studies, among girls, we found an attenuation of relationship between the timing and tempo of puberty and risk of overweight or obesity in adulthood when we controlled for childhood BMI.

Controlling for childhood BMI as a possible confounder is a first step in better understanding the nature of these relationships. We also performed a mediation analysis to determine whether puberty is a mediator on the causal pathway between anthropometric measures at childhood and adulthood. We found a strong relationship between childhood anthropometric measures (height and BMI) and adult anthropometric measures (height and BMI), and we found that in general, puberty did not mediate this relationship. Future research could use more sophisticated methods, such as path analysis, to further elucidate these relationships and determine whether puberty is a mediator on the pathway between child BMI and adult BMI, or whether childhood BMI is a confounder of the relationship between puberty and adult BMI.

Limitations

A limitation of this study is that the Tanner SMS ratings were self-reported by the adolescents from ages 12-16y. The gold standard for pubertal staging is typically physical examination by a trained clinician using Tanner criteria (33). However, self-assessment using the Tanner SMS has been validated in many populations, including a highly comparable population of South African adolescents (36). Therefore, self-rating of pubertal stage can be considered reasonably valid in this study. Also, while measurement error associated with self-assessment could impact conclusions drawn about the level of pubertal development at any one cross-section within the study, the consistent use of self-rating from 12-16y means that interpretation of trends across time would be unlikely to be biased, as measurement error is equally likely at all ages.

The association we found between BMI status and breast development in females should be interpreted with caution, as it has been suggested that using the Tanner SMS to characterize breast development, in the absence of physical examination by a clinician, may result in measurement error for overweight or obese girls (33). The Tanner SMS is most accurately used to describe female breast development when a trained clinician uses palpation to distinguish between actual breast tissue and adipose tissue. Overweight or obese females using Tanner self-assessment may be prone to overestimate their level of breast development, since adipose tissue can be easily mistaken for breast tissue (33).

We used body mass index as a measure of body fat, however this commonly-used proxy for adiposity does not allow for differentiation between the relative contribution of fat mass and fat free mass. Therefore, there may be differences in the extent to which BMI represents "fatness" in males vs. females. Additionally, overweight and obesity were relatively rare outcomes in our population of South African males, and some of the models for this outcome had small sample sizes.

Better understanding the nature of the relationship between pubertal development and adult anthropometric outcomes is important, given secular trends showing a reduction in menarcheal age (24, 25), earlier development of breasts and pubic hair among girls (18, 26-29), and earlier genital and pubic hair development in boys (28-30). We found that earlier pubertal development and faster pubertal development among girls is associated with reduced adult height, even when height at 8 years is controlled for in the analysis. However, we found that when childhood BMI is included as a confounder in the model, previously observed relationships between the timing and tempo of puberty and adult risk of overweight and obesity disappeared. We also found a strong relationship between childhood anthropometric measures (height and BMI) and adult anthropometric measures (height and BMI), which was not attenuated (or mediated) by pubertal development indicators. Our results confirm other findings that suggest child BMI tracks to adulthood (20-22). From these findings, and those presented in **Chapter 7**, it seems likely that childhood BMI is associated with earlier puberty, and tracks to adulthood, but early puberty is not an independent cause of adult overweight and obesity risk.

There is an association between the timing and tempo of pubertal development and adult risk of overweight and obesity, particularly among females. However, our results suggest that this relationship is mostly accounted for by the influence of childhood BMI. Therefore, pubertal staging could be a useful screening tool in clinical practice, to assess risk of overweight and obesity in young adulthood and beyond. However, prevention of childhood overweight and obesity is important in reducing adult risk for these outcomes, given strong tracking throughout life. Adult obesity confers a greatly increased risk of chronic diseases such as diabetes and cardiovascular disease (45), and understanding these risk factors for adult obesity is important in prevention efforts.

Conclusion

When childhood body mass index is controlled for, the timing and tempo of breast and pubic hair development in girls are not associated with adult risk of overweight or obesity. Controlling for childhood height, girls with earlier pubertal development and faster pubertal development have a reduced adult height. Males with faster pubic hair development have an increased risk of adult overweight or obesity, and those with faster genital development are shorter at adulthood.

Table 8.1: Selected Characteristics of the Study Population, Birth-to-Twenty

	Females (n=990)	Males (n=928)
Ethnicity, %		
Black	84.7	85.0
White	2.7	2.9
Coloured	11.4	10.7
Indian	1.2	1.4
Caretaker monthly income quintiles (Rands)[a], %		
1 (0 - 2,400 Rands)	24.2	22.6
2 (2,401 - 7,800 Rands)	29.9	33.5
3 (7,801 - 10,800 Rands)	16.5	13.4
4 (10,801 - 19,200 Rands)	21.1	21.2
5 (19,201 - 48,000 Rands)	8.3	9.3
Adult Height (cm), mean ± SD	159.6 ± 6.2	171.2 ± 6.7
Adult BMI (kg/m^2), mean ± SD	23.1 ± 4.7	20.6 ± 3.5
Adult BMI status, %		
Normal or underweight	72.2	91.5
Overweight	19.1	5.9
Obese	8.7	2.6
Age at menarche (years), mean ± SD	12.7 ± 1.2	-

a 545 females and 514 males had information on caretaker monthly income. In analyses using this variable, a sixth category for missing is included to preserve the sample size. In 1990, the South African Rand (ZAR) to U.S. Dollar (USD) conversion rate was 0.38956. Therefore, the ranges of ZAR in this table correspond to the following USD:
0 - 2,400 ZAR = 0 - 934.94 USD
2,401 - 7,800 ZAR = 935.33 - 3,038.57 USD
7,801 - 10,800 ZAR = 3,038.96 - 4,207.25 USD
10,801 - 19,200 ZAR = 4,207.64 - 7,479.55 USD
19,201 - 48,000 ZAR = 7,479.94 - 18,698.9 USD

Table 8.2: Mean Height, Mean BMI, and Percentage Overweight and Obese at Adulthood by Pubertal Growth Trajectory Classes and Tanner Stage at 12 Years, Females (n=990)

	%	Height (cm) mean ± SD	BMI (kg/m^2) mean ± SD	Normal Weight (BMI < 25.0) %	Overweight (BMI 25.0 - 29.9) %	Obese (BMI ≥ 30.0) %
Trajectory Classes						
Pubic Hair						
Class 1	32.8	159.4 ± 6.1	22.5 ± 4.6	75.7	19.1	5.2
Class 2	54.7	159.7 ± 6.3	23.1 ± 4.7	72.8	18.5	8.7
Class 3	12.5	159.8 ± 6.3	24.7 ± 4.9	60.5	21.8	17.7
P-value		0.823[a]	<0.001[a]	0.001[b]		
Breast						
Class 1	23.3	160.2 ± 6.1	21.7 ± 4.4	84.4	11.3	4.3
Class 2	25.5	160.1 ± 6.6	22.3 ± 3.6	78.3	18.2	3.6
Class 3	36.6	158.9 ± 6.0	23.5 ± 5.1	70.0	19.8	10.2
Class 4	14.5	159.6 ± 6.1	25.8 ± 4.7	47.9	31.3	20.8
P-value		0.035[a]	<0.001[a]	<0.001[b]		
Pubertal Stage at 12y						
Pubic Hair[c]						
Stage 4 or 5	19.5	159.6 ± 6.4	24.4 ± 5.1	65.7	18.3	16.1
Stage 3	38.2	159.7 ± 6.0	23.2 ± 4.2	69.4	23.1	7.5
Stage 1 or 2	42.3	159.8 ± 6.2	23.0 ± 5.0	73.4	18.9	7.7
P-value		0.977[a]	0.002[a]	0.027[b]		
Breast[d]						
Stage 4 or 5	23.1	158.7 ± 6.3	24.3 ± 5.0	63.2	22.7	14.1
Stage 3	40.2	160.1 ± 6.1	23.8 ± 5.0	66.9	22.9	10.2
Stage 1 or 2	36.7	160.0 ± 6.1	22.2 ± 4.1	79.2	15.8	5.0
P-value		0.084[a]	<0.001[a]	0.001[b]		

a. Trend test to determine if mean adult height and BMI systematically increase or decrease across classes or groups. b. Chi-square test to determine whether there was a significant difference among pubertal development groups in the proportion of participants who were normal weight, overweight, and obese. c. Tanner stage for pubic hair development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development relative to peers. d. Tanner stage for breast development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development relative to peers.

Table 8.3: Mean Height, Mean BMI, and Percentage Overweight or Obese at Adulthood by Pubertal Growth Trajectory Classes and Tanner Stage at 12 Years, Males (n=928)

	%	Height (cm) mean ± SD	BMI (kg/m^2) mean ± SD	Normal Weight (BMI < 25.0), %	Overweight/Obese[a] (BMI ≥ 25.0), %
Trajectory Classes					
Pubic Hair					
Class 1	28.2	169.7 ± 6.3	20.0 ± 3.2	96.2	3.8
Class 2	58.4	171.7 ± 6.5	20.6 ± 3.6	91.3	8.7
Class 3	13.4	172.8 ± 7.6	22.1 ± 3.5	82.3	17.7
P-value		<0.001[b]	<0.001[b]	<0.001[c]	
Genital					
Class 1	5.7	170.3 ± 6.1	19.9 ± 3.6	92.5	7.6
Class 2	36.3	169.9 ± 6.5	20.5 ± 3.4	93.2	6.8
Class 3	50.2	172.1 ± 6.5	20.7 ± 3.7	90.6	9.4
Class 4	7.8	172.7 ± 7.8	21.5 ± 2.6	88.9	11.1
P-value		<0.001[b]	<0.001[b]	0.453[c]	
Pubertal Stage at 12y					
Pubic Hair[d]					
Stage 3, 4, or 5	31.2	171.7 ± 7.0	21.4 ± 4.0	86.6	13.4
Stage 2	44.7	171.0 ± 6.3	20.5 ± 3.4	93.8	6.2
Stage 1	24.2	170.4 ± 6.6	19.9 ± 2.8	94.9	5.1
P-value		0.056[b]	<0.001[b]	0.005[c]	
Genital[e]					
Stage 3, 4, or 5	32.4	171.4 ± 6.9	21.2 ± 4.2	89.4	10.6
Stage 2	45.0	171.2 ± 6.3	20.4 ± 3.0	93.4	6.6
Stage 1	22.7	170.2 ± 6.7	20.4 ± 3.3	91.8	8.2
P-value		0.138[b]	0.016[b]	0.278[c]	

a. There were an insufficient number of males who were overweight and obese to model the risk of these outcomes separately. Therefore, overweight and obese are combined into one category. b. Trend test to determine if mean adult height and BMI systematically increase or decrease across classes or groups. c. Chi-square test to determine whether there was a significant difference among pubertal development groups in the proportion of participants who were normal weight and overweight or obese. d. Tanner stage for pubic hair development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development relative to peers. e. Tanner stage for genital development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development relative to peers.

Table 8.4: Prediction of Adult Body Mass Index Categories by Pubertal Development Trajectory Group and Tanner Stage at 12 Years, Females (n=990)

	ONO (BMI 25.0 - 29.9) vs. NU (BMI<25.0)[a]			OB (BMI≥30.0) vs. NU (BMI<25.0)[a]			OO (BMI≥25.0) vs. NU (BMI<25.0)[b]		
	Unadjusted	Adjusted[c]	Adjusted[d]	Unadjusted	Adjusted[c]	Adjusted[d]	Unadjusted	Adjusted[c]	Adjusted[d]
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Trajectory Classes									
Pubic hair[e]									
Class 3 vs. 1	1.43 (0.85, 2.40)	1.43 (0.84, 2.44)	0.87 (0.39, 1.93)	4.24 (2.14, 8.41)	4.27 (2.13, 8.55)	0.88 (0.20, 3.89)	2.03 (1.31, 3.16)	2.05 (1.31, 3.22)	0.84 (0.39, 1.82)
Class 2 vs. 1	1.01 (0.71, 1.44)	1.03 (0.72, 1.47)	0.94 (0.57, 1.55)	1.73 (0.97, 3.07)	1.73 (0.97, 3.10)	1.94 (0.66, 5.68)	1.16 (0.85, 1.59)	1.18 (0.85, 1.63)	1.02 (0.62, 1.65)
Breast[f]									
Class 4 vs. 1	4.89 (2.81, 8.52)	5.09 (2.90, 8.94)	3.91 (1.69, 9.06)	8.48 (3.94, 18.25)	8.44 (3.89, 18.30)	2.77 (0.64, 12.09)	5.89 (3.63, 9.54)	6.05 (3.70, 9.87)	3.74 (1.71, 8.20)
Class 3 vs. 1	2.13 (1.31, 3.46)	2.03 (1.24, 3.33)	1.67 (0.81, 3.42)	2.84 (1.38, 5.85)	2.75 (1.32, 5.71)	0.81 (0.19, 3.39)	2.32 (1.53, 3.54)	2.22 (1.45, 3.41)	1.51 (0.77, 2.95)
Class 2 vs. 1	1.74 (1.04, 2.93)	1.74 (1.03, 2.95)	1.72 (0.82, 3.62)	0.89 (0.35, 2.23)	0.88 (0.35, 2.23)	0.51 (0.10, 2.66)	1.50 (0.95, 2.39)	1.49 (0.93, 2.39)	1.51 (0.75, 3.03)
Pubertal Stage at 12y									
Pubic hair[g]									
Stage 4 or 5 vs. 3	0.83 (0.49, 1.41)	0.85 (0.50, 1.44)	0.60 (0.28, 1.26)	2.27 (1.18, 4.38)	2.23 (1.15, 4.33)	1.67 (0.41, 6.89)	1.18 (0.76, 1.84)	1.19 (0.77, 1.86)	0.68 (0.34, 1.38)
Stage 1 or 2 vs. 3	0.77 (0.51, 1.16)	0.80 (0.53, 1.21)	0.71 (0.40, 1.25)	0.98 (0.52, 1.84)	0.98 (0.52, 1.85)	0.96 (0.26, 3.60)	0.82 (0.57, 1.18)	0.84 (0.58, 1.21)	0.74 (0.42, 1.29)
Missing vs. stage 3	0.62 (0.41, 0.96)	0.75 (0.48, 1.17)	0.42 (0.20, 0.85)	0.88 (0.46, 1.68)	0.96 (0.49, 1.88)	1.41 (0.38, 5.22)	0.69 (0.47, 1.00)	0.80 (0.54, 1.19)	0.52 (0.27, 1.00)
Breast[h]									
Stage 4 or 5 vs. 3	1.05 (0.66, 1.68)	1.02 (0.63, 1.63)	1.27 (0.66, 2.45)	1.46 (0.80, 2.66)	1.40 (0.77, 2.57)	1.12 (0.29, 4.30)	1.18 (0.79, 1.76)	1.14 (0.76, 1.71)	1.25 (0.66, 2.36)
Stage 1 or 2 vs. 3	0.58 (0.38, 0.91)	0.59 (0.38, 0.92)	0.84 (0.46, 1.53)	0.42 (0.21, 0.82)	0.40 (0.20, 0.80)	0.74 (0.21, 2.69)	0.53 (0.36, 0.79)	0.53 (0.36, 0.78)	0.84 (0.47, 1.51)
Missing vs. stage 3	0.62 (0.40, 0.94)	0.72 (0.46, 1.13)	0.54 (0.27, 1.11)	0.63 (0.35, 1.14)	0.67 (0.36, 1.26)	1.19 (0.35, 4.08)	0.62 (0.43, 0.90)	0.71 (0.48, 1.04)	0.65 (0.34, 1.25)
Menarche age, years	0.83 (0.72, 0.95)	0.84 (0.74, 0.97)	0.91 (0.75, 1.11)	0.62 (0.51, 0.75)	0.62 (0.51, 0.75)	0.87 (0.59, 1.29)	0.76 (0.67, 0.85)	0.77 (0.68, 0.86)	0.91 (0.75, 1.10)

a. Multinomial logistic regression comparing the relative risk of overweight but not obese (ONO; BMI 25.0 - 29.9) vs. normal or underweight (NU; BMI<25.0), and obese (OB; BMI≥30.0) vs. normal or underweight (NU; BMI <25.0). RRR= relative risk ratio. b. Logistic regression comparing the odds of overweight or obese (OO; BMI≥25.0) vs. normal or underweight (NU; BMI<25.0). OR=odds ratio. c. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), and adult height. d. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), adult height, and BMI at 8 years. Adding BMI at 8 years to the model reduces the sample size to n=545. e. Prediction of adult body mass index categories using the 3 growth trajectory groups for pubic hair development. f. Prediction of adult body mass index categories using the 4 growth trajectory groups for breast development. g. Prediction of adult body mass index categories based on Tanner stage for pubic hair development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development. h. Prediction of adult body mass index categories based on Tanner stage for breast development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development.

Table 8.5: Prediction of Adult Body Mass Index Categories by Pubertal Development Trajectory Group and Tanner Stage at 12 Years, Males (n=928)

(Continued on next page)

	OO (BMI≥25.0) vs. NU (BMI <25.0)[a]					
	Unadjusted		Adjusted[b]		Adjusted[c]	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Trajectory Classes						
Pubic hair[d]						
Class 3 vs. 1	5.44	(2.49, 11.88)	3.86	(1.70, 8.81)	3.68	(1.07, 12.67)
Class 2 vs. 1	2.39	(1.19, 4.81)	2.06	(1.01, 4.20)	2.15	(0.74, 6.27)
Genital[e]						
Class 4 vs. 1	1.53	(0.44, 5.38)	0.80	(0.21, 3.03)	0.13	(0.01, 1.24)
Class 3 vs. 1	1.28	(0.44, 3.71)	0.93	(0.31, 2.77)	0.50	(0.10, 2.55)
Class 2 vs. 1	0.90	(0.30, 2.71)	0.81	(0.27, 2.47)	0.19	(0.03, 1.11)

a. Logistic regression comparing the odds of overweight or obese (OO; BMI≥25.0) vs. normal or underweight (NU; BMI<25.0). b. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), and adult height. c. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), adult height, and BMI at 8 years. Adding BMI at 8 years to the model reduces the sample size to n=540. d. Prediction of adult body mass index categories using the 3 growth trajectory groups for pubic hair development. e. Prediction of adult body mass index categories using the 4 growth trajectory groups for genital development. f. Prediction of adult body mass index categories based on Tanner stage for pubic hair development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development. g. Prediction of adult body mass index categories based on Tanner stage for genital development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development.

Table 8.5: Prediction of Adult Body Mass Index Categories by Pubertal Development Trajectory Group and Tanner Stage at 12 Years, Males (n=928)
(Continued from previous page)

	OO (BMI≥25.0) vs. NU (BMI <25.0)[a]					
	Unadjusted		Adjusted[b]		Adjusted[c]	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Pubertal Stage at 12y						
Pubic hair[f]						
Stage 3, 4, or 5 vs. 2	2.33	(1.24, 4.35)	2.09	(1.10, 3.96)	1.17	(0.46, 2.93)
Stage 1 vs. 2	0.81	(0.34, 1.91)	0.81	(0.34, 1.92)	0.51	(0.14, 1.87)
Missing vs. stage 2	1.52	(0.81, 2.83)	1.18	(0.60, 2.35)	1.21	(0.39, 3.79)
Genital[g]						
Stage 3, 4, or 5 vs. 2	1.68	(0.88, 3.19)	1.64	(0.85, 3.17)	2.27	(0.80, 6.44)
Stage 1 vs. 2	1.27	(0.60, 2.70)	1.40	(0.65, 3.02)	3.01	(1.01, 8.99)
Missing vs. stage 2	1.43	(0.77, 2.64)	1.18	(0.60, 2.32)	2.46	(0.74, 8.23)

a. Logistic regression comparing the odds of overweight or obese (OO; BMI≥25.0) vs. normal or underweight (NU; BMI<25.0). b. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), and adult height. c. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), adult height, and BMI at 8 years. Adding BMI at 8 years to the model reduces the sample size to n=540. d. Prediction of adult body mass index categories using the 3 growth trajectory groups for pubic hair development. e. Prediction of adult body mass index categories using the 4 growth trajectory groups for genital development. f. Prediction of adult body mass index categories based on Tanner stage for pubic hair development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development. g. Prediction of adult body mass index categories based on Tanner stage for genital development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development.

Table 8.6: Prediction of Adult Height by Pubertal Development Trajectory Group and Tanner Stage at 12 Years, Females (n=990)

(Continued on next page)

	Unadjusted		Adjusted[a]		Adjusted[b]	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Trajectory Classes						
Pubic hair[c]						
Class 3 vs. 1	0.36	(-0.94, 1.65)	0.02	(-1.28, 1.32)	-1.76	(-3.07, -0.45)
Class 2 vs. 1	0.28	(-0.58, 1.14)	0.15	(-0.71, 1.02)	-0.74	(-1.53, 0.05)
Breast[d]						
Class 4 vs. 1	-0.59	(-1.89, 0.70)	-0.63	(-1.92, 0.66)	-2.19	(-3.45, -0.94)
Class 3 vs. 1	-1.34	(-2.36, -0.31)	-1.40	(-2.43, -0.38)	-1.83	(-2.80, -0.87)
Class 2 vs. 1	-0.13	(-1.24, 0.98)	-0.33	(-1.45, 0.78)	0.37	(-0.63, 1.38)

a. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands). b. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), and height at 8 years. Adding height at 8 years to the model reduces the sample size to n=545.
c. Linear regression to determine the association between adult height and the 3 trajectory groups for pubic hair development.
d. Linear regression to determine the association between adult height and the 4 trajectory groups for breast development.
e. Linear regression to determine the association between adult height and Tanner stage for pubic hair development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development. f. Linear regression to determine the association between adult height and Tanner stage for breast development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development. g. Linear regression to determine the association between adult height and age at menarche.

Table 8.6: Prediction of Adult Height by Pubertal Development Trajectory Group and Tanner Stage at 12 Years, Females (n=990)

(Continued from previous page)

	Unadjusted		Adjusted[a]		Adjusted[b]	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Pubertal Stage at 12y						
Pubic hair[c]						
Stage 4 or 5 vs. 3	-0.08	(-1.36, 1.21)	-0.08	(-1.37, 1.20)	-0.75	(-1.97, 0.48)
Stage 1 or 2 vs. 3	0.04	(-0.99, 1.07)	0.12	(-0.92, 1.15)	1.35	(0.40, 2.30)
Missing vs. stage 3	-0.37	(-1.42, 0.67)	-0.28	(-1.37, 0.81)	0.49	(-0.59, 1.57)
Breast[f]						
Stage 4 or 5 vs. 3	-1.32	(-2.52, -0.12)	-1.25	(-2.44, -0.05)	-2.23	(-3.36, -1.11)
Stage 1 or 2 vs. 3	-0.01	(-1.06, 1.04)	0.05	(-1.00, 1.09)	0.99	(0.04, 1.93)
Missing vs. stage 3	-0.78	(-1.80, 0.24)	-0.71	(-1.78, 0.37)	-0.10	(-1.14, 0.94)
Menarche age, years[g]	0.57	(0.26, 0.88)	0.60	(0.29, 0.91)	1.00	(0.70, 1.29)

a. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands). b. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), and height at 8 years. Adding height at 8 years to the model reduces the sample size to n=545.
c. Linear regression to determine the association between adult height and the 3 trajectory groups for pubic hair development.
d. Linear regression to determine the association between adult height and the 4 trajectory groups for breast development.
e. Linear regression to determine the association between adult height and Tanner stage for pubic hair development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development. f. Linear regression to determine the association between adult height and Tanner stage for breast development at 12 years: earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2) development. g. Linear regression to determine the association between adult height and age at menarche.

Table 8.7: Prediction of Adult Height by Pubertal Development Trajectory Group and Tanner Stage at 12 Years, Males (n=928)

	Unadjusted		Adjusted[a]		Adjusted[b]	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Trajectory Classes						
Pubic hair[c]						
Class 3 vs. 1	3.15	(1.73, 4.56)	2.60	(1.15, 4.05)	-0.38	(-1.72, 0.95)
Class 2 vs. 1	1.99	(1.01, 2.96)	1.79	(0.80, 2.77)	0.23	(-0.67, 1.13)
Genital[d]						
Class 4 vs. 1	2.32	(-0.02, 4.67)	1.65	(-0.73, 4.03)	-2.29	(-4.49, -0.09)
Class 3 vs. 1	1.75	(-0.13, 3.63)	1.44	(-0.45, 3.34)	-1.38	(-3.10, 0.34)
Class 2 vs. 1	-0.40	(-2.32, 1.51)	-0.51	(-2.43, 1.41)	-1.72	(-3.45, 0.01)
Pubertal Stage at 12y						
Pubic hair[e]						
Stage 3, 4, or 5 vs. 2	0.71	(-0.50, 1.91)	0.48	(-0.73, 1.68)	-0.44	(-1.48, 0.60)
Stage 1 vs. 2	-0.68	(-1.98, 0.62)	-0.59	(-1.90, 0.72)	0.59	(-0.56, 1.74)
Missing vs. stage 2	0.56	(-0.54, 1.66)	0.43	(-0.72, 1.59)	0.77	(-0.35, 1.90)
Genital[f]						
Stage 3, 4, or 5 vs. 2	0.17	(-1.03, 1.36)	0.05	(-1.13, 1.24)	-0.76	(-1.81, 0.29)
Stage 1 vs. 2	-1.06	(-2.39, 0.27)	-0.91	(-2.24, 0.42)	0.27	(-0.87, 1.41)
Missing vs. stage 2	0.43	(-0.67, 1.52)	0.38	(-0.77, 1.52)	0.70	(-0.42, 1.82)

a. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands). b. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands), and height at 8 years. Adding height at 8 years to the model reduces the sample size to n=540. c. Linear regression to determine the association between adult height and the 3 trajectory groups for pubic hair development. d. Linear regression to determine the association between adult height and the 4 trajectory groups for genital development. e. Linear regression to determine the association between adult height and Tanner stage for pubic hair development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development. f. Linear regression to determine the association between adult height and Tanner stage for genital development at 12 years: earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1) development.

Table 8.8: Mediation Analysis: Prediction of Adult Height and BMI by Height and BMI at 5y and 8y, With and Without Measures of Pubertal Development, Females (n=715) and Males (n=655)

	Females		Males	
	Coeff.	95% CI	Coeff.	95% CI
Prediction of adult height by height at 5y				
Unadjusted	0.90	(0.83, 0.97)	1.05	(0.97, 1.13)
Adjusted				
Ethnicity and caretaker income[a]	0.90	(0.83, 0.98)	1.08	(1.00, 1.17)
Pubic hair trajectory classes[a, b]	0.93	(0.85, 1.00)	1.08	(1.00, 1.17)
Breast/genital trajectory classes[a, c]	0.95	(0.88, 1.02)	1.08	(1.00, 1.16)
Pubic hair stage at 12y[a, d]	0.94	(0.87, 1.01)	1.09	(1.01, 1.17)
Breast/genital stage at 12y[a, e]	0.95	(0.88, 1.02)	1.09	(1.01, 1.17)
Age at menarche (years)[a, f]	0.99	(0.93, 1.06)	-	-
Prediction of adult height by height at 8y				
Unadjusted	0.70	(0.64, 0.76)	0.80	(0.73, 0.86)
Adjusted				
Ethnicity and caretaker income[a]	0.70	(0.64, 0.77)	0.82	(0.75, 0.89)
Pubic hair trajectory classes[a, b]	0.71	(0.65, 0.77)	0.82	(0.76, 0.89)
Breast/genital trajectory classes[a, c]	0.74	(0.68, 0.80)	0.83	(0.76, 0.89)
Pubic hair stage at 12 y[a, d]	0.73	(0.66, 0.79)	0.83	(0.76, 0.90)
Breast/genital stage at 12 y[a, e]	0.73	(0.66, 0.79)	0.83	(0.76, 0.90)
Age at menarche (years)[a, f]	0.75	(0.69, 0.82)	-	-
Prediction of adult BMI by BMI at 5y				
Unadjusted	1.81	(1.62, 2.00)	1.42	(1.25, 1.59)
Adjusted				
Ethnicity and caretaker income[a]	1.77	(1.58, 1.96)	1.46	(1.29, 1.63)
Pubic hair trajectory classes[a, b]	1.75	(1.56, 1.94)	1.44	(1.27, 1.61)
Breast/genital trajectory classes[a, c]	1.69	(1.51, 1.88)	1.47	(1.29, 1.64)
Pubic hair stage at 12 y[a, d]	1.77	(1.58, 1.96)	1.45	(1.27, 1.62)
Breast/genital stage at 12 y[a, e]	1.74	(1.55, 1.93)	1.46	(1.29, 1.64)
Age at menarche (years)[a, f]	1.72	(1.53 1.91)	-	-
Prediction of adult BMI by BMI at 8y				
Unadjusted	1.50	(1.37, 1.64)	1.44	(1.30, 1.57)
Adjusted				
Ethnicity and caretaker income[a]	1.48	(1.35, 1.62)	1.43	(1.29, 1.56)
Pubic hair trajectory classes[a, b]	1.48	(1.34, 1.62)	1.41	(1.27, 1.55)
Breast/genital trajectory classes[a, c]	1.42	(1.28, 1.56)	1.45	(1.31, 1.58)
Pubic hair stage at 12 y[a, d]	1.48	(1.34, 1.62)	1.43	(1.29, 1.56)
Breast/genital stage at 12 y[a, e]	1.48	(1.34, 1.62)	1.43	(1.29, 1.57)
Age at menarche (years)[a, f]	1.46	(1.32, 1.60)	-	-

a. Adjusted for ethnicity, quintiles of caretaker monthly income (in Rands). b. Adjusted for the 3 trajectory groups for pubic hair development. c. Adjusted for the 4 trajectory groups for breast/genital development. d. Girls: adjusted for Tanner stage for pubic hair development at 12 years – earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2). Boys: adjusted for Tanner stage for pubic hair development at 12 years – earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1). e. Girls: adjusted for Tanner stage for breast development at 12 years – earlier (stage 4 or 5), medium (stage 3), and later (stage 1 or 2). Boys: adjusted for Tanner stage for genital development at 12 years – earlier (stage 3, 4, or 5), medium (stage 2), and later (stage 1). f. Girls: adjusted for age at menarche (years).

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Chapter 9: Summary, Conclusions, and Implications

Following is a summary of the key findings of this dissertation, in relation to the stated aims of the research.

Table 9.1: Summary of Key Findings in Relation to Stated Aims of the Dissertation
(Continued on next page)

Specific Aims	Key Findings
Specific Aim One: Characterize patterns of linear growth, including stunting and recovery from stunting, across numerous time points from birth to adulthood. Contribute to the debate on methods for assessing recovery and catch-up growth.	**Chapter 3:** ➢ There is substantial growth recovery among children who are stunted post-infancy. ➢ Child growth trajectories are determined in part by size at age 1y, however, there is significant variation in growth after age 1y. ➢ While prevention of early-life stunting must continue to be a top priority, policy makers should consider targeting for further nutritional interventions children who are stunted post-infancy. **Chapter 4:** ➢ From age 2y to adulthood, mean height-for-age z scores increased, despite increasing absolute height deficits from the reference. ➢ Catch-up growth after 2y may be a statistical artifact. ➢ Absolute height difference from the reference median should also be assessed when determining the existence of catch-up growth.
Specific Aim Two: Identify predictors of adolescent pregnancy in South African girls and explore the association between adolescent pregnancy and maternal attained height.	**Chapter 5:** ➢ Girls who had an adolescent pregnancy experienced menarche earlier and were taller at 11y and 12y. ➢ After controlling for age at menarche and pre-pregnancy height, adolescent pregnancy was not associated with maternal attained height.

Table 9.1: Summary of Key Findings in Relation to Stated Aims of the Dissertation
(Continued from previous page)

Specific Aims	Key Findings
Specific Aim Three: Characterize patterns of obesity incidence among South African children from infancy to late adolescence, and determine gender differences in overweight and obesity.	**Chapter 6:** ➢ Among girls, overweight and obesity increased throughout childhood. ➢ Overweight and obesity were not widely prevalent among boys. ➢ Early childhood and post-puberty may be important periods for intervention among girls.
Specific Aim Four: Determine the association between childhood growth measures – height and body mass index – and the timing and tempo of pubertal development. Determine the association between the timing and tempo of pubertal development and adult height and body mass index.	**Chapter 7:** ➢ Among both males and females, there was a positive association between both height and body mass index in early childhood and the tempo of pubertal development. This relationship emerged by age 5y. ➢ Among females, greater childhood height and body mass index were associated with earlier pubertal development, but there was no association among males. **Chapter 8:** ➢ When childhood body mass index is controlled for, the timing and tempo of breast and pubic hair development in girls are not associated with adult risk of overweight or obesity. ➢ Girls with earlier pubertal development and faster pubertal development have a reduced adult height. ➢ Males with faster pubic hair development have an increased risk of adult overweight or obesity, and those with faster genital development are shorter at adulthood.

Discussion of the Key Findings for Each Specific Aim

The key findings, public health implications, and areas for future research will be discussed within the context of each specific aim.

Specific Aim One

In Chapter 3, we concluded that among children who are stunted post-infancy, there is a fair amount of growth recovery in terms of movement across the -2.0 SD HAZ threshold. The potential for growth recovery post-infancy suggests there may be value in also targeting resources toward programs aimed at promoting growth recovery and preventing growth faltering after the first 1,000 days. However, it is important to understand whether nutrition interventions after the first 1,000 days are associated with improvements in linear growth, and whether improvements in linear growth after this period are associated with longer-term cognitive and educational benefits. Several studies have explored the effect of nutritional supplementation on linear growth stratified by age, and have shown that nutritional supplementation is associated with a greater impact among infants and younger children (1-3). A study in Guatemala showed that supplementation of 100kcal/day during the first three years of life was associated with improved linear growth, with the greatest benefit seen in the first year (2). There was no benefit of supplementation from 3-7 years of age (2). Another study in India found that children who received caloric supplementation experienced an increase in height compared to

non-supplemented children, but this difference decreased as the age of supplementation increased: 1-2y (2.8 cm), 2-3y (1.7 cm), 3-4y (1.7 cm), and 4-5y (1.1 cm) (1). Colombian children under 3 years who received supplementation experienced the greatest height benefits during the periods from 3-6 months and 9-12 months (3). While the height benefits associated with supplementation may be greatest at younger ages, there is potential for improvement in linear growth with supplementation after three years of age. Another study in Cali, Colombia found that caloric and protein supplementation of children enrolled from 3.5 to 6.1 years resulted in significant improvements in height (4). However, these differences in height did not persist 3 years after the intervention (4). Studies of malnourished children who are adopted show that an improved living environment can result in catch-up growth, but primarily when the adoption occurs in infancy or the early childhood years (5-8).

Some recent evidence has suggested that improvements in linear growth post-infancy may be associated with better cognitive outcomes (9, 10). A study of Filipino children found that the change in height-for-age z score from 24 months to 11 years was positively associated with cognitive ability at 11 years (9). The work of our colleagues, Crookston et al, which built upon our analysis of growth in the Young Lives study, showed that improvements in child growth after early faltering were associated with benefits in terms of schooling and cognitive achievement (10). They found that height at 8 years, independent of height at 1 year, was positively associated with schooling and cognitive scores (10). However, few studies have been able to explore whether improvements in height after 2 years are associated with cognitive and educational benefits, and more

longitudinal studies after the first 1,000 days are needed. It is also important to understand the predictors of improvements in height after 2 years.

We know, of course, that -2.0 SD HAZ is an arbitrary threshold, and small movements around this cut-off point do not always represent significant improvements in nutritional status. In Chapter 4, we discuss the merits of two approaches for evaluating patterns in linear growth in a population over time, and for evaluating the existence of "catch-up" growth. The first approach evaluates changes in the mean height-for-age z score in a population, and the second approach assesses changes in the distance between the mean height in the population and the median height in a reference population. Both approaches have their merits, however, we concluded that there was an increase in mean height-for-age z scores from age 2y to adulthood, despite increasing absolute height deficits from the reference. Furthermore, concluding the existence of catch-up growth based solely on increasing mean HAZ in a population could be incorrect, as increasing HAZ throughout childhood and adolescence could be a statistical artifact only. It is recommended to evaluate both changes in HAZ and changes in the absolute height difference from the reference median when determining the existence of catch-up growth in a population. An important area for further research is determining whether changes in HAZ over time or changes in the absolute height difference better predict adult outcomes.

Specific Aim Two

In Chapter 5, we explored the association between adolescent pregnancy and maternal attained height. We controlled for age at menarche and HAZ immediately preceding adolescent pregnancy, factors that are related both to the risk of adolescent pregnancy, as well as adult height. We found that when you control for these factors, adolescent pregnancy is not associated with adult height. Our study represents a significant methodological improvement over previous research on this topic, as other studies were not able to control for the effect of pre-pregnancy height. We also found that girls who had an adolescent pregnancy experienced menarche earlier and were taller at 11 and 12 years of age than all other girls in the cohort. This is an interesting finding, in light of our conclusions from Chapter 7 pertaining to the strong association between child growth measures and the timing and tempo of puberty. It is possible that programs aimed at improving linear growth in childhood could have an unintended effect on early puberty, which could in turn increase risk of adolescent pregnancy.

An interesting difference in the findings between Chapter 5 and Chapter 8, is the association between early puberty and adult height. In Chapter 5, we found that girls with an adolescent pregnancy experienced menarche earlier than all other girls in the cohort, but this experience of earlier puberty did not translate into reduced adult height. Conversely, in Chapter 8, we found that girls with earlier menarche were shorter at adulthood. The difference in these two findings is likely due to the fact that in Chapter 8, when examining the association between puberty timing and tempo and adult height, we

controlled for height at 8y of age. Given an identical height at 8y of age, girls with earlier menarche were shorter as adults. These results suggest there may be a biological reason that puberty timing, independent of earlier childhood growth, impacts adult height. In the adolescent pregnancy study in Chapter 5, when comparing the adult height of girls with an adolescent pregnancy to all other girls in the cohort, we did not control for childhood height measures.

Specific Aim Three

In Chapter 6, we found that among girls, overweight and obesity increased throughout childhood, and by late adolescence, the prevalence of overweight and obesity began to rival that which is seen in higher income countries (11). This was not the case for boys, among whom overweight and obesity were not widely prevalent. The gender disparity in overweight and obesity prevalence found in our study is consistent with the results of other studies of South African children and adolescents, which also found that females are more likely to be overweight or obese than males (12-14). The children in our study population were predominantly black. The significantly higher prevalence of overweight and obesity among females in our study is consistent with studies of black South African adults (15, 16), whereas the gender gap among white South African adults is much smaller (16).

Gender differences in obesity prevalence are widespread in low- and middle-income countries (LMICs) (17). Women have a $\geq$ 50% increased risk of being obese compared to

men in 106 of the 189 countries that report obesity prevalence data to the World Health Organization (WHO) (17, 18). The countries without a gender disparity tend to be higher-income countries (17, 18). However, these stark gender differences in obesity prevalence can also be seen in black populations in high-income countries. In the U.S., 57% of black women are obese vs. 37% of black men (19). The gender difference in obesity prevalence among black adults in the U.S. is larger among foreign-born blacks from Africa or the Caribbean, versus U.S. born blacks (20). In contrast, among white adults in the U.S., there is almost no gender disparity in obesity prevalence: 34% of white women and 33% of white men are obese (19). This gender difference in obesity among black Americans is apparent among children as well, primarily later in adolescence from 12-19 years, with fewer differences from 6-11 years of age (21). Additionally, similar gender differences in overweight exist among black African and black Caribbean children in England, with smaller gender differences among white English children (22). In certain Caribbean countries like Jamaica with predominantly black populations, as well as some Latin American countries such as Ecuador, adult women have an overweight or obesity prevalence that is twenty to thirty percentage points higher than men (23). The gender disparity in obesity has been described as a problem that is common "in countries experiencing rapid economic development and historically poor populations in economically developed countries (24)."

Greater adiposity in females has a clear evolutionary purpose. Larger fat stores are necessary for reproduction, to fuel fetal growth, and one would therefore expect women to have greater adiposity stores than men. However, in many countries the increased

prevalence of obesity among women is drastic, and it is important to understand the potential causes. Several researchers have attempted to explain the gender disparity in overweight and obesity that is common in black populations as well as in low- and middle-income countries (17, 24). It is known that early life nutritional deprivation has a differential impact on females versus males, with females who have experienced early deprivation tending to have greater fat deposition than males in similar circumstances (17, 25). It is hypothesized that the hypothalamus of females and males reacts differently to early life deprivation, with consequences for appetite regulation, energy expenditure, and fat deposition (17). It has been suggested that this is particularly deleterious for the female offspring of low socioeconomic status mothers in countries going through the nutrition transition, as early life deprivation results in adaptations that enable greater fat deposition in later environments of caloric excess (24). This possible explanation for the gender disparity in obesity is consistent with evidence which shows that the gender disparity in obesity among blacks in the U.S. is greatest among those from low socioeconomic status families and parents with lower levels of education (26). It is also consistent with several studies of famines, which have shown that female offspring who were in gestation during famines have an increased risk of obesity later in life, which is not the case for males (24, 25, 27). Adult socioeconomic status may also have a differential impact on obesity risk among men and women. In a study of South African adults, it was found that higher socioeconomic status is positively related to obesity risk in women, but among men there is no association (17). This same study concluded that the effects of early life deprivation and adult socioeconomic status accounted for 96% of

the difference in obesity rates between men and women in this South African sample (17).

Numerous other factors have been cited as possible reasons for the gender differences in obesity seen among black populations and populations in LMICs. Researchers have been interested in whether differences in the prevalence of depression could play a role, as depression has been found to be positively associated with obesity in women, but not among men (17) (28). However, in one study of South African adults, depression had no association with obesity risk for both men and women (17). Researchers have explored the potential role of gender inequality, and found that in the 192 countries for which the WHO has obesity data, several indices of gender inequality were significantly associated with country-level sex differences in obesity prevalence (29). It has also been suggested that in LMICs, there is a gender difference in the perception of body size, with females more likely to desire a heavier body, as they rate heavier bodies as more attractive and healthy (17). Child-bearing is another factor that has been implicated, with black women being more than twice as likely as white women to retain more than 20 pounds postpartum, despite similar weight gain during the pregnancy (16, 30).

Differences in dietary and physical activity behaviors among South African adolescents could explain the stark gender disparity we found in the prevalence of overweight and obesity. Gender differences in dietary patterns within the Birth-to-Twenty cohort have been investigated (31). It was found that females consume breakfast less regularly, eat with the family less often, consume more snacks while watching television, and eat more

junk food (chips and sweets) than males (31). Gender differences in physical activity among South African adolescents could also play a role. A study of South African adolescents found that girls had lower levels of physical activity than boys, and in both genders, low activity levels were associated with overweight and obesity (13). However, in a study of black adolescents in the U.S., it was found that while black females have less leisure-time physical activity than black males, setting this behavior equal for males and females did not reduce the gender disparity in obesity incidence (32).

Among South African girls, and to some extent among boys as well, overweight and obesity during infancy/toddlerhood and early childhood were highly predictive of risk for obesity at 16-18y. This is consistent with many previous studies showing childhood body mass index tends to track into adulthood (33-35). These findings confirm the importance of early prevention of overweight and obesity. Our study also found that among girls, the peri-pubertal years were a period of increased risk for the development of obesity. This is consistent with another study among South African adolescents, which suggested that the peri-pubertal period is an important period for intervention to prevent obesity among girls (13). Future research should evaluate the effectiveness of interventions designed to prevent overweight and obesity among South African females in the early childhood and pubertal years.

Specific Aim Four

The results of our analyses in Chapters 7 and 8 generally support the conceptual framework presented in Chapter 2. Childhood growth was strongly associated with pubertal progression. We found that greater height and body mass index in early childhood were associated with a faster tempo of pubertal development among both males and females, and earlier pubertal development at 12y among females.

Globally there has been a marked decline in the age of menarche (36, 37), as well as trends toward earlier development of breasts and pubic hair among girls (38-42), and earlier genital and pubic hair development in boys (41-43). Our study is consistent with other research, which has found that height in children is inversely associated with age of pubertal onset (44-47), and the global shift toward earlier pubertal onset has been concurrent with increases in height (48). Furthermore, secular trends in pubertal development have mirrored the increase in body mass index among children (49, 50), and our study was consistent with other research, which found an association between higher BMI in childhood or adolescence and earlier onset of puberty among girls (39, 44, 47, 51-56).

Pubertal development can be influenced by numerous factors, including genetics, race and ethnicity, diet, prenatal influences, psychosocial stress, physical activity, and environmental exposures (57-62). As much as 50-80% of the variation in pubertal timing is determined by genetic factors (63), however, the remaining portion is influenced by

modifiable factors such as child growth measures. While our study does not prove causality, childhood growth may be causally related to the timing and tempo of puberty. Particularly in females, there have been hypothesized biological mechanisms to suggest that this relationship is causal. Increased adipose tissue contributes to the conversion of androgens to estrogen, and overweight females have higher levels of estrogen, potentially expediting the pubertal process (64, 65).

The global shift toward earlier puberty is of concern. Pubertal development can have profound social implications, especially for females, as it signifies the beginning of reproductive capabilities, one's potential readiness for sexual activity and marriage, and the possibility for childbearing and motherhood (66-68). Additionally, the timing of puberty is linked to numerous psychosocial outcomes, with early puberty among girls leading to a higher risk of depression, eating disorders, substance abuse, poor academic achievement, and risky sexual behaviors (67). Improved nutrition and socioeconomic conditions resulting from the nutrition transition may have contributed to the trend toward earlier puberty, and programs aimed at improving child growth may also contribute to shifts in pubertal timing in LMICs.

In Chapter 8, we aimed to determine whether the timing and tempo of puberty are associated with adult BMI and height, independent of childhood BMI and height. In females, we concluded that the association between earlier timing and faster tempo of puberty and higher adult BMI is largely explained by childhood BMI. When we controlled for childhood BMI, the associations between the timing and tempo of breast

and pubic hair development in girls and adult risk of overweight or obesity disappeared. This is consistent with other research, which found that the relationship between puberty and adult BMI in girls is largely explained by childhood BMI (47). Our mediation analysis revealed that puberty does not seem to be a strong mediator on the pathway between childhood and adult BMI. Therefore, it is likely that childhood BMI is associated with pubertal development (possibly causally). Childhood BMI also tracks to adulthood, and therefore is likely a confounder of the relationship between puberty and adult BMI. Future research could utilize path analysis to better understand these relationships between childhood BMI, puberty, and adult BMI. However, given current evidence, childhood BMI is likely the key factor, impacting both pubertal development and adult risk of overweight and obesity. Prevention of childhood obesity is therefore important in preventing early onset of puberty and adult obesity.

We found that controlling for height at 8y, girls with earlier pubertal development and faster pubertal development have a reduced adult height. Peak height velocity occurs earlier in girls who have early menarche, and after menarche, the pace of linear growth declines significantly (69). The end result is that girls who experience earlier menarche miss out on several years of rapid pre-pubertal growth, resulting in a reduced adult height (69). An unanswered question, however, is whether improving linear growth in children, with its potential impact on earlier puberty among girls, would result in a net benefit or detriment to adult attained height.

Strengths

There are several strengths of the research presented in this dissertation. The first is the quality of the data from the four Young Lives cohorts and the five birth cohorts that are a part of the larger COHORTS collaboration. These are carefully followed longitudinal cohorts, which in some cases have been observed for several decades and have given rise to countless studies on the growth, health, and development of the participants. Local research teams invested significant time and resources toward training data collectors to ensure valid and consistent measurement of child growth and development indicators. Given the longevity of these cohorts, retention of participants has generally been high. In the South African Birth-to-Twenty study, over 70% of the cohort was still being followed at 16 years of age (70). The inclusion and exclusion criteria for each paper within this dissertation varied based on the research question. However, we performed sensitivity analyses, and generally found few differences between those included in the study and those who did not have adequate data to allow inclusion. Finally, the conclusions of our research are highly consistent with findings in other settings, suggesting good quality of our data.

The use of rich longitudinal growth data with anthropometric measurements at multiple time points confers significant benefits over the commonly-used cross-sectional growth data in LMICs. This enabled us to better understand how children in LMICs grow from birth to young adulthood, and to assess the degree to which growth recovery is possible

across many time points. Another strength of this research was the use of longitudinal data on the development of secondary sexual characteristics from ages 9-16y in both boys and girls. Much of the research on puberty has focused on girls, and has emphasized only the timing (not tempo) of puberty, narrowly defining puberty timing as age at menarche. Another important contribution of this dissertation to the understanding of pubertal development, was the use of Latent Class Growth Analysis (LCGA) to identify distinct groups with common developmental trajectories. To our knowledge, no other study has used LCGA to model different pubertal development trajectories in a population. We were also fortunate to have longitudinal data that allowed us to control for childhood growth measures when exploring the association between puberty and adult anthropometric outcomes. Few other studies have done this. An interesting area for future research would be to use LCGA to model both child growth measures, and pubertal development, allowing for an exploration of the association between these two sets of trajectories.

Limitations

There were a few limitations of the research. The pubertal development data were self-reported from 12-16y. Clinician assessment of pubertal staging is considered to be more valid than self-assessment. However, clinician assessment is less socially acceptable within the context of research studies and can be a deterrent to participation. We also had a small sample size for adolescent pregnancies in our study of the relationship between adolescent pregnancy and adult height. This could have made it difficult to detect a

statistically significant difference in adult height. However, the mean adult heights in the adolescent pregnancy and comparison groups were virtually identical, and in fact, girls with an adolescent pregnancy were 0.1 cm taller, which would not support the previous hypothesis of maternal-fetal competition for nutrients.

Conclusions

Low- and middle-income countries throughout the world are going through the nutrition transition and now face the dual burden of both stunting as well as rising overweight and obesity among children. Programs aimed at improving nutrition in the first 1,000 days and beyond seek to improve linear growth so that children can achieve their genetic height potential and the associated cognitive, schooling, and adult income benefits. The challenge will be to promote nutrition that enables improved linear growth, while not increasing overweight and obesity among children in LMICs. It will be important to identify which interventions – e.g. micronutrient supplementation, breastfeeding promotion, protein supplementation – will promote optimal linear growth in the first two years of life without increasing excess weight gain after two years (71). Program impact studies should assess the effect of interventions on both linear growth, as well as weight-for-height among children. The solutions to the dual burden faced by LMICs will be complex, as a host of environmental, economic, and social factors influence overweight and obesity. A particular focus on the prevention of obesity among females is needed, given the stark gender disparity in obesity observed in many LMICs. Additionally, improving growth among children in LMICs could impact pubertal development, and

further research is needed to determine how to mitigate the potential social and psychological consequences of early puberty. Social support mechanisms and schooling opportunities should be in place to ensure earlier puberty does not have a deleterious impact on human capital.

Chapter 9 References

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