# SHORT AND FAT: EARLY GROWTH AND ADIPOSITY IN MEXICAN CHILDREN

By

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# ABSTRACT OF THE DISSERTATION

Short and Fat: Early Growth and Adiposity in Mexican Children

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According to nationally representative surveys, since the 1980s, obesity has been on the rise in Mexico, with a current prevalence of over 30 % in adults. Obesity is a serious public health problem as it contributes to type II diabetes, asthma, cancer, osteoporosis, and heart disease. Substantial evidence suggests that the path to obesity is established in early life. According to cohort studies in low- and middle-income countries (LMICs), the risk of chronic disease increases in children who were undernourished or experienced rapid growth post-infancy. However, these cohorts included children born before the recent changes brought about by nutrition transition, so it is unclear if these findings can be generalized to LMIC populations.

The objective of this dissertation is to study the longitudinal relationship between early growth and the development of childhood obesity and body composition in late childhood in children living in Cuernavaca, Mexico. Study participants were a sub-sample of a longitudinal cohort study. The study participants were the offspring of women (n=1094) who participated

in the POSGRAD study, a double-blind, randomized, placebo-controlled trial designed to assess the effects of prenatal supplementation with DHA on offspring growth and development (NCT00646360) that was conducted from 2004-2006, and followed up through age 8-10 y. Body composition measurements were obtained using bioelectric impedance in a subsample of 545 children from the POSGRAD cohort at age 8-10y. In this cohort, growth-retarded children had higher body mass index z-scores (BMIZ), fat mass (FM), and lower fat-free mass (FFM) at follow-up in comparison with their non-growth-retarded peers. Using latent class growth analysis, two distinct trajectories of growth for height and weight in both genders were identified. In the first set of analyses, with the outcomes at seven years, we observed that belonging to the high-weight trajectory for both girls and boys was associated with higher odds of being overweight or obese at age seven in comparison with the low-weight trajectory. This association was inverted, however, in the height-growth trajectory analysis, where remaining taller during the first five years of life had a negative relationship on obesity status at follow-up. When using body composition as an outcome at a later follow-up period, we observed three height trajectories for boys and two for girls. The lowest-height trajectory class in boys was associated with increased FM and lower FFM at follow-up and the high-height trajectory class was associated with lower FM and higher FFM in comparison with the intermediate-height trajectory class. No significant association was observed between growth trajectories and body

composition in girls. Our research suggests that early adverse growth patterns (rapid weight gain or growth retardation) influence body composition or obesity status later in life. Future research needs to focus on discrete aspects of growth and the development of obesity to better understand how to prevent or reverse the double burden of disease.

# ABBREVIATIONS

ANSA: Acuerdo Nacional de Salud Alimentaria

BIA: Bioelectrical Impedance Analysis

BF%: Body Fat percentage

BMI: Body Mass Index

CVD: Cardiovascular Disease

DHA: Docosahexaenoic Acid

DOHaD: Developmental Origins Health and Disease Hypothesis

FM: Fat Mass

FFM: Fat Free Mass

FTO: Fat Mass and Obesity-associated gene

GC: Glucocorticoids

GDP: Gross Domestic Product

GI: Glycemic Index

GL: Glycemic Load

GWAS: genome wide association studies

HAZ: Height-for-Age

HPA: Hypothalamic–pituitary–adrenal

INPS: Instituto Nacional de Salud Publica

LCGA: Latent Class Growth Analysis

LCHT: Latent Class Height Trajectory

LCWT: Latent Class Weight Trajectory

LMIC: low-income countries

MVPA: Moderate-to-Vigorous Physical Activity

MOH: Ministry of Health

NR-NCD: Nutrition Related Non-communicable Diseases

OR: Odds Ratio

OSAS: Obstructive Sleep Apnea Syndrome

PA: Physical Activity

PAR: Predictive Adaptive Responses

PE: Physical Education

POSGRAD: Prenatal Omega-3 fatty acid Supplementation and child GRowth And Development study

SD: Standard Deviation

SES: Socioeconomic Status

SF: Skinfold

SSB: Sugar Sweetened Beverage

T2DM: Type 2 Diabetes Mellitus

TV: Television

WHtR: Waist-to-Height ratio

WC: Waist Circumference

WHO: World Health Organization

## DEDICATION

I dedicate this dissertation to my loved ones.

My mother and father, Lidia and Alfredo Barrios, are my inspiration. My parents have taught me that hard work always pays off, that I should always follow my mind and heart, and that I should always make the best of all situations. I was only able to do this because they have sacrificed so much to make my life so much easier than theirs was. I will never be able to pay them back for all they have given me. Thank you for your unconditional support, love and patience. Los adoro!

My husband Mike is one of the most structured humans in the world. He has taught me that one should never give into resistance and that you can always make time for what is important. I am lucky enough to be one of the most important things for him – thanks for taking care of me for the past 6 years. Te amo.

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Thank you to my father, my mother, my sisters, Patricia and Estela. You have always been there, and I am here today because of you. Finally, thank you to my husband. Thank you for cooking, cleaning, taking care of the pets and the yard, for waking me up every morning, and for reading the first draft of everything I write. I love you.

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# Chapter 1: Introduction

The prevalence of obesity in Mexican adults is now over 30% [1, 2]. Nationally representative surveys have documented a rise in the prevalence of obesity in Mexico since the 1980s, and it is estimated that by 2050 it will be over 37% for both men and women [2]. Similarly, in school-aged children (5-11 years old) overweight and obesity prevalence is 32.2% and for adolescents (12-19 years old) 36.3% [1]. In 2016 a high body mass index (BMI: defined as a person's weight in kilograms divided by the square of his height in meters ($kg/m^2$)) was ranked as the number two risk factor contributing to early death and disability, second only to high fasting plasma glucose levels [3]. A high BMI contributes to type 2 diabetes (T2DM), asthma, cancer, osteoporosis, and heart disease [4]. Substantial evidence suggests that the path to obesity is established in early life, during both prenatal and postnatal growth periods [5-7]. Identifying the factors that contribute to obesity and understanding how they work in shaping children's growth trajectory is key to attenuating excess weight gain.

The influence of rapid growth in childhood on obesity in later life is one of the most concerning contributing factors to the development of obesity [6-8]. Studies have documented that rapid weight gain in the first two years of life is related to a risk of being overweight and developing metabolic disorders in later life [9-13]. Similarly, cohort studies conducted in low- and middle-income countries (LMICs) have documented that the risk of chronic disease in adulthood was higher in participants who were undernourished during the

first two years of life and experienced rapid weight gain post-infancy [14]. Results from a recent Chilean study of normal birth weight children indicate that rapid BMI gain in early life (6-24 months old) is positively associated with adiposity and CVD risk factors in four-year-olds [15]. While it is widely accepted that rapid weight gain during infancy is associated with overweight/obesity risk, less is known about its impact on body composition and adipose tissue depot [16] and merits further exploration.

Although rapid weight gain is associated with obesity and related outcomes [9, 17, 18], there are inconsistent results with regard to the effects of poor linear growth on the development of excess adiposity in later years [19-21]. For example, studies have shown that stunted children have a higher risk of becoming overweight or obese compared to children of normal height [22, 23]. The implication is that poor growth may contribute to the double burden of disease—the coexistence of undernutrition with nutrition-related noncommunicable diseases (NR-NCD) within a population—in LMICs [24, 25]. However, other prospective studies reported that stunting in early childhood was associated with a lower BMI or less body fat in childhood [19, 26]. These conflicting results may be due to differences in methodologies or environmental factors and demonstrate that a more nuanced understanding of how growth influences adiposity is needed to develop effective interventions that reduce the prevalence of childhood obesity.

It is unclear if the current evidence linking poor growth and obesity development can be generalized to LMICs. This is because the evidence comes from high-income countries, where undernutrition is uncommon, or from longitudinal cohorts in LMICs that included children born before the recent increase in obesogenic environments due to the nutrition transition[1]. The effect of growth patterns on obesity development is understudied in LMICs experiencing the nutrition transition, such as Mexico [27], where the transition may be contributing to the recent rapid increase in obesity prevalence [1]. While the prevalence of the double burden (concurrent overweight and stunting) is currently low, it remains a concern as Mexico continues to experience the nutrition transition [28]. To that end, this dissertation will focus on the relationship between early growth and the development of childhood obesity and body composition in late childhood in children living in Cuernavaca, Mexico.

[1] Nutrition Transition: Dynamic changes in dietary intake and physical activity patterns and trends in obesity and NR-NCDs.

# Chapter 2: Background and Review of Literature

## 2.1 Overview of overweight and obesity in Latin America

In 2016, more than 1.9 billion adults over the age 18 were overweight, with more than 650 million categorized as obese [29]. The global prevalence of obesity (overweight and obesity is defined as BMI ≥ +1 standard deviations (SD) z-score and ≥ +2 SD z-score, respectively [30].) has tripled since 1975 [29]. This rise in overweight and obesity has also been observed in children. According to 2016 estimates, over 41 million children under the age of five were overweight, of which 31 million lived in developing countries [29]. In a recent systematic review of Latin American countries, researchers estimated that between 42.5 and 51.8 million children under the age of 18 were overweight or obese between 2008 and 2013 [31], representing 20-25 % of this population [31]. The most recent Mexican national health survey confirmed that 9.7% of preschool-aged children, 32% of school-aged children, and 36% of adolescents were overweight or obese [1, 32]. These statistics are alarming given the negative physiological and psychological effects obesity has during childhood [33, 34] and on overall health throughout life [35].

### 2.1.1 Nutrition transition in Mexico

The way that the global population eats, drinks, and exerts itself has changed over the last several decades, with a shift toward more eating and drinking and less physical activity. Latin American countries, in particular, have undergone important health, nutrition, and demographic transitions [36]. These changes clash with human biology, resulting in major changes to body

composition [37]. During the last ten years, Mexico's prevalence of overweight, obesity, and T2DM has increased significantly, while undernutrition concerns have been fading into localized, targeted subpopulations [36, 38, 39]. The nutrition transition goes along with these demographic and epidemiologic shifts toward NR_NCDs, including T2DM, CVD, osteoporosis, and certain cancers [40]. Nutrition transition has been associated with rapid urbanization and economic growth, steady declines in physical activity, and changes in food patterns and dietary intake, including increased consumption of energy-dense processed foods [41].

Energy imbalance appears to be the main driver for the increase in NR-NCDs. In Mexico, the National Institute of Public Health (INSP, per its abbreviation in Spanish), attempted to identify and understand the main drivers of this change by analyzing various databases for trends and patterns in food expenditure, transportation, leisure time activities, and other factors associated with obesity and NCDs [42]. It was found that low-cost processed foods with high quantities of sugar, fat, and sodium were more available [43] and an increase in exposure to marketing for ready-to-eat foods and beverages as well as new technologies was associated with lower physical activity [44]. In addition, time given toward food preparation had decreased, while eating away from home and fast food consumption had increased [36, 43]. In light of these findings, the Mexican Ministry of Health (MOH) identified the need to develop

and implement programs to tackle high mortality and morbidity rates attributed to obesity-related diseases.

### 2.1.2 Mexico's policies targeting obesity

Mexico is one of the few countries with initiatives to systematically curb the obesity epidemic. The Mexican MOH, with support from the INSP and scholars, developed the National Agreement for Healthy Nutrition (ANSA, per its abbreviation in Spanish) based on the World Health Organization (WHO) Global Strategy on Diet, Physical Activity and Health [45]. The ANSA designed statutory regulations to ensure the availability and accessibility of healthy foods and safe water and to reduce access to unhealthy items such as sugar-sweetened beverages (SSBs) in Mexican schools [42].

The primary goal of ANSA was to address calories consumed from beverages, which included whole milk, SSBs, and sugar-sweetened flavored waters termed "agua frescas" (fruit juice, water, and added sugar) [46]. ANSA developed the Beverage Guidance Panel whose first recommendation was that government programs should replace whole milk with 1.5% milk [47]. In schools, the government mandated the removal of most foods and beverages with high sugar and high saturated fat content [47] and the promotion of water, vegetables, fruits, and healthy dishes. SSBs were, banned and sweetened or salty snacks restricted to one day a week in compliance with nutritional standards [48].

Finally, the sugar tax and the non-essential foods tax went into effect in January 2014. The sugar tax is a one-peso-per-liter (slightly less than 10%) tax on any non-alcoholic and non-dairy beverage with added sugar [49]. The second tax is an 8% sales tax on non-essential or "junk" food (products high in sodium, added sugars, or solid fats) [47]. After two years of implementation, results show a 7.6% decrease in purchases of taxed beverages between 2014 and 2015 [50]. There was also a slight increase (2.1%) in the purchase of untaxed beverages (e.g., diet sodas, sparkling and plain water, 100% juices, flavored water with non-caloric sweeteners, and milk without added sugar; within this category was a 13% increase in plain water purchases) [51]. Results from an analysis of the non-essential foods tax showed a 10.2% decline in purchases in low socioeconomic status (SES) households. While there were no changes in high SES households, investigators state that the tax is helping the population with the highest disease burden [52]. These results are promising, but it is unclear if the overall impact on diet quality will translate into actual weight loss. In addition, there is still a need for more integrated nutrition programs focused on healthy eating for all age groups.

## 2.2 Childhood obesity: causes and consequences

### 2.2.1 Childhood and adult consequences

Childhood obesity is known to have a significant impact on physical and psychological health [53]. Evidence suggest that childhood obesity tracks into adulthood [54, 55] and is related to increased mortality in middle age [56].

Obese children are also at high risk for comorbidities that were once only associated with adults. For example, having a high BMI in childhood and adolescence is associated with an increased risk of CVD in adulthood [57]. A prospective cohort study reported that a positive association exists between BMI, waist circumference (WC), and total fat mass measured between ages 9-12 and CVD risk factors at ages 15-16 [58]. The prevalence of insulin resistance, T2DM, and fatty liver disease in children have also been reported [55, 59]. This early onset of T2DM contributes to a more rapid deterioration of glycemic control and a progression of diabetes-related complications (microalbuminuria, dyslipidemia, and hypertension), compared with those who develop the disease later in life [60-62]. Insulin resistance has also been associated with short sleep duration and obstructive sleep apnea syndrome (OSAS) in obese children [63]. OSAS, along with reactive airway disease, are also more frequently seen among obese children, and prevalence and severity rise with increasing BMI [64, 65]. In a recent systematic review of BMI and mortality, a dose-response relationship was also observed between the length of time an individual is obese and subsequent risk of adult onset CVD and all-cause mortality [66].

The psychological consequences of childhood obesity are likely to be more prevalent than the medical complications. Obese children suffer discrimination and stigmatization at the hands of their peers and can negatively impact a child's emotional development [67]. As well, obese children

are more prone to be bullied and have low self-esteem and more behavioral problems [68]. Overweight children and adolescents frequently report reduced health-related physical, emotional, and social quality of life aspects [69, 70]. A recent study by Booth et al. reported that children who are obese at 11 years of age had significantly reduced academic attainment at 16 years of age compared to non-obese children [71]. The economic burden of obesity related bias may have an impact on adult employment and socioeconomic status [72].

The consistent evidence of childhood overweight and obesity having long-term adverse consequences, coupled with the increased prevalence of these conditions, merits early assessment and detection to ensure the health and wellbeing of future generations.

### 2.2.2 Determinants of overweight and obesity

Obesity is a complex and major global public health problem. Characterized by excess body fat and caused by a positive energy balance [73], obesity is mostly influenced by environmental factors. However, the near tripling of global prevalence since 1975 suggests that genetics could play a small role.

#### *2.2.2.1 Genetic factors associated with childhood obesity*

Genetic factors play a role in the individual variation of body weight and human adiposity. It has been suggested that 40-70% of inter-individual variability of BMI is attributable to genetic factors [74]. In the 1990's, Whitaker et al. found that parental obesity more than doubled the risk of adult

obesity in both obese and non-obese children under 10 years of age in comparison with children of non-obese parents [75]. A male twin study demonstrated that there is a common source of genetic variance predisposing the clustering of hypertension, diabetes, and obesity among related individuals [76], providing evidence that the development of adulthood cardiometabolic disease is affected by genetic factors [73].

In recent years, genome-wide association studies (GWAS) have provided evidence for the role of variant genes in the development of childhood obesity. For example, in a study from eight European cohorts, researchers identified a relationship between a fat mass and obesity related locus (FTO) rs9939609 variant and accelerated adiposity rebound in early childhood, and it was also associated with higher BMI by 0.1 $kg/m^2$ per allele from birth to adolescence [77]. In a different study, using a genetic propensity score, calculated by summing the number of alleles with anthropometric traits, children with a raised obesity risk score were heavier and longer at six weeks of age [78]. While it is suggested that less than 5% of cases of childhood obesity are caused by genes that carry functional defects [79], it seems that the link between genetic predispositions in the presence of an obesogenic environment results in most cases of childhood obesity. For example, FTO's effect on BMI is exacerbated by a sedentary lifestyle [80]. Some mechanistic insights between the interaction of environmental risk factors and genetic susceptibility to obesity have been explored [81], but may be confounded by environmental factors shared within

families. More research into these genes and their complex interaction with environmental factors will help target obesity lifestyle interventions.

#### *2.2.2.2 Lifestyle behaviors*

2.2.2.2.1 Urbanization and physical activity

Over the past 50 years, the influx of people into urban areas has increased by 20 %, with more than half of the world's population now living in cities [82]. This trend is expected to continue, with a rise of 1.84% per year between 2015 and 2020 [82]. Among other changes this causes in a society, living in an urban setting influences the development of obesity. Urban living allows for an increased variety of food options and technological advancements and conveniences alter physical activity patterns [83]—energy requirements and diet quality decrease while extra calories quickly accumulate due to dietary changes [37].

Mexico has seen a decrease in physical inactivity (PA) among the general population [84] and in adolescents during the past two decades. The shift from outdoor play to indoor television- (TV) and Internet-based activities has been linked to the rapid increase in childhood obesity [85]. Recently it was estimated that Mexican adolescents have an average of three hours/day of screen time, and two-thirds of the population exceed the recommended guidelines of ≤2 hours/day [86]. Time spent on indoor entertainments such as TV viewing and video games has been positively associated with overweight

and obesity [87]. Likewise, a strong inverse relationship between PA levels and obesity was found among adult males [88].

The WHO recommends that 5- to 17-year-olds should participate in at least 60 minutes of moderate-to-vigorous physical activity (MVPA) daily [89]. Recent estimates from 105 countries suggest that 80.3% of 13- to 15-year-olds do not meet this recommendation [90]. The 2012 National Health and Nutrition Survey in Mexico reported that 58.6 % of children and adolescents 10 to 14 years of age are not physically active [32]. A key contributing factor may be that MVPA is significantly reduced from kindergarten to primary school, mostly due to a drop in MVPA during school activities [91]. Public primary schools in Mexico are not reaching national or international recommendations regarding physical education (PE) class time during the school day and PA outside of PE class is often forbidden [92].

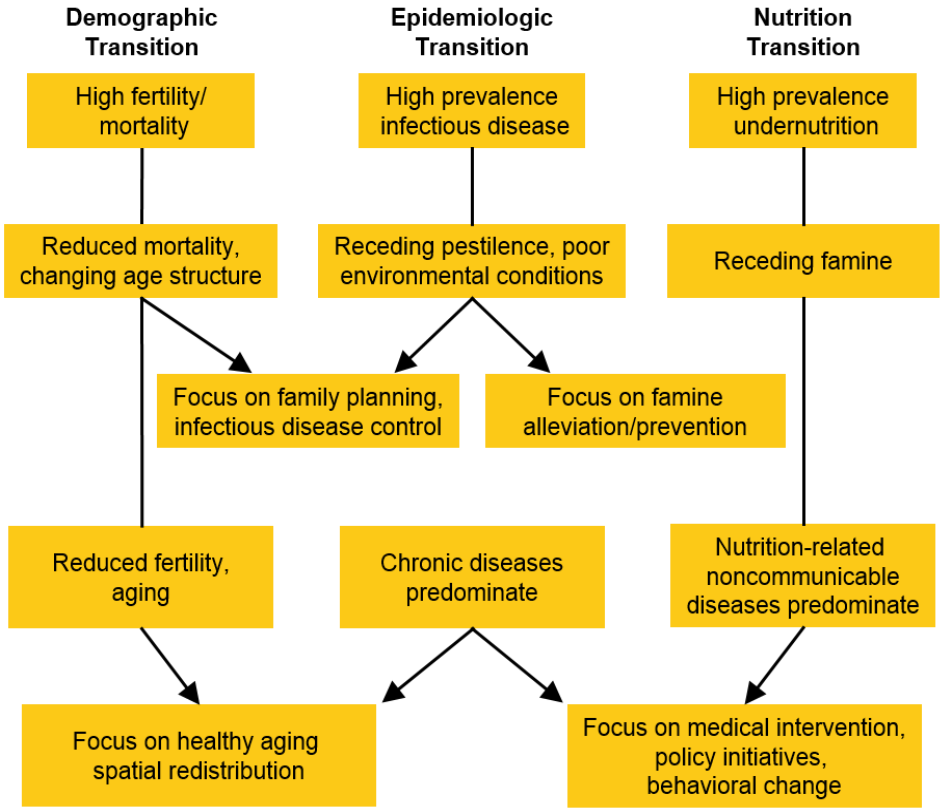
As changes to the built-in living environment in countries such as Mexico continue, so will the reduction of PA and quality of diet—factors that clearly contribute to overweight and obesity development.

2.2.2.2.2 Health, nutrition and demographic change

The demographic and epidemiological transitions that preceded or occurred simultaneously with nutrition transition are a main precursor of obesity and metabolic syndrome in developing countries. The demographic transition is the shift from high to low fertility and mortality rates (seen in modern industrialized countries) [93]. The epidemiological transition [94] is

the shift from a pattern of high prevalence of infectious disease—associated with malnutrition, periodic famine, and poor sanitation—to one with a high prevalence of chronic and degenerative disease associated with urban-industrial lifestyles [95]. The nutrition transition is related to the latter of these processes and is characterized by large shifts in dietary and physical activity patterns that are reflected in changes in nutritional outcomes such as average stature and body composition [93]. The relationship between these three transitions are displayed in Figure 1.

**Figure 2.1** Stages of health, nutrition, and demographic change [93]



2.2.2.2.2.1 Patterns of the nutrition transition

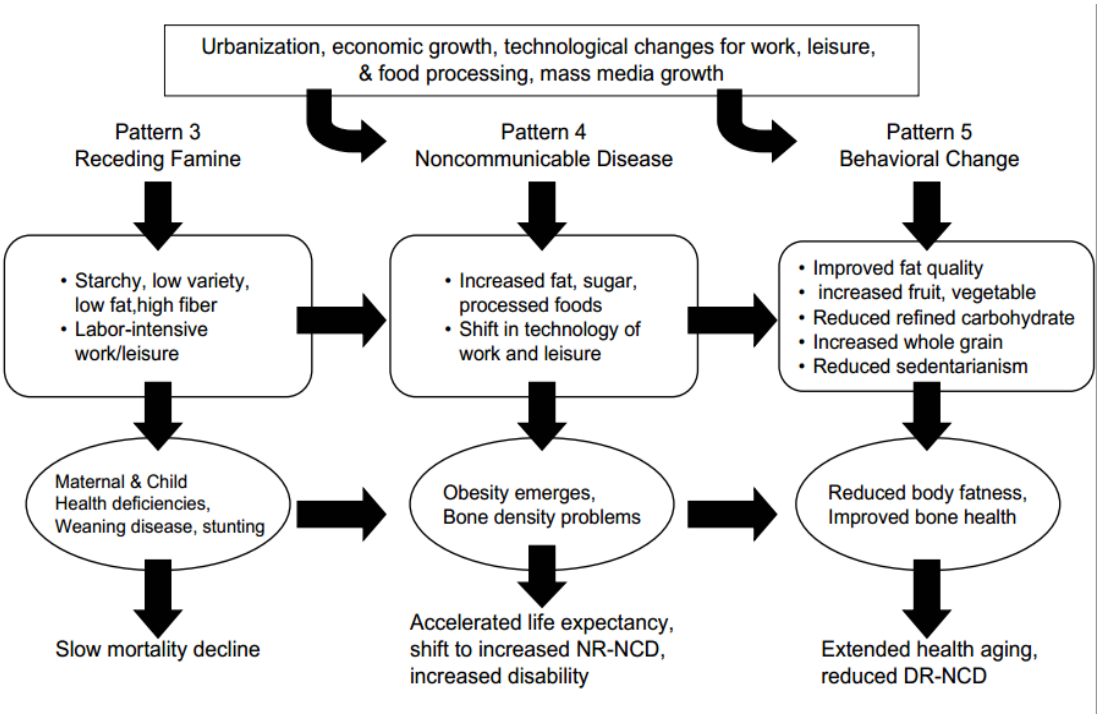
Major shifts have occurred in the human diet, activity patterns, and nutritional status around the world. Five patterns of nutrition transition have been identified from historical references of human development. A description of these patterns by Popkin is presented in Table 2.1 [93].

**Table 2.1** Patterns of Nutrition Transition

| | |
|---|---|
| ***Pattern 1: Collecting Food*** | Characterized by hunter-gatherer populations and comprises diets rich in carbohydrates and fiber and low in fat (especially saturated fat) with a high-activity profile and lean body phenotype. |
| ***Pattern 2: Famine*** | Individuals exist in a famine-like situation (low-calorie, low-protein, and low-fat diets), have growth retardation, and low body fat and fat-free mass. |
| ***Pattern 3: Receding Famine*** | Famine declines and nutrition improves, with increases in the consumption of fruits, vegetables, and animal proteins. This pattern is associated with increased inactivity. |
| ***Pattern 4: NR-NCD*** | Currently the most prevalent pattern in developing countries, conducive to development of obesity, the metabolic syndrome, T2DM, and CVD [96]. This pattern is driven by aggressive advertising practices, the relatively low-cost of energy-dense foods, and improved purchasing power. Children and adolescents increasingly consume foods high in saturated fat and refined carbohydrates, sweetened carbonated beverages, and diets low in polyunsaturated fatty acids and fiber. |
| ***Pattern 5: Behavioral Change*** | Characterized by increases in the prevalence of T2DM and CVD and awareness of the benefits of balanced diets and regular physical activity. People attempt to change their dietary and physical activity profiles to prevent or delay diseases. This pattern, unlike previous patterns, is driven by an individual's desire to seek healthy behavior, hence it may not be evident in large segments of a population, and is likely to be adopted initially by affluent people. |

Urbanization, economic growth, technological change, and culture are all factors driving nutrition transition. For example, results from an analysis of 33 nationally representative health and nutrition surveys between 1990 and 2008 from developing countries suggest that maternal obesity is positively associated with economic development positing that the benefits of an increased income may be offset by reduced access to nutrient dense food [97]. In Thailand, a qualitative study details how supermarkets have begun to spring up in rural, agriculturally rich regions and the impact of these changes affect local food access and availability along with the loss of livelihood for women, the main stallholders of the 'fresh markets' [98]. Consequently, the increase in less nutrient dense food options have a profound impact in the shift from undernutrition to overnutrition. The three most recent patterns of the nutrition transition are described in more detail in Figure 2.

**Figure 2.1** Stages of the nutrition transition [93]



2.2.2.2.3 Diet

An increase in Gross Domestic Product (GDP) provides families with increased incomes. However, in conjunction with the changes brought about by urbanization, a higher income promotes overnutrition and positive energy balance through the greater access to low-quality, high-energy dense foods and the increased purchasing power of consumers [99, 100].

Over the past four decades, many fast food restaurants have expanded worldwide. There are now more than 36,000 McDonald's franchises in more than 100 countries and territories, serving around 69 million customers each day [101], roughly one percent of the world's population. A number of studies have shown frequent consumption of fast food to be positively associated with weight gain along with adverse metabolic outcomes [102-105]. This is due to the high calorie content, increased portion sizes, high amounts of processed meat, sugary beverages, highly refined carbohydrates, unhealthy fats, and high levels of salt and sugar found in food items from these establishments [106].

There has also been an increase in multinational, regional, and large local supermarkets that are replacing fresh food markets and farm shops [99]. In developing countries, Latin America leads in the growth of supermarkets. Before and during the 1980s, supermarkets existed in major cities and predominantly in wealthier neighborhoods, accounting for 10-20% of national food retail sales [107]. By the year 2000, this number had risen to 50-60% [107].

Supermarkets are a source of highly processed foods and SSBs and may have a substantial effect on diet quality and obesity.

While dietary patterns vary between and within countries, it is apparent that there was a worldwide rise in the consumption of fats and animal products [99, 100]. There was an increase of 119% in meat consumption between 1963 and 2003 in developing countries [108]. During the same period, the consumption of cereals and vegetables decreased, while the consumption of vegetable oils increased dramatically ~200% [108]. In fact, a number of epidemiological studies have found a positive association between increased consumption of processed meat and weight gain, T2DM, heart disease, some cancers, and mortality [109-113].

The transition from the consumption of whole grains to more refined carbohydrates has also been documented during the last few decades. Refined carbohydrates have a high-glycemic-index (GI) and glycemic load (GL), meaning high intake of high GI foods cause spikes in blood sugar and eventually lead to an increased risk for T2DM [114]. Another concurrent change in dietary patterns has been increased SSB consumption. Mexico has one of the highest consumption rates of soft drinks in the world, averaging 28 gallons per capita per year [115], in addition to high consumption of "agua frescas." Caloric beverages contribute 20–23% of the total energy intake in the Mexican population [116, 117]. Epidemiologic studies have shown strong

associations between SSB intake and weight gain or obesity [109, 118], T2DM [119], and CVD [120, 121].

#### *2.2.2.3 Developmental origins of health and disease*

In the late 1980's and early 1990's, Barker and colleagues published results from epidemiological studies of infant and adult mortality that became the bedrock upon which the fetal origins hypothesis [122-124] was constructed. These influential articles provided insight into the relationship between restricted fetal growth, small size at birth due to nutrient deficiency *in utero*, and the increased risk of T2DM and CVD [122, 123, 125, 126]. With additional clinical evidence, this concept evolved into the "developmental origins of health and disease" (DOHaD) hypothesis.

The DOHaD hypothesis states that if the developing fetus has suffered "intrauterine stress" caused by stress, poor nutrition, and/or drugs [127] it will respond by developing predictive adaptive responses (PARs). PARs are responses that foster an immediate benefit, but also prepare the fetus for when it encounters a similar environment later in life [128, 129]. For example, when a fetus is exposed to a limited nutrient supply and adapts by downregulating metabolic and/or organ functions [130]. The long-term effects can be irreversible, since disruptions in gene expression, cell differentiation, and proliferation can change the structure and function of vital organs (i.e., skeletal muscle, lungs, pancreas, kidneys) permanently [131]. If this child later grows up in an environment with the opposite experiences as *in utero*, such as an

overabundance of food, this could predispose them to a higher risk of NCDs [127]. More important, the risk for NCD may be further increased by excess postnatal weight gain and by the aging process itself [129, 132]. Some of the postulated underlying mechanisms of this early life programming are listed below and in Figure 3.

*Hypothalamic–pituitary–adrenal axis dysregulation:*

The hypothalamic–pituitary–adrenal (HPA) axis is our central stress response system and is highly susceptible to programming during fetal and neonatal development and GCs act as the primary mediators of HPA programming [133, 134]. Different environmental exposures during early life (such as maternal stress, infections, undernutrition) have been linked with HPA abnormalities [135]. For example, high levels of GCs can change the activity of this neuroendocrine system, which in turn influences the development and regulation of various organs (brain, liver, and pancreas), that may result in a permanent alteration of physiology and health later in life. In addition, when levels of maternal cortisol remain high for an extended period of time, the exposure of high levels of circulating cortisol can alter the fetal stress response system and program stress reactivity for their adult life [136].

*Exposure to high levels of glucocorticoids in utero:* Glucocorticoids (GCs - stress hormones) are steroid hormones that regulate specific aspects of homeostasis (control of blood pressure and glucose metabolism) and fetal maturation [137]. In rodents, high exposure to GC *in utero* leads to growth

retardation and increased risk of glucose intolerance and high blood pressure in adulthood [137, 138]. Animal studies that increase maternal GC levels with different manipulations such as undernutrition or stress result in lower offspring birthweight [139, 140]. These and other similar studies suggests that GCs might be a potential programming mechanism.

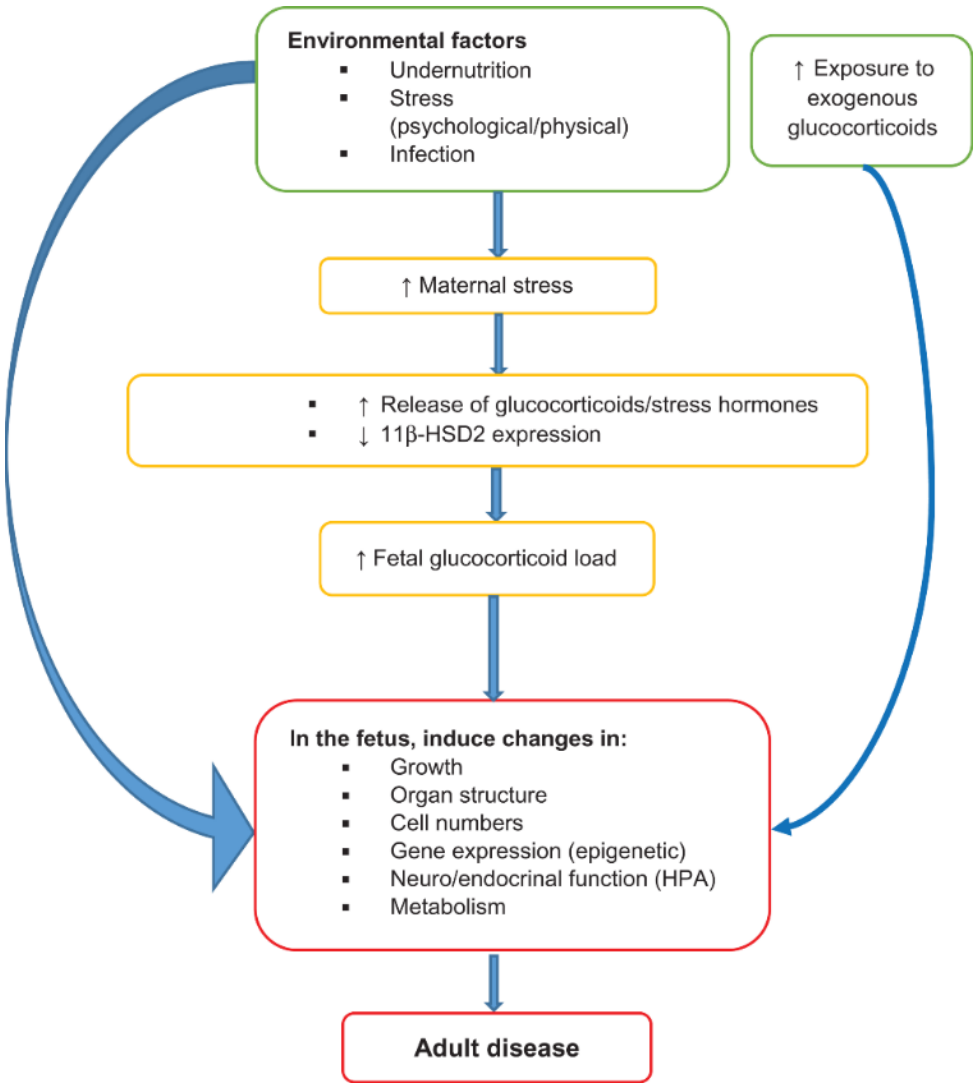
*Irreversible changes to organ structure:* Exposure to intrauterine stress can lead to permanent structural changes in the fetus' organs. Insults, such as undernutrition and hypoxia *in utero,* have been associated with decreased kidney function due to a decrease in the number of nephrons as a result of diminished nephrogenesis or renal progenitor cells [141, 142]. As well *in utero* stress is linked to reduced liver function due to a decreased number of pancreatic ß-cell numbers/islet vascularization and liver lobules [143].) These irreversible changes, resulting in decreased nephrons and impaired glucose regulation with the reductions of ß-cell mass, can increase the risk of hypertension and renal disease [144].

*Alterations in gene expression:* Epigenetic alterations, such as DNA methylation and histone modification, are important for normal development and cell differentiation. Animal and human studies have shown that prenatal insults, such as undernutrition or increased GCs, can influence epigenetic marks. For example, individuals who were exposed to the Dutch Famine *in utero* had reduced methylation for a gene that codes for an insulin-like growth factor II that is vital for growth and development [145], suggesting that this

may have influence growth. . Undernutrition *in utero* has also been linked with altered methylation rates in key enzymes and hormonal receptor sites (11ß-HSD2 and GC receptors) that can lead to high GC concentrations in the fetus [146]. Transcription factors are attractive targets for developmental programming as they can influence the modulation of a network of genes. Transcription factors that have been epigenetically programmed by histone modifications through suboptimal environments in early growth include *PPARs*, *Hnf4a,* and *Pdx1.* These are critical to normal tissue and organ development (adipose tissue, pancreas, liver) [147].

It is clear that DOHaD points to the critical role of developmental factors on the risk of developing NCDs (heart disease, diabetes, and obesity) in later life [127, 148, 149].

**Figure 2.3** A theory of glucocorticoids as a potential common mechanism through which various environmental factors exert their programming effects [150].



2.2.2.3.1 The DOHaD paradigm in developing countries

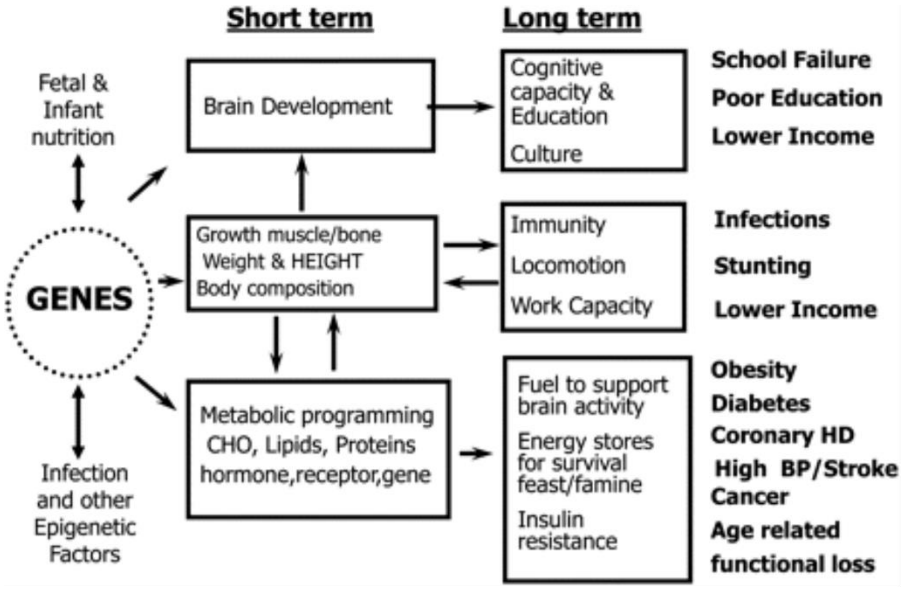
The NR-NCDs has been increasing over the past two decades [151]. Deaths due to NCDs in LMICs reached 30.7 million in 2015 [152]. While LMICs are still struggling with undernutrition and infectious diseases, they now have to deal with the double burden of disease due to increased obesity prevalence [153]. These conditions, once thought to be mutually exclusive, are now present in many Latin American countries due to urbanization and economic development—both of which have rapidly changed diets and physical activity patterns [24]. The main risk factors contributing to NCDs are unhealthy diets, lack of physical activity, exposure to tobacco smoke, and harmful use of alcohol [154]. However, while present, these risk factors do not fully explain the rapid increase in NCDs in developing countries.

The DOHaD hypothesis may play a critical role in LMIC countries that experienced a high prevalence of undernutrition for many generations and are now experiencing an abundant food environment with less physical activity. NR-NCDs epidemics in developing countries seem to differ from those in developed countries. For example, NCDs in LMICs tend to occur earlier in life [3, 155] and they represent three quarters of the NCD-related premature deaths worldwide [152]. This severe and earlier onset of NCDs may be due to the mismatch between early and later environments. New evidence indicates that the predisposition to NCDs may be established *in utero* [142, 156] and maternal diet and body composition during pre-conception and pregnancy are linked with a predisposition to obesity and NCDs such as diabetes, blood

pressure, and lipid disorders in offspring [157, 158] (Figure 4). Given the increased global obesity prevalence in the general population (including women of reproductive age and those expecting children), there is potential for a transgenerational transmission of risk of obesity and NCDs in the near future.

The DOHaD paradigm provides an opportunity to understand health and nutrition transition that have long-term and multigenerational effects. It also provides an opportunity to identify preventive actions to deal with these effects.

**Figure 2.4** Schema representing short- and long-term consequences of nutrition-gene-environment conditions in early life on relevant health and disease outcomes that have potential social and economic effect [159].



#### *2.2.2.4 Stunting*

Childhood stunting, the most prevalent form of undernutrition, is considered the best indicator of a child's well-being. Currently, 151 million children under the age of five suffer from stunting [160], defined as children falling below −2 SD from the median reference to the length-for-age/height-for-age WHO Child Growth Standards [30]. While cut-offs are important to set limits to what is considered normal, it is important to keep in mind that growth faltering is a gradation, and children slightly above -2 SD are at the same risk as children meeting the formal definition of stunting [161].

Stunting often begins *in utero* and continues into the first few years of postnatal life. During the first 1,000 days of life, rapid physiological changes occur that can have significant, long-lasting effects and failure to grow during this critical period results in stunting [162]. Some cohort studies have estimated that around 20% of stunting occurs *in utero* [163]. However, this may be an underestimation as programming occurred *in utero* that influences post-birth growth [164]. Prenatal determinants of stunting vary across regions. In Indonesia, birth length was the strongest predictor of height-for-age (HAZ) at one year of age over any other factor [165]. In India, growth faltering was already present at birth in 44-55 % of the population depending on the year [166]. During the post-natal period, sustained growth faltering (continuous HAZ decline) has been observed in different regions [162], while healthy children experienced maximal growth velocity during the same period [167].

It has recently been proposed that in poor environments growth faltering continues beyond the 1,000 day period, presenting a new opportunity to address stunting [168, 169]. Studies from several LMICs has shown a substantial recovery from early stunting among school-age children [170-172]. Additionally, data from the Consortium of Health Orientated Research in Transitioning Societies (COHORTS) study (Brazil, Guatemala, India, Philippines, and South Africa) and from rural Gambia offers the prospect of breaking the cycle of stunting during adolescence as these adolescents begin to have children of their own [168].

Over the past several years there has been a debate as to whether recovery from stunting should be discussed in terms of relative or absolute gains, that is, measuring gains using HAZ scores or in centimeters [169, 173-175]. In a study using data from 51 countries comparing relative and absolute measures, it was reported that HAZ scores level-off between 24 and 60 months of age [169]. When analyzing the same data using absolute measures, 70 % of the absolute deficit accumulated by 60 months was attributed to growth faltering in the first 1,000 days while the other 30 % was due to deficits between 24 to 60 months [169]. Addressing the question of potential recovery beyond the first 1,000 days will help us understand if interventions would help increase lean mass rather than increase risk for long-term obesity.

There is substantial literature on the relationship between maternal height and child size [164, 176, 177]. As stunting is a recurrent process, women

who are stunted tend to be at greater risk of having stunted children. Some of the possible mechanisms explaining these intergenerational effects on linear growth are epigenetic effects, programming *in utero*, and shared genetic characteristics. Socio-cultural factors also play a role as families tend to stay in the same environment for generations [164]. Despite the clear evidence of intergenerational effects, improvements in linear growth have been achieved through migration [178] and following rapid economic and social development in one generation. This is supported by a study that identified that even short-term nutritional improvements in early life can reduce growth retardation in a generation; when children in the study were measured as adults, they were eight centimeters taller than their parents [179]. This indicates that if women of reproductive age are provided with adequate health and nutrition, reduction in height deficits can be achieved.

2.2.2.4.1 Consequences of stunting

Stunting can be indicative of multiple disorders associated with an increased risk of morbidity and mortality, chronic disease in adulthood, and reduced neurodevelopmental and cognitive functioning [180]. Detailed reviews on the short- and long-term consequences of stunting have been published [180-184], for the purposes of this dissertation, however, this dissertation will only focus on a few of these outcomes.

Short-term consequences of stunting are associated with increased morbidity and mortality from infections like pneumonia and infectious

diarrhea [185-187]. Malnutrition and bacterial gastrointestinal and respiratory infections can result in a vicious cycle by worsening nutritional status and increasing incidence and severity of infections. Children with infections use available nutrients for the immune response instead of growth and this leads to a decrease in appetite, impaired intestinal absorption, and increased catabolism [188]. This worsening of nutrition status leads to undernutrition which in turn increases the risk of infection by its negative impact on the epithelial barrier function and altered immune response [189].

Regarding the medium-term consequences, stunting is a major factor in preventing full developmental potential [190]. Studies have linked stunting in children with impaired behavioral development, making them less likely to enroll in school or enroll late, and have lower grades and poor cognitive abilities when compared to their non-stunted counterparts [191-195] as the first 24 months of life are critical for brain development. Results from two infant studies indicate that undernutrition experienced during the first months of postnatal life could affect the growth of pyramidal cells, especially the formation of basilar dendrites, which may be an underlying cause of altered cerebral function [196, 197]. However, the associations between impaired neurodevelopment and growth retardation are not well understood.

Metabolic syndrome, which is usually associated with energy imbalance, is more frequently observed in adults who were stunted in early childhood than in those who experienced normal growth [183]. Researchers have published

consistent associations between infants born with low birthweight and elevated blood pressure, renal dysfunction, and altered glucose metabolism in later life [198, 199]. Low birthweight and greater undernutrition in childhood have been associated with an increased risk for high glucose concentrations, high blood pressure, and harmful lipid profiles during adulthood [183]. Evidence linking stunting or short stature with obesity risk or altered energy expenditure is mixed [200-202]. More recently, new longitudinal evidence suggests a null or negative relation between childhood stunting and later obesity [19-21, 26, 203, 204]. These inconsistencies may be due in part to the use of different methods to measure adiposity as studies often rely on estimates of body fat and fat distribution from standard anthropometry.

The development of childhood overweight is not only due to the changes in the built-in environment. Certain periods in childhood may also play a critical role in the development of this disease [205, 206]. A life-course approach to growth-pattern analysis can be especially helpful in shedding light on these factors related to obesity development.

#### *2.2.2.5 Growth patterns*

Childhood overweight and obesity have become major challenges for public health as comorbidities begin emerging at a young age. Ideally, most of our efforts should be focused on prevention as treatment is very difficult [207]. Rapid weight gain early in life has been associated with adolescent and adult

obesity [208], and identifying important age periods for obesity development would benefit preventive efforts.

Infancy and early childhood have been identified as age periods critical for obesity development, [9, 209-215] however, there is no consensus on which period is most critical. A recent longitudinal study reported that high birth weight and an increasing BMI SD score during the first nine months after birth and a high BMI at two years of age are important landmarks for the onset of overweight at eight years of age [216]. While Willers et al. suggest that there is no specific critical period, their research showed that, starting in the first year of life, a rapid increase in BMI SD score each year was significantly associated with overweight risk at the age of eight [215]. As well, a prospective cohort study in the United States reported that rapid increases in weight-for-length in the first six months of life were associated with an increased risk of obesity by three years of age [213].

In regard to linear growth, some prospective studies report that stunting in early childhood is associated with decreased BMI or body fat in childhood [19, 26] or adolescence [20, 217, 218], while other studies have found null associations [20, 21]. It is unclear, however, if these findings can be generalized to current LMIC populations as the majority of subjects were from high-income countries or longitudinal cohorts from LMICs during 1970 to 1990, which included children born before nutrition transition.

Most studies indicate that early weight gain is associated with being overweight later in life, however, these studies often have limitations such as a small number of participants [219, 220] or are based on self-reported data [212]. To overcome these issues, larger population-based studies are necessary in order to evaluate the relationship between early growth patterns and the subsequent development of overweight and obesity in LMICs.

## 2.3 Group-based trajectory models

Childhood growth patterns have been identified as important predictors of health during early childhood and adulthood. Earlier studies failed to uncover the more subtle patterns in growth trajectories due to the statistical methods employed. With regards to metrics of early growth, the most common measurements used are length, weight, and BMI, and most researchers quantified growth by subtracting anthropometric measurements made at two time points, sometimes without adjusting for the time interval [221]. This is of concern due to the variability of growth rate, meaning that any comparisons of absolute BMI, weight, or length gains over different periods of growth will be affected by growth rates and may result in misleading inferences about their relative importance for later outcomes. More recently, new techniques in statistics have made it possible to study the heterogeneity in growth during childhood [222, 223], assuming that there are different developmental trajectories in the study population and children have different pathways in the development of obesity. The categorization of groups of individuals with

similar patterns of growth over a period of time can provide insight into different pathways of development during childhood.

### 2.3.1 Latent class growth analysis

Latent class growth analysis (LCGA), also known as semi-parametric group-based modeling, will be used in the longitudinal analyses of this dissertation. Group-based trajectory models are different from standard methods because they assume that the population is heterogeneous and in the existence of sub-populations with different trajectory parameters, instead of one trajectory with a single population mean [224]. Group-based trajectory models are a type of structural equation model in which a response variable (i.e., weight or height) is measured at different points over time (T1, T2, T3…T*i*). This responsive variable is then used to gather individuals into meaningful subgroups (classes) that show statistically similar trajectories [224, 225]. LCGA is a person-centered statistical approach that does not rely on pre-determined groups [226], but provides a statistical method to identify groups of distinctive trajectories and accommodates missing data by using all information available using maximum likelihood estimation [227]. LCGA predicts the trajectory of each group, the form of each trajectory, and estimates the probability for each individual of group membership and assigns them to the group for which they have the highest probability of belonging [226, 228-230]. This method cannot estimate random effects within each class or allow variation across individuals within classes as it holds the variance of intercept

and slope at zero and allows modeling to be simpler and less likely to have convergence problems, allowing for distinct trajectories [227].

#### *2.3.1.1 Model estimation*

Since the LCGA method allows for trajectories to emerge from the data itself, it provides a metric for evaluating the precision of group assignments [230]. Deciding on the number of classes can be difficult and should involve consideration of the research question, fit indices, and the substantive meaning of each solution [231].

Below is a guide for making decisions about model selection adapted from Ram et al. and Berlin et al. [232, 233] (Table 2.3). Researchers using group modeling should be able to defend their judgment about the optimal model using a combination of model results, theory, and fit statistics.

**Table 2.3** Selection Model Guide

| | |
|---|---|
| **1** | Examine the output of each model estimated for potential problems. Review of output making use that classes are not overlapping or too similar. |
| **2** | Remaining models can be compared using relative fit such as the Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), and Adjusted BIC (lower values indicate better fit) [234]. |
| **3** | Models can be evaluated with respect to the accuracy or confidence with which individuals have been classified as belonging to one group or another. Entropy, a statistic that ranges from 0 – 1, higher scores representing higher accuracy. |
| **4** | The Lo–Mendell–Rubin (LMR) and bootstrap likelihood ratio test (BLRT) tests compare the improvement between neighboring class models (i.e., comparing models with two vs. three classes, and three vs. four, etc.) and provide p-values that can be used to determine if there is a statistically significant improvement in fit for the inclusion of one more class. |
| **5** | Smallest class should have more than 25 members |

## 2.4 Definitions of childhood overweight and obesity

The WHO defines obesity as a medical condition where excess body fat is associated with impaired health [235]. Body Mass Index is defined as "a person's weight in kilograms divided by the square of his height in meters ($kg/m^2$)" [30]. It is difficult to develop one simple index for the measurement of overweight and obesity because of physiological changes children and adolescents experience as they grow. Different methods are available depending on the age and gender of the child. For children aged 0-5 years, there is the WHO Child Growth Standards, launched in 2006, where overweight is defined as BMI-for-age Z score of 1 or higher and obesity as BMI-for-age Z score of 2 or higher [30]. For older children and adolescents aged 5-19 years, the WHO developed Growth Reference Data, where overweight is defined as >+1SD (equivalent to BMI 25 $kg/m^2$ at 19 years) and obesity as >+2SD (equivalent to BMI 30 $kg/m^2$ at 19 years) [236].

## 2.5 Assessment of body composition in a child

BMI is a simple index of weight-for-height commonly used to classify overweight and obesity in adults [235]. In children, BMI shows age-related variations and is a suitable clinical index because of its simplicity. While BMI correlates to body fat, it does not provide information on body fat distribution, nor does it distinguish between fat and lean mass [237]. BMI is, however, a good parameter in estimating the risk for metabolic syndrome and CVD [238, 239].

The use of waist-to-height ratio (WHtR) was suggested by McCarthy and Ashwell [240] as a means to measure central adiposity. Various studies have found WHtR to be a good cardio metabolic risk indicator in children and adolescents [241-245] because of its simplicity and ability to be used in large-scale studies. Another benefit of WHtR is that it can identify abdominal obesity in individuals who would not be classified as overweight or obese by BMI [246]. Indeed, it has been proposed that a single WHtR cut-off value of 0.5—irrespective of age, sex, or ethnicity—is a valid predictor of higher cardio metabolic risk [243, 247-250]. For obese children, however, one study has proposed a cut-off value of 0.6 [251]. More recently though, the 0.5 cut-off has been validated as a way to diagnose obesity in Mexican children [252] and will be used in the current dissertation.

We can obtain more accurate information on fat mass by measuring skinfold thicknesses (SF) [253]. However, BMI is considered at least as accurate as SF in identifying children who are at metabolic risk [254]. SF measurements are performed with a caliper, and usually measured at sub-scapular, supra-iliac and triceps skinfold sites. These measurements require observers with careful training and skills. Population-specific knowledge is also required. Ultimately however, the need for careful training and poor reproducibility of results are arguments against SF measurements clinical usage [253, 254].

### 2.5.1 Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) is based on the resistance (R) and reactance (Xc) measurements of body tissues against a small alternating electric current (50 kHz for single frequency BIA) [255]. The current flows easily through tissues with high water/electrolyte content (fat-free mass) which results in low R-values, while tissues such as fat present high R-values [255]. Reactance (capacitance) arises from cell membranes and the R from extra and intracellular fluid. Impedance is the term used to describe the combination of the two [255].

BIA assumes that the body is a cylindrical conductor of a specified length (L) or height (Ht) and an area (A) or volume (V). Although the body is not a uniform cylinder and its conductivity is not constant, we can establish an empirical relationship between the impedance quotient ($Length^2/R$) and the volume of water, which contains electrolytes that conduct the electrical current through the body.

Prediction equations have been developed with Caucasian subjects [256] and, more recently, with African-American and Hispanic subjects [257]. The prediction equation used in this project was specifically developed and validated for Mexican children [258]. Ethnic-specific impedance-based equations for body composition are justified because of differences in body build, frame size, and relative leg lengths among different groups [258-260].

BIA is a relatively simple, low-cost, and safe technique that can be used to assess body composition in health and disease [256, 261]. The use of BIA has

increased because the equipment is portable and safe, the procedure is simple and noninvasive, and the results are reproducible and rapidly obtained.

# Chapter 3: Rationale

## 3.1 Statement of the problem

Nationally representative surveys document an increased prevalence of obesity in Mexico during the last two decades. There was an overall increase in obesity for all age groups, but, most noticeably, in children. One of every three children is now overweight or obese in Mexico [1, 42],is mainly due to the nutrition transition that has resulted in one of the most significant increases in the prevalence of nutrition-related, non-communicable chronic diseases (NR-NCD), even as undernutrition remains a concern [36, 38, 39]. In 2016, having a high BMI was second on the list of the top ten risk factors contributing to death and disability in Mexico [3]. A high BMI also contributes to a host of illnesses including type 2 diabetes, asthma, cancer, osteoporosis, and heart disease [4]. This is of great concern in Mexico as obese children and adolescents are five times more likely to be obese in adulthood [262]. It has also been reported that the development of these NR-NCD epidemics in developing countries differs from developed countries, as NCDs in LMICs tend to occur earlier in life [3, 155] and contribute to three-quarters of premature deaths worldwide.[152]. An explanation for this severe and early onset of NCDs may be the mismatch between early and later environments, as explained in the DOHaD hypothesis. There is substantial evidence to suggest that the path to obesity is established in early life, in prenatal and postnatal periods of growth [5-7]. Identifying such factors and how they work in shaping children's growth trajectory is key. The focus of this dissertation is to study the relationship between growth retardation and growth patterns in early childhood on the

development of childhood obesity and body composition in late childhood in children living in Cuernavaca, Mexico.

### 3.2 Significance of the research

Early childhood growth has been identified as an important predictor of health during late childhood and adult life. While some aspects of growth, such as weight and BMI gain in early life have been associated with adolescent and adult obesity [6, 16, 263, 264], this is not the case for linear growth. These results are mixed [200-202], and longitudinal studies suggest a null or negative relationship between childhood stunting and later obesity [19-21, 26, 203, 204]. However, it is unclear if these findings can be generalized to current LMIC populations, given that the majority are from high-income countries or from longitudinal cohorts in LMICs from 1970 to 1990, which included children born before the recent changes due to nutrition transition. The focus of this study is to uncover the subtler patterns in growth trajectories using latent class growth analysis (LCGA)—a new statistical method—and examine any association between different trajectories of growth and growth retardation in early life as well as adiposity in late childhood.

### 3.3 Objectives and specific aims of the research

The objective of my dissertation research is to determine the relationship between early growth and adiposity in children in late childhood in Cuernavaca, Mexico. The main hypothesis of this project is that children with adverse growth patterns (rapid weight gain or growth retardation) before the age of five will develop obesity or will have higher body fat compared to

their healthy counterparts in late childhood. This objective will be achieved through the following aims:

1. To determine if growth retardation (HAZ ≤ 1.5 Z score) at 24 months of age influences obesity development and body composition in late childhood (8-10 years of age).
2. To identify groups of children with distinct trajectories of growth (birth-5 years of age) using a novel method, latent class growth analysis (LCGA), and to examine any association between different growth trajectories (weight and height) in early life and obesity development at age seven.
3. To identify the relationship between height growth patterns (birth – 5 years of age) using latent class growth analysis (LCGA) and body composition in late childhood (8-10 years of age).

This study will test the following hypotheses:

1. Growth-retarded children at 24 months of age will carry higher body fat and less fat-free mass in late childhood compared to non-growth-retarded children.
2. Children with adverse growth patterns (rapid weight gain or growth retardation) from birth to age five will have higher odds of developing obesity compared to their normal growth counterparts in late childhood.

3. Children classified in the high growth trajectory (taller children) from birth to five years of age, will have less body fat and higher fat-free mass compared to short counterparts.

**Fig 3.1** Sample Selection for dissertation

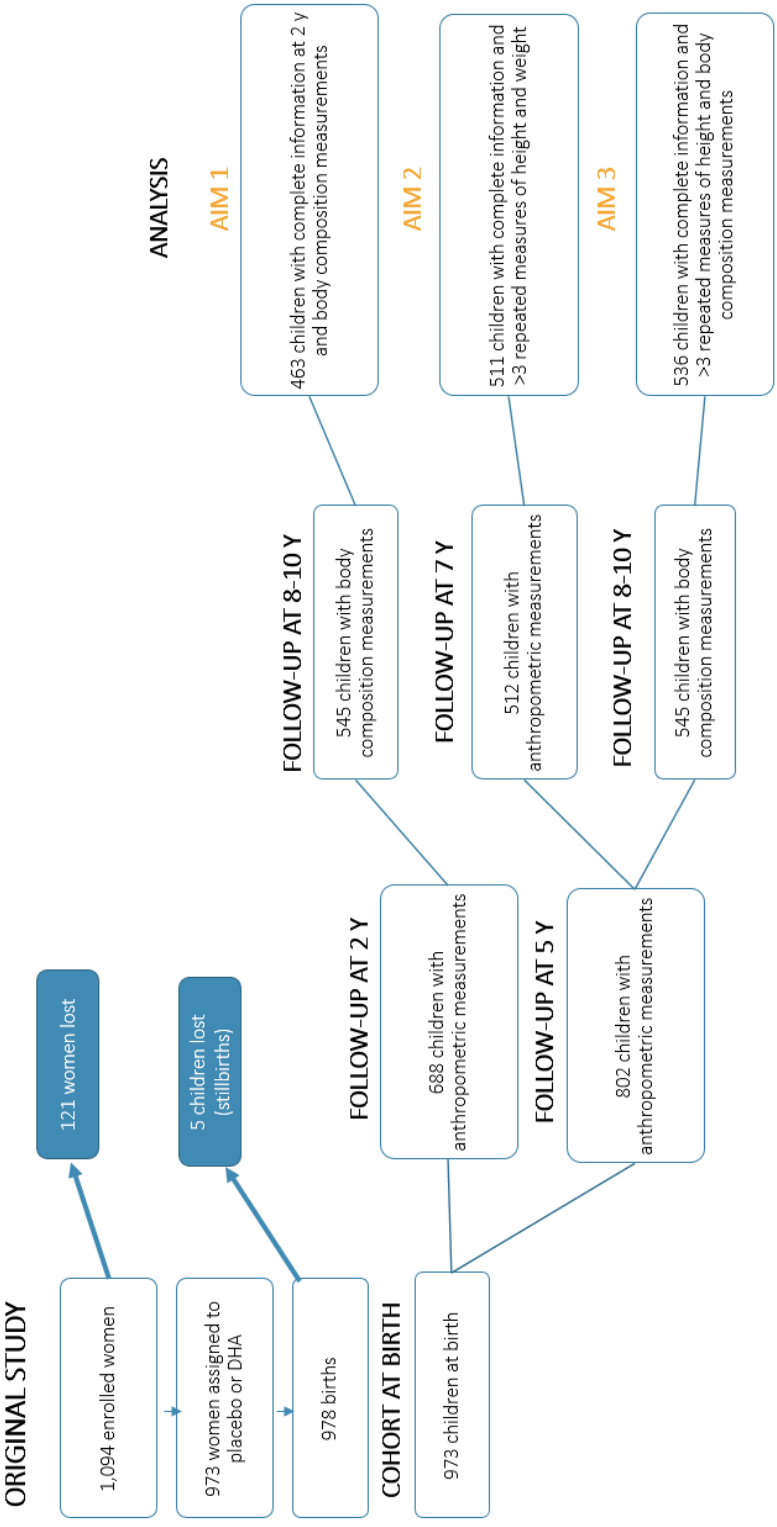
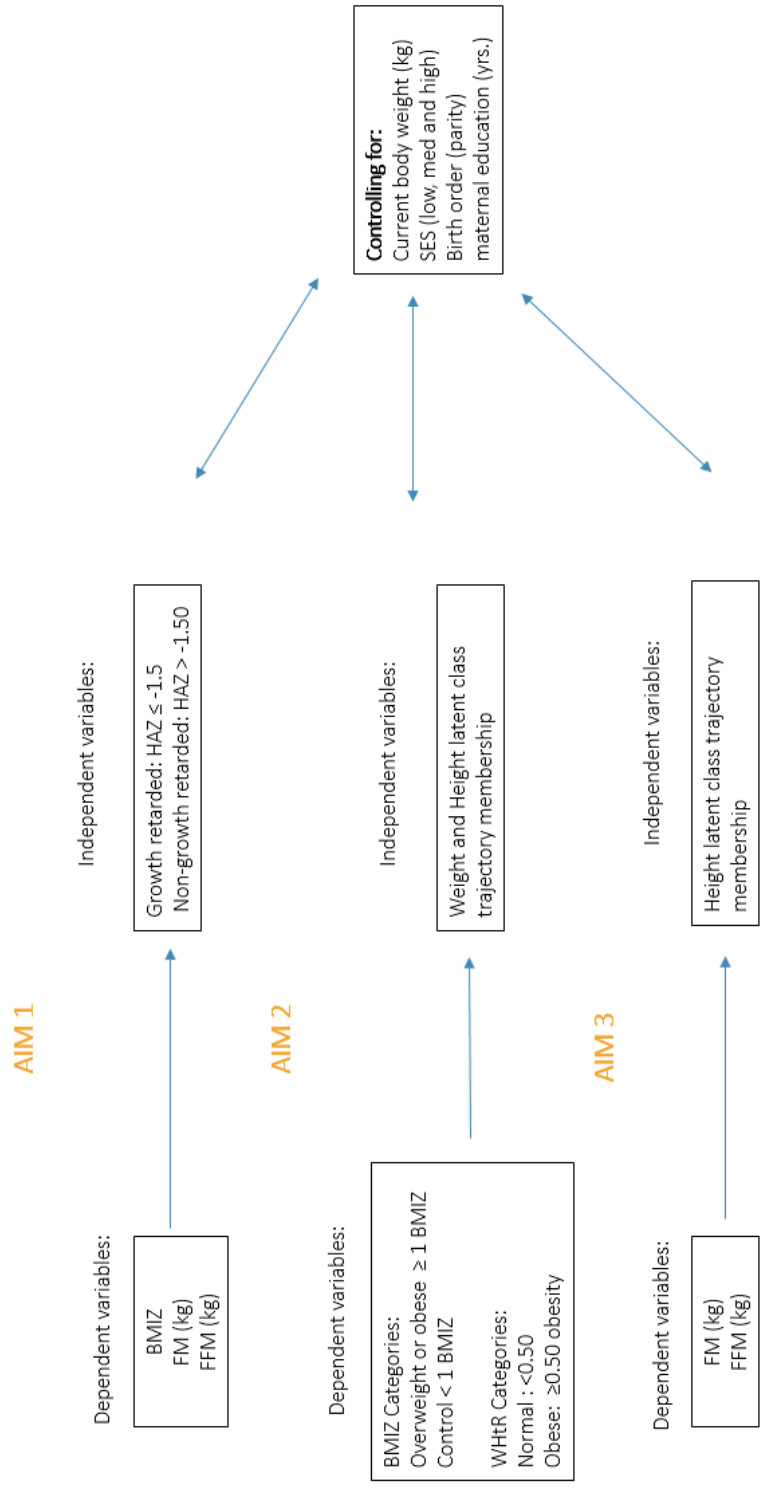


**Fig 3.2** Study Framework




*SES calculated using principal component analysis – details in appendix 6.2

# Chapter 4: Growth Retardation and Body Fatness in Childhood

## 4.1 Abstract

**Objectives:** The prevalence of obesity continues to rise in many transitional and less developed countries. Previous studies have reported an association between chronic undernutrition and later risk for obesity, but most studies have been cross-sectional or were conducted among older birth cohorts from the 1970s, limiting broad conclusions. The objective of this study was to determine the relationship between poor growth and adiposity in children living in a transitional country, Mexico. The primary hypothesis of this study was that children who experience moderate growth retardation were more likely to have greater adiposity compared to children who were of normal height.

**Methods:** Study participants were a sub-sample of a longitudinal cohort study (236 boys, 227 girls). The study participants were the offspring of women (n=1094) who participated in the POSGRAD study, a double-blind, randomized, placebo-controlled trial designed to assess the effects of prenatal supplementation with DHA on offspring growth and development (NCT00646360) that was conducted from 2004-2006, and followed up through age 8-10 y. Body composition measurements were obtained using bioelectric impedance in a subsample of 545 children from the POSGRAD cohort at age 8-10y. Of the 545 children who participated in the body composition measurements 15% (82) were excluded for having not height and/or weight measurements at 24 months of age and there were no significant differences

on follow-up measurements and maternal characteristics between those included and excluded in the analysis. Multivariate linear regression analysis was used to determine the relationship between being HAZ status (category) at 24 months and FM (kg), and FFM (kg) as the outcome variables controlling for current body weight (kg), SES (low, med and high), parity, and maternal education (yrs.). Statistical significance was set a $p< 0.05$.

**Results:** The mean age of the cohort was 8.9 years with an average weight of 31.6 kg ± 7.6, height of 132cm ± 6.5, HAZ of 0.01 ± 0.97, FM 9.8 kg ± 4.2. FFM 21.80 kg ± 3.9 and BMIZ 0.67 ± 1.39. The cohort was split into growth-retarded (HAZ < -1.5) or control (HAZ > -1.50) with 70 and 393 children in each group, respectively. The growth-retarded group had a significant positive association with FM (kg) such that growth-retarded children had more FM 0.55 kg CI 0.18 – 0.92 ($p< 0.001$), and less FFM -0.55 kg CI -0.92 – -0.18 ($p< 0.001$) than non-growth-retarded peers independent of weight, sex, maternal education, parity and socioeconomic status.

**Conclusions**: These results indicate that even moderate degrees of growth retardation in early childhood is associated with increased adiposity later in life. These data support the need for policy makers to continue to focus on strategies that promote healthy growth in transitional and less developed countries.

**KEYWORDS**
Short stature, FFM, FM, childhood obesity

## 4.2 Introduction

The global prevalence of the "double burden of disease", a concurrent high prevalence of both over- and undernutrition, continues to increase and is a serious public health problem [25, 265]. Mexico is just one of a large number of low and middle income countries (LMICs) that is affected by the double burden. As of 2016, the prevalence of childhood obesity reached a new high in which 32% of school children were classified as overweight or obese [1]. During the same time, there are approximately 5.1 million stunted children in Latin America [160] with 1.5 million were in Mexico [1]. Childhood stunting is the most prevalent form of malnutrition worldwide, affecting over 150 million children under five years of age in 2017 [160]. While the prevalence of stunting in Latin America and the Caribbean has decreased over the past three decades [266], it remains a public heath priority due to its long-term consequences. In fact, several studies have reported that stunted children are at a higher risk of becoming obese when dietary and other environmental conditions are favorable, conditions consistent with the nutrition transition [267, 268]. Thus, it is of interest to better understand the relationship between poor growth early in life and the development of obesity, the focus of this study.

Stunting has a complex etiology that involves diet, household environment, socioeconomic and cultural factors [184]. Previous research suggests that stunting or growth faltering is a critical factor in promoting obesity and obesity-related comorbidities later in life [269, 270]. However, evidence linking stunting with obesity or altered energy expenditure is

conflicting [200-202]. More recently, longitudinal evidence suggests a null or negative association between childhood stunting and later obesity [19-21, 26, 203, 204]. The inconsistencies may be partly explained by the use different methods used to assess adiposity as the majority of studies used estimates of body fat and fat distribution.

Childhood undernutrition has been linked to an increased risk of obesity in later life [271, 272] and particularly with increased abdominal fat [180, 273, 274]. With regards to body composition, in a longitudinal study in Senegal where body composition was assessed using the skinfold method, revealed that stunted girls were more likely to accumulate subcutaneous fat in the trunk and arms than non-stunted girls, independent of BMI [275]. In Guatemala, stunted children had a BMI above the median for US children of the same age [276]. In the same cohort, adults who were severely stunted as children had greater central fat, independent of total fat mass and other confounding factors, compared to moderately or never stunted counterparts [164, 274, 277, 278]. However, other prospective studies reported that stunting in early childhood was associated with decreased BMI or body fat in childhood [19, 26], suggesting that difference in methodologies or environmental factors may contribute to differences in results between these studies. The lack of consensus on this topic suggests that a more nuanced understanding of how growth influences adiposity is critical to develop appropriate interventions to reduce the prevalence of childhood obesity.

In Mexico, the prevalence of stunting has declined since 1988, but is still high in some regions, whereas overweight and obesity have increased at alarming rates in all age and socioeconomic groups [28]. There is a need to determine how poor growth may contribute to this high prevalence, as Mexico continues to experience the nutrition transition [28]. At the same time it is important to start thinking about stunting in broader terms. The international agreed upon definition of stunting is when a child falls below -2 SDs from the WHO Child Growth Standards [30]. While cut-offs are important to set limits of what is considered "normal", it is important to keep in mind that growth faltering is a gradation and children slightly above -2SD are at the same risk as children meeting the formal definition of "stunting" [161]. In this study, we studied the relationship between growth retardation at 2 years of age set at ≤ -1.5 SD height-for-age Z score and body composition in late childhood in children living in Cuernavaca, Mexico.

## 4.3 Methods

Study participants were selected from a sub-sample of a cohort that participated in the 8-10 y follow-up of the POSGRAD study, a double-blind, randomized, placebo-controlled trial designed to assess the effect of prenatal supplementation with DHA on offspring growth and development, described in detail elsewhere (NCT00646360) [279]. POSGRAD was conducted in Mexico from 2004 to 2006 with 1,094 women randomly assigned to receive 400 mg/day of algal DHA or placebo from 18 to 22 weeks of gestation through delivery. Birth outcomes (968 live births and 5 stillbirths) were obtained within 24 hours

of delivery. Offspring were followed and anthropometric measurements and body composition were obtained at follow-up.

A total of 545 children completed the body composition measurements at age 8-10, nine repeated measures were excluded due to excess movement during the body composition measurement. Of the 545 individuals who participated in the body composition measurements, 15% (82) were excluded for having not height and/or weight measurements at 24 months of age and there were no significant differences on follow-up measurements and maternal characteristics between those included and excluded in the analysis (supplemental Table 4.1). The final analysis included 463 participants (236 boys, 227 girls) (Figure 4.1).

### 4.3.1 Data collection and variable specification

*Anthropometric Measurements*

Weight and length/height were measured at 24 months and at their 8 – 10 year follow-up, and waist circumference was measured at follow-up, all via the use of standardized procedures [280, 281]. Children were weighed with the use of a portable electronic pediatric scale accurate to 10 g, which was calibrated daily with a known reference weight. Standing height was measured utilizing a stadiometer accurate to 0.1 cm. Waist circumferences (WC) were obtained with the use of a fiberglass tape accurate to 0.1 cm. All measurements were performed twice. Data collection was conducted by trained study

personnel at the Mexican Social Security Institute's Hospital General I in Cuernavaca, Mexico.

*Anthropometric indices calculated*

Standard z-scores of height for age (HAZ) and BMI for age (BMIZ) were estimated using age in days, and calculated age-specific z scores relative to school-aged children and adolescent WHO standards [282] for their follow-up at seven years. WC divided by height was used to calculate the waist–to–height ratio. Our predictor of interest was growth-retardation at age 2 y, defined as HAZ ≤ -1.5. Using children's 24 month HAZ score they were categorized into two groups, growth-retarded HAZ ≤ -1.5 or control HAZ > -1.50.

*Body Composition*

Body composition was estimated with a tetrapolar bioimpedance analyzer (Impedimed DF50) and validated equations for raw values of resistance Ω and reactance Ω for Mexican children [258]. P.L.B. and trained personnel made all the measurements using a standardized protocol. Briefly, distal and proximal electrodes were placed 5cm apart and all measurements were made on right wrist and the right ankle with the participant supine. We took the average of two trials (between 4.0 and 4 min 59 s) as the final impedance value. Maximum allowable differences between two measurements were 3 Ω for both resistance (R) and reactance (Xc) [258]. Mothers were instructed to bring the child after a four-hour fast (no caffeinated beverages or food) and 500ml of sweet juice drink was offered 60 minutes prior testing to

ensure proper hydration for children nine years of age who chose to participate in venous blood sample and come in with an overnight fast. All children were instructed to restrict extraneous PA for > 8 hours and void before the measurement.

*Covariates*

Maternal age, education and socioeconomic status were obtained at recruitment. Socioeconomic status was calculated using a list of assets obtained by interview [279]. The Emory University Institutional Review Board and the National Institute of Public Health Biosafety, Investigation, and Ethics Committees both approved the protocol. Written informed consent was obtained from participating mothers after they received a detailed explanation of the study at baseline and during their offspring follow-up and assent of participating children.

## 4.4 Statistical analysis

We stratified the data on growth-retarded status at age 24 months and calculated descriptive statistics. We tested differences in covariate values between growth-stunted and non-growth-stunted children at 24 months, gender and included vs. excluded due to missing measures at 24 months with the use of Pearson's chi-square test, and Student's t test.

Multivariate linear regression analysis was used to determine the relationship between being HAZ status (category) at 24 months and FM (kg), and FFM (kg) as the outcome variables controlling for current body weight (kg),

SES (low, med and high), parity, and maternal education (yrs.). All statistical analyses were conducted using STATA 15 (StataCorp LLC, College Station Texas, USA), and statistical significance was determined at $P < 0.05$.

## 4.5 Results

Seventy (15.1%) children were growth-retarded at 2 years of age and they were not only significantly shorter (83.42 cm ± 4.20 vs. 89.51cm ± 4.85) but also significantly lighter (10.85 kg ±1.39 vs. 12.89 kg ± 1.79) than their non-growth-retarded peers ($p < 0.05$) (Table 4.1). They were also younger, but by only 0.05 years on average, which is equivalent to 18 days not statistically significant. Growth-retarded children had significantly lower BMIZ scores (-0.19 ± 1.03 vs. 0.19 ± 0.96) and HAZ scores (-1.91 ± 0.37 vs. -0.21 ± 0.79) compared to their counterparts at age 2. At follow-up (8-10 yrs.), non-growth-retarded children remained significantly heavier, taller, had higher WC, greater FFM (kg), FM (kg), higher BMIZ and HAZ scores than their growth-retarded counterparts ($p < 0.05$). Growth-retarded children's moms were significantly shorter, by 2.9 cm on average and no significant differences were found in maternal age, weight, BMI, schooling and SES. At follow-up, the average age was 8.89 yrs. and 51% were boys (Table 4.2). On average, girls had 2.4% more body fat and less FFM, 1.33 kg. There were no significant differences in weight, height, WC, BMIZ or HAZ between both genders.

Growth retardation at two years of age was a significant predictor of greater FM ($\beta = 0.55$ kg, $p < 0.05$) and lower FFM ($\beta = -0.55$ kg, $p < 0.05$) after

adjusting for covariates (Table 4.3). At follow-up, girls had significantly higher FM (β = 0.94 kg, $p < 0.05$), significantly lower FFM (β = - 0.94 kg, $p < 0.05$), compared to boys (Table 4.3). Finally, growth-retarded children had significantly higher BMIZ compared to normal height peers BMI Z (β = 0.46, $p < 0.05$).

## 4.6 Discussion

The prevalence of overweight and obesity for children at age 8-10 years of age in this prospective cohort study was 41%, and there was no significant difference in the prevalence of overweight and obese children between the growth-retarded group and the non-growth-retarded group. However, after controlling for confounding variables, growth-retarded children had a higher BMI Z score compared to non-growth-retarded children. We also observed that children in the growth-retarded group had higher FM and lower FFM at follow-up compared to their non-growth-retarded counterparts. Our results suggest that a relationship exists between stunting in early childhood and overweight/obesity in later childhood. Previous cross-sectional studies have reported a positive relationship between stunting and obesity in countries undergoing nutrition transition, such as Mexico [22] and other populations. [23, 283] However, recent prospective studies have reported a decreased BMI or FM at different ages and stunting in early childhood [19, 20, 26, 217, 218, 274] and several others that have reported null results [20, 21]. It may well be that the relationship between stunting and childhood obesity emerges only

when environmental conditions that favor obesity, such as changes in dietary patterns and physical activity, such as Mexico where approximately 70% of adults are obese [1].

Various studies have touched upon this association, stunting in childhood has been linked to later obesity via fat deposition at puberty [273, 284, 285]. In our cohort, growth retardation at age two was associated with 0.55 kg more of FM compared to non-growth-retarded children. At the same time growth-retarded children had less FFM, -0.94 kg, compared to non-growth-retarded children. Our study contributes to the current literature, as we are the first to investigate association between growth retardation in early childhood with body composition in later childhood using a validated body composition equation for Mexican children [258]. As well, it will inform and understanding of how being short at age two is associated with high FM and FFM in a country currently undergoing nutrition transition.

Apparent differences in reported associations between growth and adiposity limit the generalizability of findings and their association may be context-specific [286]. In a recent study, environmental differences were the key determining for results observed in the relationship between BMI with increasing stature in Peru [287]. The study authors suggested that differences between rural and urban populations may arise from environments that present different opportunities for catch-up growth and the accrual of adipose tissue. We considered the differences in environment by controlling for SES in

our analysis, despite our urban study location of Cuernavaca. Childhood household SES likely functions as a proxy for a number of important factors that influence the early life environment, such as access to health care [288].

The increased prevalence of obesity in stunted children in developing countries is of concern as it contributes to the double burden of diseases [25, 153]. Our results indicate that although Mexican children in our study are not classified as stunted HAZ <-2 [30], but having expanded the range to HAZ ≤ -1.5 to include growth-retarded children, short children have a higher FM and lower FFM, and this is more pronounced in girls. Linear growth retardation has been shown to be associated with decreased adult lean mass in previous studies [289-291] and our findings corroborated this as we showed that growth-retarded children in early childhood have less lean mass in later life. This is of concern as it has been suggested that stunted children would have a higher predisposition to develop obesity and metabolic complications later in life due to decreased energy expenditure; these associations have been replicated in some studies of developing countries but not in all [26, 218, 272, 292]. Thus, evidence linking stunting or linear growth and adult body composition remains inconsistent. In the present study non-growth-retarded children at two years of age had more FFM and less FM. Effects of early-life stunting on adiposity development later in childhood are not well understood, specifically with respect to age in the onset of adult overweight and obesity.

As with any study, there are limitations that merit discussion to most fully appreciate the results presented. First, it is always possible that unknown confounding factors that were not measured limit the ability to infer causality from the relationships presented. Second, we did not have clinical data on pubertal development that may have influenced growth, including rapid changes in body size and composition, and some of our children were already 10 years of age. In fact, the sexually dimorphic differences between boys and girl may have influenced regional distribution of body fat [293] as we observed in our study sample with the higher FM and lower FFM in the girls in our study. There are a number of important strengths to our study. For example, the final sub-sample at follow-up was well balanced with respect to maternal and SES characteristics. Finally, body composition was assessed using a valid and precise methodology (BIA) and FM was calculated from raw data and a validated equation for Mexican children.

## 4.7 Summary and conclusions

In summary, based on the results of this study, growth retardation in early childhood contributes to excess adiposity later in childhood. As the prevalence of childhood obesity continues to increase in many developing and transitional countries, a greater understanding of how growth contributes to the double burden of disease is warranted. In particular, future research needs to focus on discrete aspects of growth and the development of obesity to better understand how to prevent or reverse the double burden of disease.

**Figure 4.1** Birth cohort study sample.

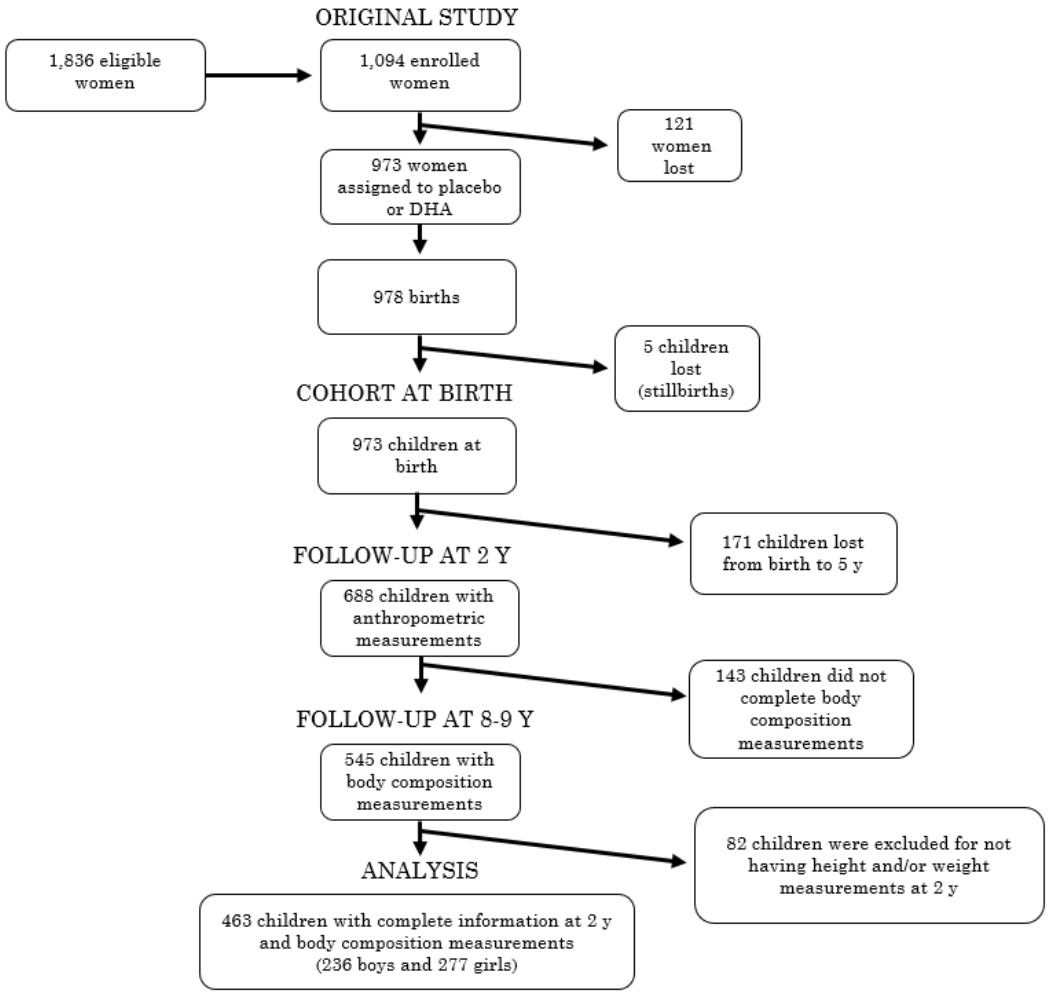


**Table 4.1** Maternal and child characteristics at 2 and 8-10 years for growth-retarded and non-growth-retarded children at age 2 in participants of the POSGRAD cohort.

| | 2 Years | | | 8-10 Years | | |
|---|---|---|---|---|---|---|
| | HAZ > -1.5 (n = 393) | HAZ ≤ -1.5 (n = 70) | p-value[a] | HAZ > -1.5 (n = 393) | HAZ ≤ -1.5 (n = 70) | p-value[a] |
| **Children Characteristics** | Mean (SD) | | | Mean (SD) | | |
| Age, yrs. | 2.42 (0.49) | 2.37 (0.47) | 0.45 | 8.89 (0.52) | 8.90 (0.56) | 0.84 |
| Weight, kg | 12.89 (1.79) | 10.85 (1.39) | 0.00 | 32.32 (7.56) | 27.36 (5.95) | 0.00 |
| Height, cm | 89.51 (4.85) | 83.42 (4.20) | 0.00 | 133.09 (6.01) | 125.58 (5.63) | 0.00 |
| Waist, cm | | | | 68.03 (9.40) | 67.53 (10.29) | 0.00 |
| Waist-to-height ratio | | | | 0.51 (0.06) | 0.49 (0.08) | 0.16 |
| Fat Free Mass, kg | | | | 22.23 (3.92) | 19.37 (3.20) | 0.00 |
| Fat Mass, kg | | | | 10.09 (4.24) | 7.99 (3.16) | 0.00 |
| Fat Mass, % | | | | 30.16 (6.65) | 28.34 (5.79) | 0.03 |
| HAZ score | -0.21 (0.79) | -1.91 (0.37) | 0.00 | 0.20 (0.89) | -1.06 (0.70) | 0.00 |
| BMI Z score | 0.19 (0.96) | -0.19 (1.03) | 0.00 | 0.72 (1.37) | 0.38 (1.44) | 0.05 |
| BMI-for age Z-score >1 (%(n))[b] | | | | 42 (166) | 34 (70) | 0.21 |
| Parity | 2.03 (1.03) | 1.89 (1.11) | 0.26 | | | |
| **Maternal Characteristics** | | | | | | |
| Age, yrs. | 26.81 (4.76) | 26.72 (4.63) | 0.88 | | | |
| Height, cm | 155.67 (5.66) | 152.8 (6.33) | 0.00 | | | |
| Weight, kg | 63.70 (11.01) | 61.93 (14.73) | 0.24 | | | |
| BMI, kg/m$^2$ | 26.28 (4.29) | 26.48 (5.53) | 0.73 | | | |
| Schooling, yrs. | 12.15 (3.43) | 11.35 (3.81) | 0.08 | | | |
| | | | | | | |
| **Household Characteristics** | | | | | | |
| *SES* | N (%) | | | | | |
| 1 Lowest | 120 (31) | 26 (37) | 0.51 | | | |
| 2 | 127 (32) | 19 (27) | | | | |
| 3 Highest | 146 (37) | 25 (36) | | | | |

[a]Group differences assessed by using Student's t-test or $\chi^2$ test. [b]WHO 2006 [282] BMIZ score cut-offs for overweight and obese children.

**Table 4.2** Gender differences at follow-up (8 - 10 years of age) of the POSGRAD cohort.

| | **Boys** | **Girls** | |
|---|---|---|---|
| | Mean (SD) | | p-value[a] |
| N | 236 | 227 | |
| Age, yr. | 8.87 (0.54) | 8.91 (0.51) | 0.43 |
| Weight, kg | 31.98 (7.47) | 31.15 (7.63) | 0.28 |
| Height, cm | 132.35 (5.94) | 131.54 (7.08) | 0.18 |
| Waist, cm | 67.25 (9.98) | 67.19 (9.48) | 0.94 |
| Fat Mass, kg | 9.53 (4.15) | 10.02 (4.17) | 0.20 |
| Fat Mass, % | 28.69 (6.31) | 31.13 (6.58) | 0.00 |
| Fat Free Mass, kg | 22.45 (3.79) | 21.12 (4.02) | 0.00 |
| Waist-to-height ratio | 0.51 (0.07) | 0.51 (0.06) | 0.69 |
| BMI Z score | 0.79 (1.48) | 0.55 (1.27) | 0.06 |
| HAZ score | 0.08 (0.88) | -0.07 (1.06) | 0.10 |
| | N (%) | | |
| HAZ score ≤-1.5 at 24 m | 36 (15) | 34 (15) | |

[a]Group differences assessed by using Student's t-test or $\chi^2$ test.

**Table 4.3** Growth retardation at 2 years as a predictor of body composition, FM (kg), FFM (kg), and BMI Z-score at follow-up, adjusted models.

| | FM, kg | | | FFM, kg | | | BMI Z | | |
|---|---|---|---|---|---|---|---|---|---|
| | ß | 95% CI | p-value | ß | 95% CI | p-value | ß | 95% CI | p-value |
| **HAZ at 24 m.** | | | | | | | | | |
| >-1.5 | – | – | – | – | – | – | – | – | – |
| ≤-1.5 | 0.55 | (0.18 – 0.92) | 0.00 | -0.55 | (-0.92 – -0.18) | 0.00 | 0.46 | (0.29 – 0.63) | 0.00 |
| **Sex** | | | | | | | | | |
| Male | – | – | – | – | – | – | – | – | – |
| Female | 0.94 | (0.69 – 1.20) | 0.00 | -0.94 | (-1.20 – -0.69) | 0.00 | -0.11 | (-0.23 – 0.01) | 0.08 |
| Weight, kg | 0.52 | (0.51 – 0.54) | 0.00 | 0.48 | (0.46 – 0.49) | 0.00 | 0.17 | (0.16 – 0.17) | 0.00 |
| **SES** | | | | | | | | | |
| Low | – | – | – | – | – | – | – | – | – |
| Medium | -0.02 | (-0.35 – 0.31) | 0.93 | 0.02 | (-0.31 – 0.34) | 0.93 | 0.05 | (-0.11 – 0.20) | 0.55 |
| High | 0.01 | (-0.32 – 0.34) | 0.97 | -0.01 | (-0.34 – 0.32) | 0.97 | 0.10 | (-0.05 – 0.25) | 0.18 |
| Parity | -0.06 | (-0.19 – 0.07) | 0.39 | 0.06 | (-0.07 – 0.19) | 0.39 | 0.02 | (-0.04 – 0.08) | 0.60 |
| Maternal education, yrs. | 0.03 | (-0.01– -0.07) | 0.11 | -0.03 | (-0.07 – 0.01) | 0.11 | -0.02 | (-0.04 – 0.00) | 0.06 |

**Supplemental Table 4.1** Differences in characteristics at follow-up between the children with complete measurements vs. missing height and weight at the 24 month follow-up from the POSGRAD cohort.

| | **Included** | **Excluded** | **p-value[a]** |
|---|---|---|---|
| | Mean (SD) | | |
| N | 463 | 82 | |
| Age, yrs. | 8.89 (0.52) | 8.99 (0.54) | 0.09 |
| Weight, kg | 31.57 (7.55) | 31.62 (8.20) | 0.95 |
| Height, cm | 131.95 (6.53) | 132.30 (7.11) | 0.66 |
| Waist, cm | 67.22 (9.72) | 67.53 (10.40) | 0.79 |
| Fat Free Mass, kg | 21.80 (3.96) | 21.81 (3.99) | 0.98 |
| Fat Mass, kg | 9.77 (4.16) | 9.81 (4.74) | 0.94 |
| Fat Mass, % | 29.89 (6.55) | 29.66 (6.98) | 0.78 |
| Waist-to-height ratio | 0.51 (0.07) | 0.51 (0.07) | 0.88 |
| BMI Z score | 0.67 (1.39) | 0.57 (1.43) | 0.53 |
| HAZ score | 0.01 (0.97) | -0.03 (1.01) | 0.73 |
| Parity | 2.03 (1.03) | 1.89 (1.11) | 0.26 |
| **Maternal Characteristics** | | | |
| Height, cm | 155.24 (5.85) | 155.83 (5.49) | 0.39 |
| Weight, kg | 63.43 (11.64) | 64.21 (12.53) | 0.58 |
| BMI, kg/m$^2$ | 26.31 (4.50) | 26.35 (4.31) | 0.95 |
| Schooling, yrs. | 12.03 (3.50) | 11.70 (3.65) | 0.44 |
| | | | |
| **Household Characteristics** | | | |
| *SES* | N (%) | | |
| 1 Lowest | 146 (32) | 16 (20) | 0.05 |
| 2 | 146 (32) | 35 (40) | |
| 3 Highest | 171 (36) | 31 (38) | |

[a]Group differences assessed by using Student's t-test or $\chi^2$ test.

# Chapter 5: Early height and weight growth patterns and later overweight and obesity in middle childhood

## 5.1 Abstract

**Background and objectives:** Growth during infancy is important for future health and overall well-being and rapid weight gain during childhood has been associated with adverse health effects in adulthood. Latent class growth analysis (LCGA) identifies heterogeneity of growth patterns in cohort subgroups whereas other modeling techniques assume a single underlying trajectory per population. In LCGA, similar individuals are grouped together on the basis of their growth characteristics. The aim of this study was to derive height and weight growth trajectories from birth to 5 years of age in Mexican children and identify their association with obesity status in late childhood.

**Methods:** Study participants were a sub-sample that participated in the 7-year follow-up of the POSGRAD study, a double-blind, randomized, placebo-controlled trial designed to assess the effect of prenatal supplementation with DHA on offspring growth and development (279 boys, 232 girls). Sex-specific height and weight latent class trajectories were derived from 11 measures of height and weight from birth to 5 years of age. Analyses were conducted by using MPlus version 7.3 (Muthén & Muthén). After classifying participants into trajectories, a multivariable-adjusted logistic regression was used to determine the relationship between growth (height and weight) trajectory classes and BAZ, WC and WHtR at 7 years of age, controlling for confounders. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. All

statistical analyses were conducted with STATA 15 (StataCorp LLC, College Station Texas, USA), and statistical significance was determined at $p < 0.05$.

**Results:** The prevalence of overweight and obesity in this cohort was 32%. Two weight and height latent classes were identified in girls [height: low (46%) and high (54%), weight: low (58%) and high (42%) and two classes in boys [height: low (51%) and high (49%), weight: low (51%) and high (49%)]. The 2-class models for girls and boys had the highest entropy (sign of successful convergence), > 0.81. Classes also had the highest posterior probabilities of candidate models suggesting high class separation, all above ~0.93. In boys, remaining heavier in the first five years of life was significantly associated with being overweight or obese at seven years of age, BAZ (OR 4.8; 95% CI 2.67 – 8.65; $p < 0.05$), WHtR ≥ 0.5, (OR 2.33; 95% CI 1.34 – 4.07; $p < 0.05$), compared to boys in the low weight trajectory. The same trend was observed for girls, BAZ (OR: 6.73; 95% CI 3.66 – 12.36; $p < 0.05$) and WHtR ≥ 0.5 (OR 6.55; 95% CI 3.53 – 12.12; $p < 0.05$). Taller boys in early childhood were less likely to be categorized as overweight or obese compared to shorter boys, BAZ (OR 0.02; 95% CI 0.00 – 0.11; $p < 0.05$) and OR WHtR ≥ 0.5, 0.05; 95% CI 0.02 – 0.15; $p < 0.05$). The same was observed for taller girls, BAZ (OR 0.10; 95% CI 0.02 – 0.43; $p < 0.05$) and WHtR ≥ 0.5 (OR 0.07; 95% CI 0.02 – 0.27; $p < 0.05$).

**Conclusions:** Based on these results, distinct height and weight trajectories separate within the first months of life, suggesting that early life factors may

play a role in this separation. There is a greater need to understand how early growth (height gain and weight gain) contributes to the development of obesity, as the prevalence of childhood obesity continues to rise in many LMICs.

**KEYWORDS:** child nutrition, latent class growth analysis, height, fat mass, BIA

## 5.2 Introduction

The global prevalence of obesity continues to increase in many developing countries across the world [294-296]. Countries that were formerly known for having a high prevalence of undernutrition now face the "double burden", the co-existence of under- and overnutrition in the same communities and households [25, 265]. In low and middle income countries, the prevalence of overweight among stunted children younger than five years of age is 10% [265] and the increased prevalence of obesity in children and adolescents is greater than the decline of undernutrition [294]. Therefore, a life-course approach may be the key to understanding how growth influences future body weight and size. Thus, the objective of this study was to determine how height and weight patterns influence childhood adiposity in Mexico, a country undergoing rapid economic and dietary changes.

Rapid weight gain early in life has been reported to be associated with adolescent and adult obesity [6, 16, 263, 264]. A prospective cohort study in the USA reported that rapid increases in weight for length in the first 6 months of life were associated with an increased risk of obesity by 3 years of age [213]. A longitudinal study in England also reported that excess weight gained by 5 years of age predicted overweight at 9 years of age [297]. With regards to linear growth, some prospective studies report that stunting in early childhood is associated with decreased BMI or body fat in childhood [19, 26] or adolescence [20, 217, 218], while other studies have found null associations [20, 21].

However, it is unclear if these findings can be generalized to current low and middle income countries (LMIC) populations, given that the majority of these findings are from high-income countries or from longitudinal cohorts in LMIC from the 1970 to 1990 that included children born before the recent changes due to nutrition transition.

Earlier studies on growth patterns, have failed to uncover the more subtle patterns in growth trajectories due to the statistical methods employed. With regards to metrics of early growth, the most common measurements used are length, weight and BMI and most researchers quantified growth by subtracting anthropometric measurements made at two time points, and sometimes without adjusting for the time interval [221]. This is of concern due to the variability of growth rate, meaning that any comparisons of absolute BMI, weight or length gains over different periods of growth will be affected by growth rates and may result in misleading inferences about their relative importance for later outcomes. More recently, new techniques in statistics have made it possible to study the heterogeneity in growth during childhood [222, 223], assuming that there are different developmental trajectories in the study population and children have different pathways in the development of obesity. The categorization of groups of individuals with similar patterns of growth over a period of time can provide insight into different pathways of development during childhood.

Early detection is important for the prevention of overweight and obesity among adolescents and adults. Various measures are used for detecting obesity and the risk of obesity-related comorbidities. The most widely used measure for all ages is BMI, due to its simplicity and affordability, supplementary measures such as waist circumference (WC) and waist-to-height ratio (WHtR) are specific indexes of abdominal fat and have been proposed as markers of adiposity related morbidity in children [247, 298]. Measuring WHtR may be advantageous over BMI, as it represents abdominal fat [299] and BMI does not provide information on body fat distribution. Central obesity in children has been associated with the risk of cardiovascular and metabolic diseases [300], and poses greater health risks than total body fat [301]. Various studies find that WHtR is a good cardio metabolic risk indicator in children and adolescents [241-245], due to its simplicity and ability to be used in large scale. This methods also allows to identify abdominal obesity, particularly in individuals who would not be classified as overweight or obese by BMI [246]. It has been proposed a single WHtR cut-off value of 0.5, irrespective of age, sex, or ethnicity, as a valid predictor of higher cardio metabolic risk [243, 247-250], although for obese children, a study has proposed a cut-off value of 0.6 [251]. More recently, the same cut off (0.5) has been validated to diagnose childhood obesity in Mexican children [252].

Mexico has experienced an increase in the prevalence of overweight and obese children with a combined prevalence of 9.7% in preschool-aged children,

34.4% in school-aged children, and 35% in adolescents [32]. Although the prevalence of the double burden at an individual level was low, it is still of concern as Mexico continues to go through nutrition transition [28]. To our knowledge, we are the first study to use latent class growth analysis (LCGA), to explore the heterogeneity in height and weight gain over the life course (birth - 5 years). Therefore, the aims of the present study were two, first, to identify groups of children with distinct trajectories of growth, and to examine any association between different trajectories of growth in early life and body size at age seven.

## 5.3 Methods

Study participants were the offspring of women who participated in the POSGRAD (Prenatal Omega-3 fatty acid Supplementation and child GRowth And Development) study and completed the seven year follow-up. The POSGRAD study was a double-blind, randomized, placebo-controlled trial designed to assess the effect of prenatal supplementation with DHA on offspring growth and development, described in detail elsewhere (NCT00646360) [279]. POSGRAD was conducted in Mexico from 2004 to 2006 with 1,094 women randomly assigned to receive 400 mg/day of algal DHA or placebo from 18 to 22 weeks of gestation through delivery. Birth outcomes (968 live births and 5 stillbirths) were obtained from hospital records within 24 hours of delivery. Offspring were followed and anthropometric measurements were obtained at follow-up.

A total of 512 children completed the seven year visit with an average of 9.5 repeated measurements for both height and weight. The lowest number of repeated measures was three, the minimum value to maintain model stability when using LCGA [226], one child was removed for having less than three repeated height and weight measurements between 0 - 60 months. The final analysis included 511 participants (279 boys, 232 girls) (Figure 5.1).

### 5.3.1 Data collection and variable specification

*Anthropometric Measurements*

Birth measurements were obtained from hospital obstetric records. Weight and length/height were measured at 1, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months and 7 years, and waist circumference was measured at 7 years, all via the use of standardized procedures [280, 281]. Children were weighed with the use of a portable electronic pediatric scale accurate to 20 g (birth – 12 months) and 100g (18 - 60 months), which was calibrated daily with a known reference weight. Recumbent length was measured in children younger than 24 months and standing height was measured utilizing a stadiometer accurate to 0.1 cm. Waist circumferences (WC) were obtained with the use of a fiberglass tape accurate to 0.1 cm. All measurements were performed twice. Data collection was conducted by trained study personnel at the Mexican Social Security Institute's Hospital General I in Cuernavaca, Mexico.

*Anthropometric indices calculated*

Standard z-scores of height for age (HAZ) and BMI for age (BAZ) were estimated using age in days, and calculated age-specific z scores relative to school-aged children and adolescent WHO standards [282] for their follow-up at seven years. Overweight was defined as 1≤BAZ≥2, obesity as BAZ>2SD, according to the using the NHANES 2004 Hispanic reference [282]. Central obesity for boys was defined as WC≥90th %ile and 70.6 cm and for girls as WC≥90th %ile 69.4 cm, based on the NHANES 2004 Hispanic population at 7 years [302]. WC divided by height was used to calculate the waist–to–height ratio and WHtR cut-offs used to identify childhood obesity in Mexican children were <0.50 normal and ≥0.50 obesity [252].

*Covariates*

Maternal education and socioeconomic status variables were obtained at recruitment. Socioeconomic status was calculated with the use of principal components analysis on a list of assets obtained by interview [279]. The study protocol was approved by the Emory University Institutional Review Board and by the National Institute of Public Health Biosafety, Investigation, and Ethics Committees in Mexico. Written informed consent was obtained from participating mothers after they received a detailed explanation of the study at baseline and during their offspring follow-up.

## 5.4 Statistical Methods

Mean values and SD were calculated for continuous variables and frequency distributions for categorical variables by sex and according to LCHT

(latent class height trajectory) or LCWT (latent class weight trajectory) membership. Student's t-test was performed to assess differences in continuous variables and $\chi^2$ for categorical variables.

LCGA models were used instead of other non-latent class type models to identify homogenous subpopulations or distinct growth patterns within a larger cohort. In non-latent class type growth modeling, a single curve would be estimated for the whole population, which can potentially potential hide heterogeneity within the sample [234]. LCGA allows individuals with similar growth characteristics to be grouped together and provides each latent class its own growth curve [303]. Height and weight latent class trajectories were derived from the following 11 possible measures of height and weight: Birth, 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. Among included participants, less than 1% had three measurements and 96% had six measurements or more. Finally, sex-specific trajectories were modeled because of the potential for sex differences in growth across childhood [304].

LCGA was used to develop a series of models with 2 - 4 classes using all available data and a robust maximum likelihood estimation and 200 random starts values to avoid local solutions, generating a curve that represents the global maximum solution [226]. As there is no definitive criteria for selecting the optimal number of classes, a combination of statistical criteria and interpretability was employed [305]. Briefly, we assessed the model fit using Bayesian information criterion, the Bootstrap Likelihood Ratio Test, and the

Lo-Mendell-Rubin Likelihood Ratio Test and also took the interpretability of classes into account when determining the final model [226]. Entropy (higher value indicates greater classification accuracy, range 0-1) and posterior probabilities (probability of assigning observations to groups given the data) were used to assess the quality of the classification [234, 306]. In addition, Finally, each group had an adequate sample size of N > 25 per group [232]. Sex-specific LCHT s were derived using MPlus v.7.3 (Muthén & Muthén).

After classifying participants into trajectories, a multivariable-adjusted logistic regression was used to determine the relationship between growth (height and weight) trajectory classes and BAZ, WC and WHtR at 7 years of age, controlling for current body weight (kg), SES (low, med and high), parity and maternal education (yrs.). Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. All statistical analyses were conducted with STATA 15 (StataCorp LLC, College Station Texas, USA), and statistical significance was determined at $p < 0.05$.

## 5.5 Results

Summary characteristics of study participants at follow-up are presented in Table 5.1**.** Of the total study sample, 55% were male and the average age for girls and boys was 7.16 ± 0.22 and 7.11 ± 0.17 years, respectively. At follow-up, there was no significant differences in weight between girls and boys, yet boys were significantly taller than girls, 122 ± 5.0cm vs 120.8 ± 5.6cm, respectively. Girls' waists were significantly larger

than boys' waists, 62.5 cm ± 8.3 vs. 60.6 cm ± 7.4. At follow up, 28% of boys and 35% of girls were overweight or obese according to WHO cut-offs [282] and a greater %age of girls had higher central adiposity WC ≥ 90$^{th}$ %ile based on the NHANES 2004 Hispanic population [302] 23 % vs 12 % girls and boys respectively. More than half of the girls (55%) and only one third (33%) of boys were classified as obese using the WHtR 0.50 cut-off for Mexican children [252]. There was a difference in the %age of children classified as obese depending on the screening tool used. Using WHtR, estimated that 55% of the girls to be obese while BMI Z scores only estimated 14% the same trends are observed in boys with 33% vs 13%, respectively.

*Height and Weight Trajectories*

The best-fitting latent class growth model on the basis of model fit and quality of classification identified two LCHT and two LCWT in girls and boys. Girls' LCHT [low (46%) and high (54%)] and LCWT [low (58%) and high (42%)] (fig. 5.2A and 5.3A). Boys' LCHT [low (51%) and high (49%)] and LCWT [low (51%) and high (49%)] (fig. 5.2B and 5.3B) (Supplemental Table 5.1 and 5.2). The 2-class models for girls and boys had high entropy (> 0.81) indicating successful convergence. Classes also had the highest posterior probabilities of candidate models (>0.93), suggesting high class separation. An additional class did not improve fit suggested by the Lo-Mendell-Rubin Likelihood Ratio Test and the Bootstrap Likelihood Ratio Test (Supplemental Table 5.1 and 5.2). Among boys, around half of the participants were categorized belonging to both

low LCHT and LCWT, n=134 (48%), while only one quarter n=73 (26%) belonged to both high LCHT and LCWT. Of the 232 girls in the study, n=96 (41%) were in the low trajectory for both height and weight and n=87 (38%) belonged to both high trajectories of height and weight.

*Relationships of growth trajectories on obesity at seven years of age*

Anthropometric characteristics of the sample by class membership are shown in Table 5.2.

*Latent class height trajectories:* At age 7, children belonging to the high LCHT for both girls and boys were significantly heavier by difference of > 3.5 kg and had larger WC by > 3.1cm, compared to the low LCHT. They remained taller by > 6.9 cm, and also had a higher HAZ score at follow-up. A greater %age of children in the high LCHT were classified as obese with a BAZ of > 2 [282] with over 17 % of children obese in the high LCHT vs 9% and 8% in the low LCHT for boys and girls, respectively. A greater proportion of children were also classified as having a WC over the >90$^{th}$ %ile based on the NHANES 2004 Hispanic population [302], in the high LCHT groups for both sexes, with >17% in the high LCHT and only 8% and 13% in the low LCHT for boys and girls, respectively ($p<0.05$) (Table 5.2). Using the WHtR 0.5 cut-off [252] to diagnose obesity in Mexican children, of the girls classified in the high LCHT 64 % were classified as obese compared to 43% in the low LCHT and one third of boys were classified as obese in both high and low LCHT.

*Latent class weight trajectories:* At follow-up, children belonging to the high LCWT were significantly heavier (by > 5.7 kg), taller (by >5.9 cm), and had higher WC by at least 6.7cm compared to the children in the low LCWT in both sexes ($p<0.05$) (Table 5.2). At 7 years, a greater proportion of the children grouped into the high LCWT were classified as overweight or obese according to the WHO cut-offs [282] more than half of the children in the high LCWT were overweight or obese compared to only 18% and 19% for boys and girls, respectively who belonged in the low LCWT. Over one third of the high LCWT group had a WC over the >90th %ile cut-off based on the NHANES 2004 Hispanic population [302] compared only 6% (boys) and 8% (girls) of children from the low LCWT. Over 48% of children were classified as obese in the high LCWT using the WHtR 0.5 cut-off [252] to diagnose obesity in Mexican children, compared to 27% and 38 % for boy and girls respectively in the low LCWT groups.

Results from the linear regression analyses of BAZ and WHtR at follow-up on height and weight trajectory are shown in Table 5.3. *Weight Latent Classes:* Children classified to the high LCWT in childhood had greatly increased odds of developing overweight/obesity at age seven compared with the children in the low LCWT, after controlling for SES, parity and maternal education. In boys, remaining heavier in the first five years of life was significantly associated with being overweight or obese at seven years of age, BAZ (OR 4.8; 95% CI 2.67 – 8.65; $p <0.05$) WHtR $\geq 0.5$, (OR 2.33; 95% CI 1.34

– 4.07; p <0.05) compared to boys in the low LCWT. The same trend was observed for girls, BAZ (OR: 6.73; 95% CI 3.66 – 12.36; p <0.05) and WHtR ≥ 0.5, (OR 6.55; 95% CI 3.53 – 12.12; p <0.05). *Height Latent Classes:* Being taller in childhood was associated with decreased risk of childhood obesity at age seven compared with shorter children in the low LCHT, after controlling for SES, parity, maternal education and weight at follow up visit. Taller boys in early childhood were less likely to be categorized as overweight or obese compared to shorter boys, BAZ (OR 0.02; 95% CI 0.00 – 0.11; p <0.05) and WHtR ≥ 0.5 (OR 0.05; 95% CI 0.02 – 0.15; p <0.05). The same was observed for taller girls, BAZ (OR 0.10; 95% CI 0.02 – 0.43; p <0.05) and WHtR ≥ 0.5 (OR 0.07; 95% CI 0.02 – 0.27; p <0.05).

## 5.6 Discussion

The prevalence of overweight and obesity in this cohort at follow- up is 31.5%, corresponding with Mexico's current prevalence of children the same age at 33.2% [1]. In this cohort, we identified distinct height and weight trajectories from birth to age 5 — 2 for both girls and boys. Belonging to the heavier group in the first 5 years for both girls and boys was associated with higher odds of being overweight or obese at age seven. This association was inverted in the height analyses, where being tall, had protective effects on obesity status at follow-up. Our results suggest that growth trajectories in early childhood may be associated with obesity in later in life. Growth and body size during the first years of life have been associated with later childhood

overweight and obesity [9, 17]. However, there is lack of agreement on which growth characteristics are the best predictors of childhood overweight. To our knowledge, we are the first study to use latent class growth analysis (LCGA), to explore the heterogeneity in height and weight gain over the life course (birth - 5 years) and its relationship to overweight/obesity in late childhood.

Our findings suggest that there are two discrete height and weight trajectories from birth to age five in both girls and boys, with features that can be characterized as low and high growth. The distinct growth trajectories were evident as early as 24 months of age with a mean height difference of >4.5 cm and reaching >6 cm at 60 months and a mean weight difference was >2.3 kg at 24 months and >4 kg by 60 months for both boys and girls. A graded effect of the different trajectory groups on risk of overweight/obesity at age seven was apparent, such that the high LCWT children were associated with > 4 times increased odds of being overweight/obese in comparison with the low LCWT children. There was also a protective effect of belonging to the high LCHT group compared to the low LCHT group, with taller kids showing ≥ 90% decreased risk of obesity at age seven, suggesting that short stature in early childhood may increase the risk of developing obesity.

There is strong evidence to suggest that early rapid weight gain is a factor in childhood or later life obesity [6, 263, 264]. Several studies have focused on identifying critical periods in infancy associated with obesity in later life. For example, excessive weight gain in the first weeks of life [307] or

in the first few months of life [308], was associated with an increased risk of later obesity. While our study does not use the same methodology as previous research we observed the same trend. In our study children who remained heavier from birth to five years of age had higher odds of being obese at age 7. These findings contribute to the body of evidence of the association between early rapid weight gain and overweight/obesity in childhood, adolescence and adulthood, but they were mainly from developed countries [9, 18, 264, 309]. In keeping with other studies these analyses showed a sex difference, girls who were classified into the high LCWT had higher odds than males in the same group to develop obesity by seven years of age. This study extends the observations by providing further data on long-term weight trajectories in a LMIC population.

Poor growth in early in life has been associated with risk of obesity in adulthood. A number of cross-sectional studies [22, 23] have reported a higher prevalence of overweight in stunted children, yet they are not consistent with prospective studies that report decreased BMI or BF at different ages and stunting in early childhood [19, 20, 26, 217, 218, 274] and others that have reported null results [20, 21]. In our study, children who remained tall in height over their first five years of age had significantly lower odds of developing obesity by age seven compared to children in the low growth trajectory. Our results are aligned with previous research that suggested stunting in childhood may increase the risk of obesity later in life. An

association seen in countries going through various stages of nutrition transition [22, 310]. A suggested mechanism for this association is believed to be long-term impaired fat oxidation, a risk factor for excess weight gain [270, 311]. However, causality has yet to be established since most studies focused on this observation have been cross-sectional. Overall, our results suggest that early childhood may be a critical period for obesity development.

To the best of our knowledge, our study may be among the first to investigate associations of weight gain and linear growth trajectories using LCGA in early childhood assessing obesity with BAZ and WHtR in later childhood. It informs an understanding of how lingering short stature or higher weight during early childhood is associated with obesity during the course of later childhood. The different associations between growth and adiposity limits the generalizability of findings and their association may be context-specific [286]. In a recent study in Peru, urban lowland children showed an increase in BMI with increasing stature, while no relationship was found among rural highland children [287]. The study authors suggested that differences between rural and urban populations may arise from environments that present different opportunities for catch-up growth and the accrual of adipose tissue. We considered the differences in environment by controlling for SES in our analysis, despite our urban study location of Cuernavaca. Household SES during infancy may be considered a proxy for important factors that influence household environment, for instance access to health care [288].

As with any study, there are certain limitations that merit discussion to most fully appreciate the results presented. First, the trajectory classes developed were determined within the framework of LCGAs, allowing one to see variability within a population. Trajectory groups are latent strata [227] , meaning that the groups developed are composed of individuals following approximately the same growth course. Individuals are assigned a probability of membership to the class, but they do not necessarily belong to a class. In this study, models were selected based on the highest posterior probability (>0.92) to assess the quality of classification. Simply, LCGA classes are not concrete, but are sound statistical devices that allow one to see variabilities in distinct regions of distribution [312, 313]. Second, it is not always possible to control for unknown confounding factors that were not measured. Finally, WHtR and BAZ were used to classify children as obese. While WHtR is a simple, effective and practical screening tool for childhood obesity, previously proven effective [244, 314], the use of BMI in our study to classify overweight and obesity has limitations. Despite these limitations, we remain confident that the results presented support our conclusions as such factors are unlikely to influence the strength of several aspects of the study, such as collecting anthropometric data at 60 months in more than 90% of the original birth cohort. As well, the final sub-sample at follow-up was well balanced with respect to maternal characteristics.

## 5.7 Summary and Conclusions

In summary, based on the results of this study, remaining heavier during early childhood is associated with obesity development in later in childhood, while remaining taller in early years offers a protective effect against obesity development. There is a greater need to understand how early growth contributes to the development of obesity, as the prevalence of childhood obesity continues to rise in many LMICs. In particular, future research needs to focus on life-course influence on the development of obesity to better understand how to prevent or reverse the double burden of disease.

**Figure 5.1** Birth cohort study sample

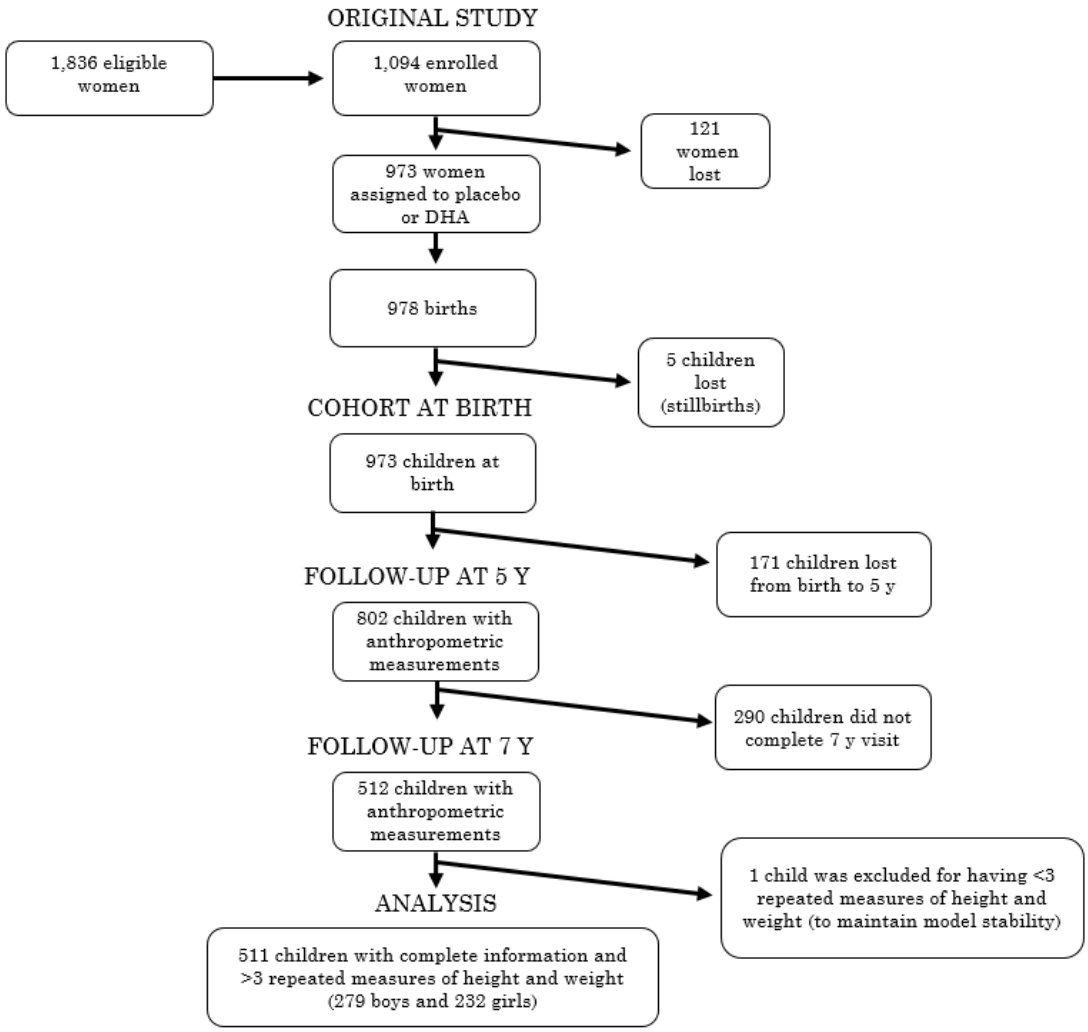
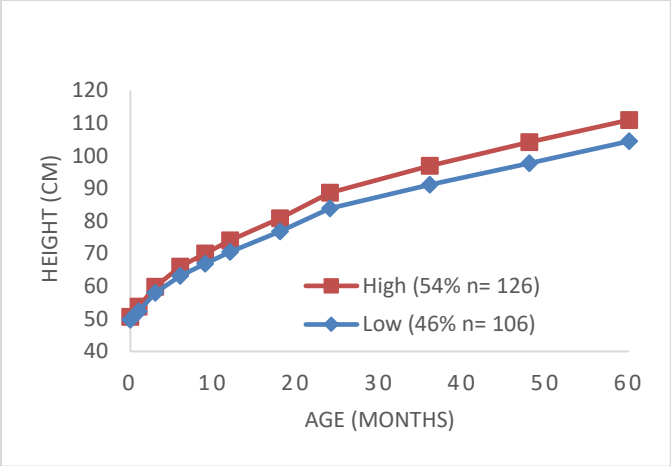


**Table 5.1** Summary of characteristics among 511 participants of the POSGRAD cohort at the 7 year follow-up.

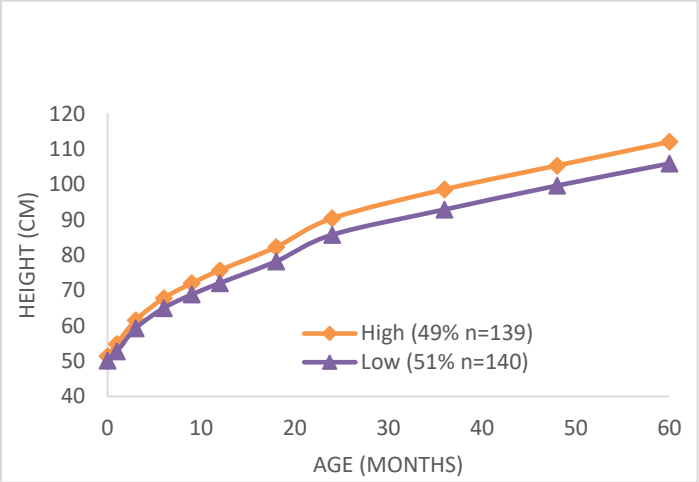
| | **Boys** | **Girls** | |
|---|---|---|---|
| | Mean (SD) | | P-value[a] |
| N | 279 | 232 | |
| **Age, yrs.** | 7.16 (0.22) | 7.11 (0.17) | 0.01 |
| **Weight, kg** | 24.63 (5.16) | 24.86 (5.62) | 0.64 |
| **Height, cm** | 122.09 (5.03) | 120.84 (5.62) | 0.00 |
| **Waist (cm)** | 60.55 (7.35) | 62.52 (8.31) | 0.00 |
| **Waist-to-height ratio** | 0.49 (0.05) | 0.52 (0.06) | 0.00 |
| **BMI Z score** | 0.36 (1.43) | 0.55 (1.25) | 0.10 |
| **BMI-for age Z-score >1 (%(n))[b]** | 28 (78) | 35 (83) | 0.06 |
| **BMI-for age Z-score >2 (%(n))[b]** | 13 (37) | 14 (33) | 0.09 |
| **HAZ score** | -0.09 (0.91) | -0.11 (1.00) | 0.85 |
| **Waist circumference > 90$^{th}$ %ile (%(n))[c]** | 12 (34) | 23 (53) | 0.01 |
| **WHtR ≥ 0.5 (%(n))[d]** | 33 (93) | 55 (127) | 0.00 |

[a]Sex differences assessed by using Student's t-test or ANOVA. [b]WHO 2006 [282] BMIZ score cut-offs for overweight and obese children. [c]NHANES III, third National Health and Nutrition Examination Survey, Waist circumference cut-offs - 90th percentile at 7 years: girls = 69.4 cm and boys = 70.6 cm.[302]. [d]WHtR cut-offs ≥0.50 obesity in children [252].

**Figure 5.2** Mean height (cm) by latent class group in girls (a) and boys (b) from a subsample of the POSGRAD study. Sex-specific height trajectories were derived from 11 possible measures of height in their first five years of life.

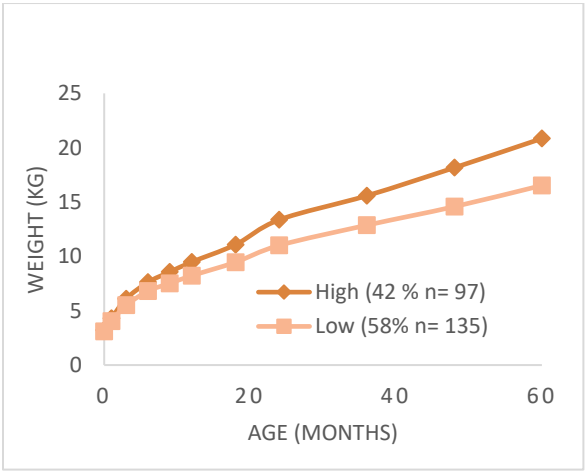



**A**.

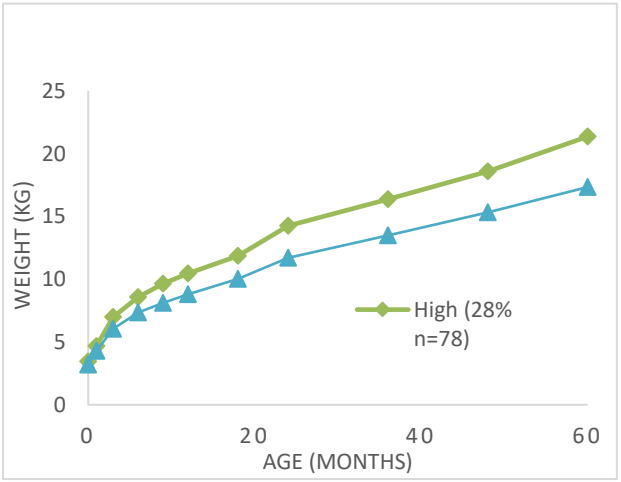



B.

**Figure 5.3** Mean Weight (kg) by latent class group in girls (a) and boys (b) from a subsample of the POSGRAD study. Sex-specific weight trajectories were derived from 11 possible measures of weight in their first five years of life.




**A.**




**B.**

**Table 5.2** Summary of characteristics by latent class membership at follow-up

| | Height Latent Classes | | | | | | Weight Latent Classes | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Boys | | | Girls | | | Boys | | | Girls | | |
| Class | High | Low | P-value[a] | High | Low | P-value[a] | High | Low | P-value[a] | High | Low | P-value[a] |
| | Mean (SD) | | | Mean (SD) | | | Mean (SD) | | | Mean (SD) | | |
| N | 139 | 140 | | 126 | 106 | | 78 | 201 | | 97 | 135 | |
| Age, yrs. | 7.17 (0.23) | 7.15 (0.20) | 0.31 | 7.13 (0.18) | 7.10 (0.15) | 0.26 | 7.18 (0.25) | 7.15 (0.20) | 0.39 | 7.12 (0.17) | 7.11 (0.17) | 0.88 |
| Weight, kg | 26.42 (5.33) | 22.85 (4.32) | 0.00 | 27.25 (5.49) | 22.00 (4.29) | 0.00 | 28.76 (0.25) | 23.02 (3.99) | 0.00 | 28.84 (5.35) | 21.99 (3.73) | 0.00 |
| Height, cm | 125.57 (3.69) | 118.64 (3.62) | 0.00 | 124.28 (4.15) | 116.74 (4.21) | 0.00 | 126.34 (4.23) | 120.44 (4.31) | 0.00 | 124.60 (4.50) | 118.13 (4.73) | 0.00 |
| Waist, cm | 62.14 (7.65) | 58.99 (6.71) | 0.00 | 65.61 (7.89) | 58.85 (7.26) | 0.00 | 65.39 (7.88) | 58.69 (6.21) | 0.00 | 68.09 (7.55) | 58.52 (6.28) | 0.00 |
| Waist-to-height ratio | 0.49 (0.05) | 0.49 (0.05) | 0.69 | 0.53 (0.06) | 0.50 (0.05) | 0.00 | 0.52 (0.06) | 0.49 (0.05) | 0.00 | 0.55 (0.05) | 0.49 (0.95) | 0.00 |
| BMI Z score | 0.49 (1.47) | 0.22 (1.37) | 0.10 | 0.88 (1.23) | 0.17 (1.18) | 0.00 | 1.24 (1.33) | 0.01 (1.31) | 0.00 | 1.33 (1.07) | 0.00 (1.07) | 0.00 |
| BMI-for age Z-score >1 (%(n))[b] | 32 (45) | 24 (33) | 0.10 | 46 (58) | 24 (25) | 0.00 | 53 (41) | 18 (37) | 0.00 | 60 (58) | 19 (25) | 0.00 |
| BMI-for age Z-score >2 (%(n))[b] | 17 (24) | 9 (13) | 0.05 | 19 (24) | 8 (9) | 0.02 | 27 (21) | 8 (16) | 0.00 | 28 (27) | 4 (6) | 0.00 |
| HAZ score | 0.54 (0.68) | -0.73 (0.63) | 0.00 | 0.50 (0.76) | -0.84 (0.73) | 0.00 | 0.68 (0.80) | -0.40 (0.76) | 0.00 | 0.57 (0.82) | -0.60 (0.82) | 0.00 |
| Waist circumference > 90th percentile (%(n))[c] | 17 (23) | 8 (11) | 0.03 | 31(39) | 13 (14) | 0.00 | 28 (22) | 6 (12) | 0.00 | 43 (42) | 8 (11) | 0.00 |
| WHtR ≥ 0.5 (%(n))[d] | 32 (45) | 34 (48) | 0.74 | 64 (81) | 43 (46) | 0.00 | 48 (38) | 27 (55) | 0.01 | 78 (76) | 38 (51) | 0.00 |

[a]WHO 2006 [282] BMI Z-score OR reference group for outcome are non-obese children < 1BAZ. [b]WHtR OR reference group children classified as normal < 0.50 [252]. [c] P- Value < 0.05. Model 2 R²: [d]$R^2$=0.11, [e]$R^2$=0.05, [f]$R^2$=0.14, [g]$R^2$=0.04

**Table 5.3** Effect of latent class weight trajectory on BMI-Z (BAZ)[a] categories and WHtR[b] at age 7 in the POSGRAD cohort.

| Weight Growth Trajectories | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Boys | | | | | | Girls | | | | | |
| | BAZ[d] | | | WHtR[e] | | | BAZ[f] | | | WHtR[g] | | |
| | OR | 95% CI | p-value[c] | OR | 95% CI | p-value[c] | OR | 95% CI | p-value[c] | OR | 95% CI | p-value[c] |
| **Model 1** | | | | | | | | | | | | |
| *Latent Class* | | | | | | | | | | | | |
| Low | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| High | 4.91 | (2.78 – 8.68) | 0.00 | 2.52 | (1.47 – 4.33) | 0.00 | 6.54 | (3.61 – 11.87) | 0.00 | 5.96 | (3.29 – 10.81) | 0.00 |
| **Model 2** | | | | | | | | | | | | |
| *Latent Class* | | | | | | | | | | | | |
| Low | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| High | 4.80 | (2.67 – 8.65) | 0.00 | 2.33 | (1.34 – 4.07) | 0.00 | 6.73 | (3.66 – 12.36) | 0.00 | 6.55 | (3.53 - 12.12) | 0.00 |
| *SES* | | | | | | | | | | | | |
| Low | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| Medium | 1.47 | (0.68 – 3.21) | 0.33 | 1.37 | (0.69 – 2.72) | 0.38 | 1.18 | (0.56 – 2.49) | 0.66 | 1.31 | (0.64 – 2.69) | 0.47 |
| High | 2.20 | (0.99 – 4.89) | 0.05 | 1.52 | (0.74 – 3.08) | 0.25 | 1.48 | (0.66 – 3.28) | 0.34 | 1.53 | (0.71 – 3.28) | 0.28 |
| *Parity* | 0.79 | (0.58 – 1.06) | 0.12 | 0.73 | (0.55 – 0.97) | 0.30 | 0.93 | (0.68 – 1.28) | 0.65 | 1.15 | (0.86 - 1.53) | 0.34 |
| *Maternal education (yrs.)* | 0.92 | (0.79 – 1.04) | 0.17 | 0.95 | (0.29 – 3.75) | 0.94 | 0.97 | (0.88 – 1.07) | 0.13 | 0.95 | (0.87 – 1.05) | 0.31 |

[a]WHO 2006 [282] BMI Z-score OR reference group for outcome are non-obese children < 1BAZ. [b]WHtR OR reference group children classified as normal < 0.50 [252]. [c]P- Value < 0.05. Model 2 $R^2$: [d]$R^2$=0.11, [e]$R^2$=0.05, [f]$R^2$=0.14, [g]$R^2$=0.04

**Table 5.4** Effect of latent class height trajectory on BMI-Z (BAZ)[a] categories and WHtR[b] at age 7 in the POSGRAD cohort

| Height Growth Trajectories | Boys | | | | | | Girls | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BAZ[d] | | | WHtR[e] | | | BAZ[f] | | | WHtR[g] | | |
| | OR | 95% CI | p-value[c] | OR | 95% CI | p-value[c] | OR | 95% CI | p-value[c] | OR | 95% CI | p-value[c] |
| **Model 1** | | | | | | | | | | | | |
| *Latent Class* | | | | | | | | | | | | |
| Low | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| High | 1.55 | (0.92 – 2.63) | 0.10 | 0.91 | (0.55 – 1.51) | 0.74 | 2.76 | (1.56 – 4.88) | 0.00 | 2.35 | (1.38 – 4.0) | 0.00 |
| **Model 2** | | | | | | | | | | | | |
| *Latent Class* | | | | | | | | | | | | |
| Low | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| High | 0.02 | (0.00 – 0.11) | 0.00 | 0.05 | (0.02 – 0.15) | 0.00 | 0.10 | (0.02 – 0.43) | 0.00 | 0.07 | (0.02 – 0.27) | 0.00 |
| *Weight (kg)* | 5.15 | 3.04 – 8.71) | 0.00 | 2.16 | (1.76 – 2.64) | 0.00 | 3.28 | (2.19 – 4.92) | 0.00 | 2.60 | (1.98 – 3.42) | 0.00 |
| *SES* | | | | | | | | | | | | |
| Low | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| Medium | 0.55 | (0.11 – 2.71) | 0.47 | 1.05 | (0.39 – 2.84) | 0.91 | 0.27 | (0.06 – 1.22) | 0.09 | 0.99 | (0.34 – 2.92) | 0.99 |
| High | 0.67 | (0.13 – 3.53) | 0.63 | 0.73 | (0.25 – 2.13) | 0.57 | 0.64 | (0.15 – 2.65) | 0.54 | 1.29 | (0.43 – 3.90) | 0.65 |
| *Parity* | 1.19 | (0.59 – 2.38) | 0.46 | 0.80 | (0.52 – 1.22) | 0.31 | 0.84 | (0.46 – 1.51) | 0.56 | 1.30 | (0.84 – 2.01) | 0.23 |
| *Maternal education (yrs.)* | 0.88 | (0.73 – 1.05) | 0.16 | 0.93 | (0.82 – 1.05) | 0.24 | 0.97 | (0.81 – 1.16) | 0.72 | 0.91 | (0.79 – 1.04) | 0.17 |

[a]WHO 2006 [282] BMI Z-score OR reference group for outcome are non-obese children < 1BAZ. [b]WHtR OR reference group children classified as normal < 0.50 [252]. [c] P- Value < 0.05. Model 2 $R^2$: [d]$R^2$=0.75, [e]$R^2$=0.52, [f]$R^2$=0.73, [g]$R^2$=0.59

**Supplemental Table 5.1** Fit Statistics for the Candidate Latent Class Height Models, by Sex, in the DHA cohort in Mexico.

| | Height | | | | | |
|---|---|---|---|---|---|---|
| | Girls ($n$ = 232) | | | Boys ($n$ = 279) | | |
| Fit Statistics | 2 Class | 3 Class | 4 Class | 2 Class | 3 Class | 4 Class |
| Log likelihood | -6,402 | -6,321 | -6,284 | -7,599 | -7,523 | -7468 |
| BIC | 12,893 | 12,746 | 12,689 | 15,288 | 15,154 | 15,060 |
| Entropy | 0.81 | 0.85 | 0.84 | 0.84 | 0.80 | 0.84 |
| LMR test | 410.4 | 153.9 | 68.7 | 501.1 | 142.9 | 104.6 |
| LMR, *P* value | 0.02 | 0.12 | 0.42 | 0.0001 | 0.16 | 0.03 |
| BLRT test | -6,621 | -6,402 | -6,321 | -7,864 | -7,599 | -7,523 |
| BLRT, *P* value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BIC, Bayesian Information Criterion; LMR, Lo-Mendell-Rubin Likelihood Ratio Test; BLRT, Bootstrap Likelihood Ratio Test.

**Supplemental Table 5.2** Fit Statistics for the Candidate Latent Class Weight Models, by Sex, in the DHA cohort in Mexico.

| | Weight | | | | | |
|---|---|---|---|---|---|---|
| | Girls ($n$ = 255) | | | Boys ($n$ = 281) | | |
| Fit Statistics | 2 Class | 3 Class | 4 Class | 2 Class | 3 Class | 4 Class |
| Log likelihood | -3,813 | -3,690 | -3,628 | -4,590 | -4,434 | -4,378 |
| BIC | 7,214 | 7,485 | 7,377 | 9,270 | 8,976 | 8,879 |
| Entropy | 0.84 | 0.88 | 0.86 | 0.90 | 0.87 | 0.89 |
| LMR test | 582.6 | 231.4 | 116.9 | 741.3 | 294.2 | 106.8 |
| LMR, *P* value | 0.008 | 0.06 | 0.16 | 0.001 | 0.006 | 0.14 |
| BLRT test | -4,069 | -3,813 | -3,690 | -4,983 | -4,590 | -4,434 |
| BLRT, *P* value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BIC, Bayesian Information Criterion; LMR, Lo-Mendell-Rubin Likelihood Ratio Test; BLRT, Bootstrap Likelihood Ratio Test.

# Chapter 6: Low Height Trajectory in is Associated with High Fat Mass in Later Childhood in Mexican Boys

## 6.1 Abstract

**Background and objectives:** In Mexico, childhood obesity is a major public health concern, with a current prevalence of 33% in school-aged children classified as overweight or obese. Previous research suggests that poor growth during early childhood may increase the risk of obesity, but others have reported that the rate of growth is more important than size at birth or early nutritional status. Therefore, the objective of this study was to determine if distinct trajectories of growth are associated with body composition in late childhood.

**Methods:** Study participants were a sub-sample that participated in the 8-10 y follow up of the POSGRAD study, a double-blind, randomized, placebo-controlled trial of prenatal DHA supplementation. Sex-specific height latent class trajectories were derived from 11 measures of height from birth to 5 years of age using MPlus v.7.3. Body composition and anthropometric measures were obtained between ages 8-10 years. Body composition was estimated using validated equations for Mexican children based on the measures from a tetrapolar bioimpedance analyzer (Impedimed DF50). Multivariate linear regression was used to determine the relationship between growth trajectory classes and FM (kg) and FFM (kg) in late childhood, controlling for current body weight (kg), SES (low, med and high), parity and maternal education. All statistical analyses were conducted with STATA 15.

**Results:** 255 girls and 281 boys and were included. Two height latent classes were identified in girls [low (58%) and high (42%)] and three classes in boys [low (17%), medium (51%) and high (32%)]. Mean FM in girls (high and low) and boys (high, medium, low) per class were 12.66 kg and 8.99 kg and 10.76 kg, 8.97 kg and 8.39 kg, respectively. In girls, there were no significant associations between classes and FM or FFM. In boys, relative to the intermediate growth class, the low class had higher FM ß = 0.69 kg, 95% CI (0.26 - 1.11) and the high class had lower FM in late childhood ß = -0.40 kg, (-0.76 - -0.05). Boy in the low class had significantly less FFM ß = -0.69 kg., (p=0.00) and boys in the high class had more FFM ß = 0.40 kg, (p=0.03), compared to the intermediate group.

**Conclusion:** Among boys, more rapid growth in early childhood is associated with lower adiposity in late childhood compared to children who grew slower.

**KEYWORDS:** child nutrition, latent class growth analysis, height, fat mass, BIA

## 6.2 Introduction

The global prevalence of obesity has more than doubled since the 1980's [29]. In Latin America, upwards of 25 % of children under 18 years of age were overweight or obese between 2008 and 2013 [315] and approximately 58% of adults in Latin America are overweight or obese [316]. Being overweight or obese as a child is a serious public health concern as it is associated a number of chronic diseases including hypertension, dyslipidemia, insulin resistance, fatty liver disease, and psychosocial complications [9, 17, 317]. In particular, it has been reported that childhood obesity tracks into adulthood [318, 319] and is related to increased mortality in middle age [320]. More important, rapid growth in childhood has been identified as a factor contributing to the development of obesity [6-8] .

While growth and body size during the early years of life are associated with later childhood overweight and obesity [9, 17], how specific growth patterns predict childhood overweight remains unclear. In one recent study, it was found that early weight gain was a key contributor to an increased incidence of obesity in later childhood among children who entered kindergarten overweight, [5]. As well, longitudinal studies have reported an increased risk of obesity from excess weight gain as early as the first 6 months of life [264]. Although rapid weight gain is associated with obesity and related outcomes [9, 17, 18], there are inconsistent results on the effects of linear growth on the development of excess adiposity in later years [19-21]. The lack

of agreement between studies may be explained by the different methods used to assess obesity, as past studies used BMI as a surrogate measure of adiposity without the ability to distinguish between fat mass and fat-free mass.

Children who grow poorly in utero or during early childhood, in particular those who are classified as stunted (height –for-age Z score (HAZ) < -2 SD) [30] are more likely to be classified as obese [22, 23] and may contribute to double burden of disease in low and middle income countries (LMIC) [24, 25]. Briefly, a study from Senegal found that girls who were stunted at age 2 years had greater truncal fat than non-stunted girls, independent of BMI [275]. In Guatemala, stunted children had a BMI above the median for US children of the same age [276] and adults who were severely stunted as children had greater central fat, independent of total fat mass, compared to moderately or never stunted counterparts [164, 274, 277, 278]. However, other prospective studies reported that stunting was associated with decreased BMI or body fat in childhood [19, 26], suggesting that difference in methodologies or environmental factors may contribute to differences in results between these studies. Precise mechanisms to support these studies vary from potential epigenetic factors to modifications in the microbiome, topics that have been covered in great depth in recent reviews [164, 277, 278, 321]. Regardless, the lack of consensus on this topic suggests that a more nuanced understanding of how growth patterns influence adiposity is critical to develop appropriate interventions to reduce the prevalence of childhood obesity.

Currently, over 70% of the adult population in Mexico is either overweight or obese and the prevalence of obesity for school-aged children and adolescents is 33% and 36%, respectively [1]. The need to determine how growth patterns may contribute to the high prevalence of childhood obesity is of great public health importance, especially as Mexico continues to experience the nutrition transition [28]. To address this question, we studied the relationship between growth patterns and adiposity in late childhood, using latent class growth analysis (LCGA) to explore the heterogeneity in gain of height over the life course in children living in Cuernavaca, Mexico.

## 6.3 Methods

Study participants were a sub-sample of a cohort that participated in the 8-10 y follow-up of the POSGRAD study (Fig. 6.1), a double-blind, randomized, placebo-controlled trial designed to assess the effect of prenatal supplementation with DHA on offspring growth and development, described in detail elsewhere (NCT00646360) [279]. POSGRAD was conducted in Mexico from 2004 to 2006 with 1,094 women randomly assigned to receive 400 mg/day of algal DHA or placebo from 18 to 22 weeks of gestation through delivery. Birth outcomes (968 live births and 5 stillbirths) were obtained within 24 hours of delivery. Offspring were followed and anthropometric measurements and body composition were obtained at follow-up.

A total of 545 children completed the body composition measures at age 8-10 years with an average of nine repeated measurements for height. The

lowest number of repeated measures was three, the minimum value to maintain model stability when using LCGA [226]. The final sample included 536 participants (281 boys, 255 girls) as nine measures were excluded due to excess movement during the body composition measurement.

### 6.3.1 Data collection and variable specification

*Anthropometric Measurements*

Birth weight (to the nearest 10g) and length (to the nearest 1mm) were measured with the use of a pediatric scale and a portable length measurement board following standard procedures [322]. Weight and length at ages 1, 3, 6, 9, 12, and 18 months were measured with the same equipment and procedures. Weight and standing height were measured at 24, 36, 48, and 60 months, and at their 8–10 year follow-up with a Tanita scale and a Seca stadiometer. Trained study personnel at the Mexican Social Security Institute's Hospital General I in Cuernavaca, Mexico performed data collection. Exact age at the 8-10 year follow-up was calculated in days by subtracting date of birth from the date of measurement, and calculated age-specific z scores relative to school-aged children and adolescent WHO standards [282].

*Body Composition*

Body composition was estimated with a tetrapolar bioelectrical impedance analyzer (Impedimed DF50) and validated equations for raw values of resistance Ω and reactance Ω for Mexican children [258]. Trained personnel

made all the measurements using a standardized protocol. Briefly, distal and proximal electrodes were placed 5cm apart and all measurements were made on right wrist and the right ankle with the participant supine. We took the average of two trials (between 4.0 and 4 min 59 s) as the final impedance value. Maximum allowable differences between two measurements were 3 Ω for both resistance (R) and reactance (Xc) [258]. Mothers were instructed to bring the child after a four-hour fast (no caffeinated beverages or food) and 500ml of sweet juice drink was offered 60 minutes prior testing to ensure proper hydration for children nine years of age who chose to participate in venous blood sample and come in with an overnight fast. All children were instructed to restrict extraneous PA for > 8 hours and void before the measurement.

*Covariates*

Maternal age, education and socioeconomic status were obtained at recruitment and socioeconomic status was calculated using a list of assets obtained by interview [279]. The Emory University Institutional Review Board and the National Institute of Public Health Biosafety, Investigation, and Ethics Committees both approved the protocol. Written informed consent was obtained from participating mothers after they received a detailed explanation of the study at baseline and during their offspring follow-up as well as assent from the children.

## 6.4 Statistical Methods

The mean and standard deviation for continuous variables were calculated for the entire sample stratified by sex. To test the main hypotheses, LCGA models were used to identify homogenous subpopulations with distinct growth patterns within the larger cohort. In non-latent class type growth modeling, a single curve would be estimated for the whole sample, which can potentially potential hide heterogeneity within the sample [234]. LCGA allows individuals with similar growth characteristics to be grouped together and provides each latent class its own growth curve [303]. Sex-specific latent class height trajectories (LCHT) were estimated from 11 possible measures of length/height including measures at birth, 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. Less than 1% of participants had only three measurements, and 96% had six measurements or more. Sex-specific trajectories were modeled to accommodate potential sex differences in growth during infancy [304].

LCGA was used to develop a series of models with 2 - 4 classes using all available data and a robust maximum likelihood estimation and 200 random starts values to avoid local solutions, generating a curve that represents the global maximum solution [226]. As there is no definitive criteria for selecting the optimal number of classes, a combination of statistical criteria and interpretability was employed [305]. Briefly, we assessed the model fit using Bayesian information criterion, the Bootstrap Likelihood Ratio Test, and the Lo-Mendell-Rubin Likelihood Ratio Test and also took the interpretability of

classes into account when determining the final model [226]. Entropy (higher value indicates greater classification accuracy, range 0-1) and posterior probabilities (probability of assigning observations to groups given the data) were used to assess the quality of the classification [234, 306]. Finally, each group had an adequate sample size of N > 25 per group [232]. Sex-specific LCHT s were derived using MPlus v.7.3 (Muthén & Muthén).

Means and standard deviations for continuous variables were calculated according to LCHT membership and Student's t-test and ANOVA were used to assess differences between LCHT groups. Multivariate linear regression analysis was used to determine the relationship between growth trajectory classes and FM (kg) and FFM (kg) in late childhood, controlling for current body weight (kg), SES (low, med and high), parity, and maternal education (yrs.). Latent class analyses were conducted using M-plus (Muthén & Muthén, Los Angeles, CA, USA) while means and regression analyses were conducted using STATA 15 (StataCorp LLC, College Station, Texas, USA), and statistical significance was determined at $P < 0.05$.

## 6.5 Results

Summary characteristics of the study participants are presented by gender in Table 6.1. There were no significant differences by sex for age, weight, height and WC at follow-up (Table 6.1). Boys had significantly greater FFM compared to girls (22.33 kg ± 3.85 and 21.19 kg ± 3.97, respectively) and girls had greater FM compared to boys (10.22 kg ± 4.15 and 9.42 kg ± 4.21,

respectively). There was a higher %age of boys classified as obese, compared to girls (25% vs. 17%), using WHO cut-offs [282] (Table 6.1). In regards to maternal and household characteristics, there were no differences between boys and girls for maternal age at birth, maternal education, or SES.

*Height trajectories*

The best-fitting LCGM for height, based on model fit and quality of classification, identified two latent classes in girls [low (58%) and high (42%)] (Fig. 6.2A), and three classes in boys [low (17%), medium (51%) and high (32%)] (Fig. 6.2B) (Supplemental Table 6.2). The 2-class model for girls and the 3-class model for boys had the highest entropy (> 0.79) indicating successful convergence. Classes also had the highest posterior probabilities of candidate models (>0.92), suggesting high class separation. An additional class did not improve the fit, suggested by the Lo-Mendell-Rubin Likelihood Ratio Test and the Bootstrap Likelihood Ratio Test (Supplemental Table 6.2). Among the girls' height trajectories, by the time they reach 24 months the difference between classes is greater than 5 cm. and increases to 6.4 cm by 60 months of age. For boys, the difference between the highest and the lowest trajectory reaches 5 cm by 9 months, rising to 8.6 cm by 60 months of age.

*Relationship between LCHT and body composition at follow-up visit*

Anthropometric characteristics of the sample by LCHT membership are shown in Table 6.2. There was no significant difference in age between the classes for both girls and boys. In both sexes, weight, height, waist

circumference, FM (kg), FFM (kg) and HAZ score were significantly different between classes (P<0.05). In girls, the mean FFM in the high class was 23.1 kg compared to 19.8 kg in the low class. In boys, for high, medium and low class, the mean FFM were 24.2 kg, 21.9 kg and 20.2 kg, respectively. The results for FM were similar for both girls and boys, higher class membership meant higher FM compared to their shorter counterparts (Table 6.2). Overweight or obese classification by LCHT at follow-up in boys from lowest to highest class were 41%, 39% and 47%, respectively. While 52% of girls were classified as obese or overweight in the high LCHT compared to 29% in the low LCHT.

Results from the linear regression analyses for the relationship between LCHT and FM and FFM are summarized in Tables 6.3 and 6.4, respectively. In girls, LCHT was not statistically associated with either FM or FFM, regardless of the model used. In boys, relative to the intermediate LCHT, the low class had higher FM ß = 0.69 kg, (p = 0.001) and the high class had lower FM ß = -0.40 kg, (p = 0.03). For FFM, boys in the low LCHT had significantly less FFM ß = -0.69 kg., (p=0.001) and boys in the high LCHT had more FFM ß = 0.40 kg, (p=0.03), compared to the intermediate group.

## 6.6 Discussion

As the global prevalence of childhood overweight and obesity continues to increase, especially in LMICs, it remains important to improve our understanding of how early growth faltering may influence the risk of obesity

later in life. In our study, boys in the lowest height trajectory class had greater FM and lower FFM compared to boys in the intermediate height trajectory. At the same time, no such relationship was determined for girls. Our results clearly support the hypothesis that poor or delayed growth in early life has a negative influence on body composition later in life. However, the fact that there may be some influence of sexual dimorphism is consistent with other studies [274, 275] and merits additional investigation in similar cohorts.

Previous research has reported that rapid growth during infancy and early childhood was associated with early BMI rebound [6, 202]. However, few studies have investigated growth in relation to body composition (FFM and FM) [323, 324]. In our study, boys who remained short to 5 years of age had significantly greater FM and lower FFM in later childhood compared to boys in the middle growth trajectory. At the same time, boys who remained tall from birth to 5 years of age had lower FM and higher FFM compared to boys in the middle growth trajectory. Linear growth retardation has been associated with decreased adult FFM in adulthood [41] and data from LMICs suggest that conditional height at 2 years of age and in mid-childhood has a positive association with FFM [202]. Most studies were based on infant weight gain and are from high income countries showing predominant positive correlation between postnatal weight gain and later FM [325-327]. Findings from a more recent study de Beer et al. were they separated, linear growth from relative weight gain suggest that faster weight gain is associated with healthier

childhood body composition, when it is caused by faster linear growth [323]. In addition, rapid weight gain mostly because of linear growth produces a greater increase in lean mass than fat mass, whereas rapid fat mass accrual during infancy is a better predictor of childhood obesity [328]. Overall, these results suggest that early childhood may be a critical period for obesity development.

A number of studies have addressed the question as to whether or not poor growth is associated with excess adiposity in adolescence and adulthood [217, 329]. For example, relative weight or height gain, but not birth weight, was positively associated with body size and fat mass in children from the Birth to Twenty Plus Cohort (Bto20) [291]. At the same time, birth size and stunting at age 2 years were negatively associated with FFM, but positively associated with visceral fat mass, in adulthood [291]. A cohort study in Peru found that the rate of weight gain, but not size at birth, was positively associated with BMI, adjusted for age and sex [330]. As well, results from the Fels Longitudinal Study (U.S) suggested that rapid weight gain from infancy to age 2 years was associated with increased FM, measured using MRI and DEXA [329]. To the best of our knowledge, our study is the first to investigate the influence of specific linear growth trajectories using LCGA in early childhood on body composition in later childhood. However, it is important to emphasize that slow growth is not necessarily reflective of growth retardation or chronic undernutrition.

Stunting, a more severe form of linear growth retardation, has been reported to increase the risk of obesity [22, 23]. One large epidemiological study of several countries (Brazil, Russia, and South Africa) found that adults who were stunted as children had a higher risk of being obese as adults [22]. Yet, a study in Peru found that stunting is negatively associated with BMI z-score and fatness, assessed using skinfold measurements [19]. Similar results were reported in Jamaica, except that it was also found that stunted children who grew more rapidly during childhood had a higher BMI at age 17 years compared to those who grew less rapidly (16). Finally, stunting at age 2 years was not associated obesity in the Bto20 [21]. Although the vast majority of Mexican children in our study (98%) are not classified as stunted, boys who were shorter than their peers early in childhood, and remained shorter for their first 5 years of life, had a greater FM compared to boys in the intermediate or high LCHT. These results are of particular concern as it has been suggested that stunted children may be predisposed to developing obesity later in life, within specific environmental conditions, due to metabolic adaptations reported in previous studies [26, 292, 331, 332].

As with any study, there are certain limitations that merit discussion to most fully appreciate the results presented. First, the trajectory classes developed were determined within the framework of LCGAs, allowing one to see variability within a population. Trajectory groups are latent strata [227] , meaning that the groups developed are composed of individuals following

approximately the same growth course. Individuals are assigned a probability of membership to the class, but they do not necessarily belong to a class. In this study, models were selected based on the highest posterior probability (>0.92) to assess the quality of classification. Simply, LCGA classes are not concrete, but are sound statistical devices that allow one to see variabilities in distinct regions of distribution [312, 313]. Second, it is not always possible to control for unknown confounding factors that were not measured. Finally, we did not have clinical data on pubertal development that may have influenced growth, including rapid changes in body size and composition. In fact, the sexually dimorphic differences between boys and girl may have influenced regional distribution of body fat [293]. Nonetheless, there are a number of important strengths to our study that lend considerable credence to the results presented. For example, we successfully collected anthropometric data at 60 months for more than 90% of the original birth cohort. As well, the final sub-sample at follow-up was well balanced with respect to maternal and SES characteristics. Finally, body composition was assessed using a valid and precise methodology (BIA) and FM was calculated from raw data using a prediction equation that had been validated for Mexican children.

## 6.7 Summary and conclusions

In summary, based on the results of this study, slower height gain during early childhood contributes to excess adiposity later in childhood. As the prevalence of childhood obesity continues to increase in many developing

and transitional countries, a greater understanding of how growth contributes to the double burden of disease is warranted. In particular, future research needs to focus on discrete aspects of growth and the development of obesity to better understand how to prevent or reverse the double burden of disease.

**Figure 6.1.** Birth cohort study sample

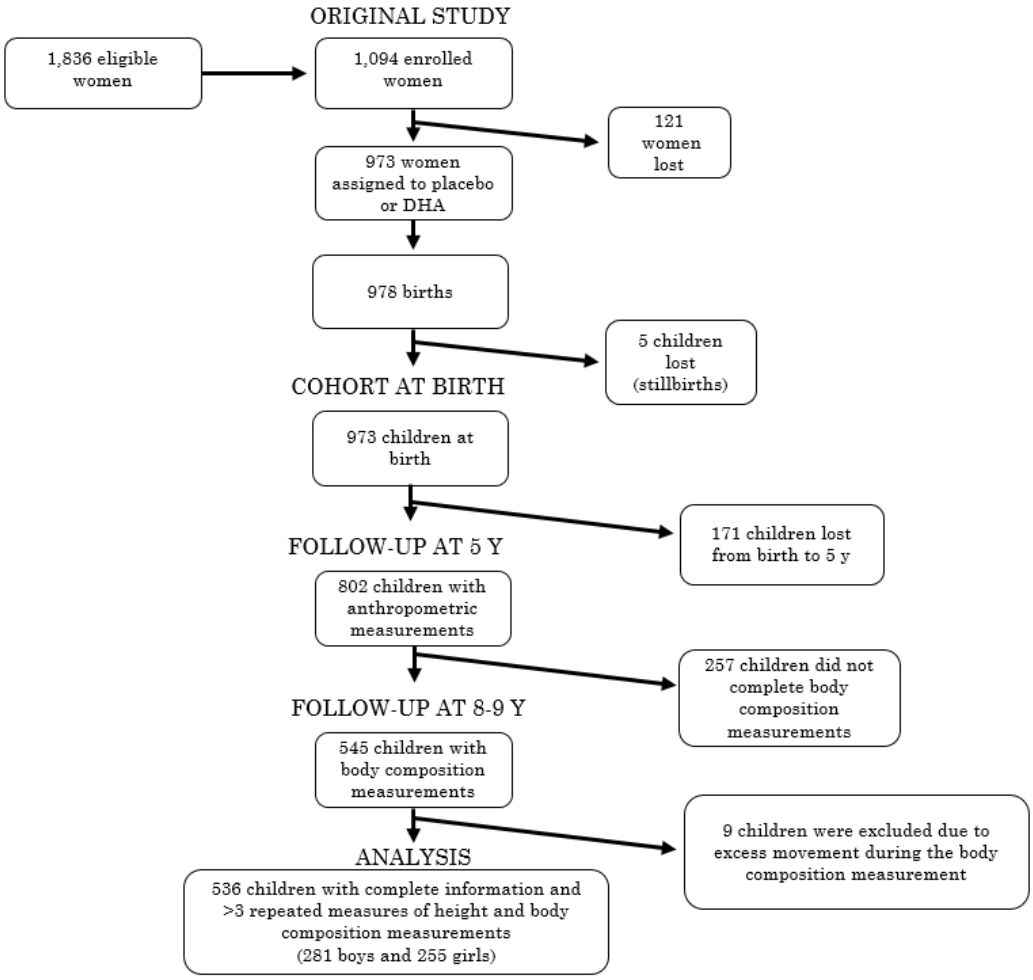


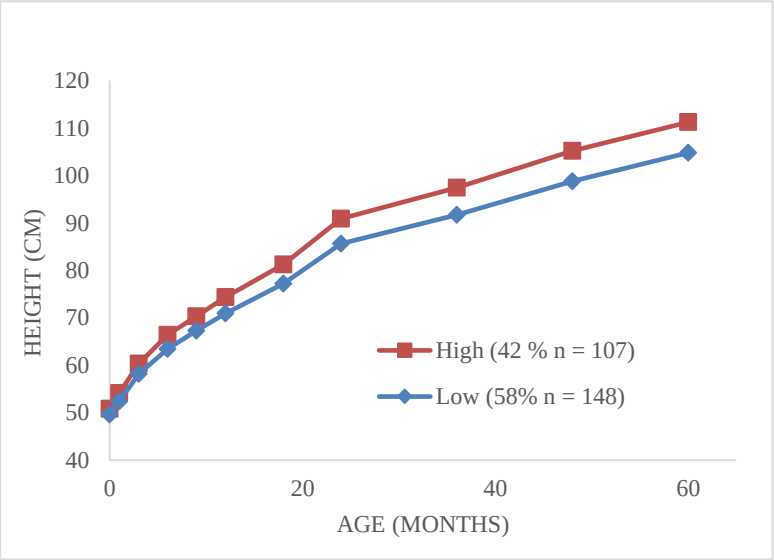
**Table 6.1** Physical and socio-economic characteristics of the POSGRAD cohort at 8-10 years of age.

| | Boys (52.43 %) | Girls (47.57%) | P-Value[a] |
|---|---|---|---|
| **N** | 281 | 255 | |
| | **Mean (SD)** | | |
| **Age, yrs.** | 8.74 (0.53) | 8.76 (0.48) | 0.57 |
| **Weight, kg** | 31.76 (7.62) | 31.40 (7.66) | 0.59 |
| **Height, cm** | 132.31 (6.05) | 131. 62 (7.01) | 0.22 |
| **Waist, cm** | 67.05 (10.03) | 67.53 (9.61) | 0.58 |
| **FFM, kg** | 22.33 (3.85) | 21.19 (3.97) | 0.00 |
| **FM, kg** | 9.42 (4.21) | 10.22 (4.15) | 0.03 |
| **FM, %** | 28.51 (6.38) | 31.52 (5.87) | 0.00 |
| **BMI Z score** | 0.71 (1.50) | 0.60 (1.27) | 0.35 |
| **Child Overweight, n (%)[b]** | 47 (17) | 55 (22) | 0.15 |
| **Child Obese, n (%)[b]** | 70 (25) | 43 (17) | 0.02 |
| **HAZ score** | 0.05 (0.90) | -0.05 (1.05) | 0.26 |
| **Parity** | 2.00 (1.03) | 2.01 (1.06) | 0.90 |
| **Maternal age at birth, yrs.** | 27 (4.72) | 26.38 (4.68) | 0.17 |
| **Maternal education, yrs.** | 12.1 (3.48) | 11.85 (3.59) | 0.42 |
| **SES, n (%)** | | | |
| **Low** | 80 (29) | 78 (30) | 0.59 |
| **Medium** | 91 (32) | 88 (35) | |
| **High** | 110 (39) | 89 (35) | |

[a]Sex differences assessed by using Student's t-test or ANOVA. [b]WHO cut-offs, Overweight: >+1SD (equivalent to BMI 25 kg/m$^2$ at 19 years), Obesity: >+2SD (equivalent to BMI 30 kg/m$^2$ at 19 years) [282]

**Figure 6.2** Mean height (cm) by latent class group in girls (a) and boys (b) from a subsample of the POSGRAD study. Sex-specific height trajectories were derived from 11 possible measures of height in their first five years of life.

**A.**




**B.**

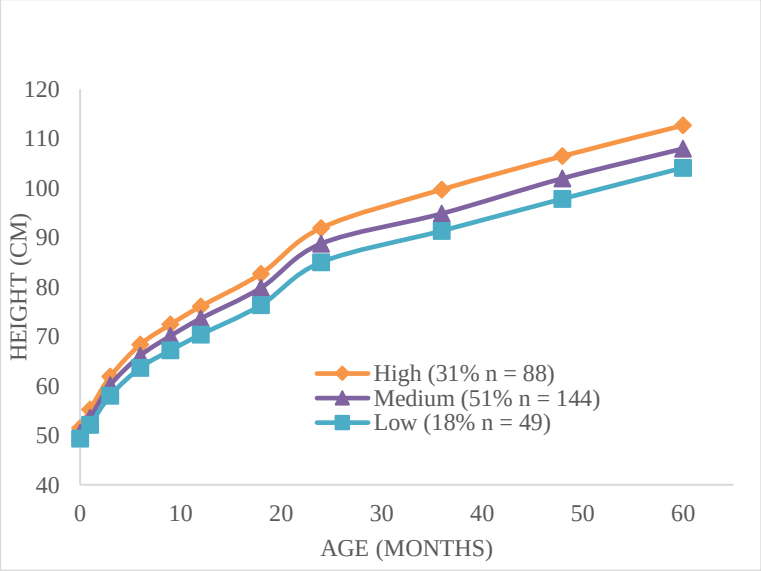


**Table 6.2** Height Latent Class Membership Characteristics at follow-up visit (8-10 years of age)

| Height Latent Classes | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Boys N = 281 (52.43 %) | | | | Girls N = 255 (47.57 %) | | |
| Class | High | Medium | Low | P-value[a] | High | Low | P-value[a] |
| | Mean (SD) | | | | Mean (SD) | | |
| N | 88 | 144 | 49 | | 107 | 148 | |
| Age, yrs. | 8.80 (0.54) | 8.92 (0.53) | 8.87 (0.51) | 0.26 | 8.9 (0.51) | 8.8 (1.05) | 0.13 |
| Weight, kg | 34.95 (8.34) | 30.88 (7.00) | 28.59 (5.98) | 0.00* | 35.25 (7.53) | 28.63 (6.48) | 0.00* |
| Height, cm | 136.82 (4.54) | 131.56 (5.12) | 126.40 (4.89) | 0.00* | 136.38 (5.64) | 128.19 (5.80) | 0.00* |
| Waist (cm) | 70.04 (10.24) | 66.21 (9.08) | 64.21 (11.15) | 0.00* | 71.57 (9.18) | 64.61 (8.85) | 0.00* |
| FFM, kg | 24.20 (3.95) | 21.91 (3.59) | 20.20 (2.89) | 0.00* | 23.11 (3.59) | 19.79 (3.65) | 0.00* |
| FM, kg | 10.76 (4.84) | 8.97 (3.85) | 8.39 (3.49) | 0.00* | 12.13 (4.40) | 8.83 (3.34) | 0.00* |
| FM, % | 29.47 (6.77) | 27.98 (6.17) | 28.36 (6.17) | 0.22 | 33.50 (5.70) | 30.08 (5.58) | 0.00* |
| Child Overweight, n (%)[b] | 14 (16) | 26 (18) | 7 (14) | - | 32 (30) | 26 (18) | - |
| Child Obese, n (%)[b] | 27 (31) | 30 (21) | 13 (27) | - | 23 (22) | 17 (11) | - |
| BMI Z score | 0.94 (1.59) | 0.58 (1.47) | 0.69 (1.41) | 0.20 | 0.95 (1.25) | 0.35 (1.23) | 0.00* |
| HAZ score | 0.87 (0.64) | -0.12 (0.65) | -0.94 (0.62) | 0.00* | 0.71 (.83) | -0.59 (0.82) | 0.00* |

[a]Class membership differences assessed by using Student's t-test or ANOVA. [b]WHO cut-offs Overweight: >+1SD (equivalent to BMI 25 kg/m$^2$ at 19 years) Obesity: >+2SD (equivalent to BMI 30 kg/m$^2$ at 19 years)[282]. *P- value <0.05

**Table 6.3** Multivariate linear regression analyses on the relationship between latent height class membership and fat mass in the POSGRAD cohort.

| | Girls | | | | | | Boys | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model 1 | | | Model 2 | | | Model 1 | | | Model 2 | | |
| | *β* | *95% CI* | *p-value* | *β* | *95% CI* | *p-value* | *β* | *95% CI* | *p-value* | *β* | *95% CI* | *p-value* |
| **Latent Class** | | | | | | | | | | | | |
| *High* | -0.11 | (-0.48 – 0.27) | 0.57 | -0.17 | (-0.54 – 0.21) | 0.19 | -0.40 | (-0.75 - -0.05) | 0.03* | -0.40 | (-0.76 - -0.05) | 0.03* |
| *Medium* | | | | | | | - | - | - | - | - | - |
| *Low* | - | - | - | - | - | - | 0.66 | (0.24 – 1.08) | 0.00* | 0.69 | (0.26 – 1.11) | 0.00* |
| **Weight (kg)** | 0.52 | (0.49 -0.54) | 0.00* | 0.52 | (0.49 – 0.54) | 0.00* | 0.54 | (0.52 – 0.56) | 0.00* | 0.54 | (0.52 – 0.56) | 0.00* |
| **SES** | | | | | | | | | | | | |
| *Low* | | | | - | | - | | | | - | | - |
| *Medium* | | | | -0.37 | (-0.46 – 0.38) | 0.86 | | | | 0.04 | (-0.26 – 0.44) | 0.84 |
| *High* | | | | 0.40 | (-0.03 – 0.07) | 0.07 | | | | -0.16 | (-0.57 – 0.24) | 0.43 |
| **Parity** | | | | -0.11 | (-0.27 – 0.05) | 0.19 | | | | -0.06 | (-.021 – 0.10) | 0.49 |
| **Maternal education (yrs.)** | | | | 0.02 | (0.03 – 0.07) | 0.48 | | | | 0.002 | (-0.05 - -6.5) | 0.91 |

*P- value = <0.05

**Table 6.4** Multivariate linear regression analyses on the relationship between latent height class membership and lean body mass in the POSGRAD cohort.

| | Girls | | | | | | Boys | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model 1 | | | Model 2 | | | Model 1 | | | Model 2 | | |
| | *β* | *95% CI* | *p-value* | *β* | *95% CI* | *p-value* | *β* | *95% CI* | *p-value* | *β* | *95% CI* | *p-value* |
| **Latent Class** | | | | | | | | | | | | |
| *High* | 0.11 | (-0.27 – 0.48) | 0.57 | 0.17 | (-0.21 – 0.54) | 0.38 | 0.40 | (0.05 – 0.75) | 0.03* | 0.40 | (0.05 - 0.76) | 0.03* |
| *Medium* | | | | | | | - | | - | - | | - |
| *Low* | - | | - | - | | - | -0.66 | (-1.08 – -0.24) | 0.00* | -0.69 | (-1.11 – -0.26) | 0.00* |
| **Weight (kg)** | 0.48 | (0.46 -0.51) | 0.00* | 0.48 | (0.46 – 0.51) | 0.00* | 0.46 | (0.44 – 0.48) | 0.00* | 0.46 | (0.44 – 0.48) | 0.00* |
| **SES** | | | | | | | | | | | | |
| *Low* | | | | - | | - | | | | - | | - |
| *Medium* | | | | 0.04 | (-0.38 – 0.46) | 0.86 | | | | -0.04 | (-0.44 – 0.36) | 0.84 |
| *High* | | | | -0.40 | (-0.83 – 0.03) | 0.07 | | | | 0.16 | (-0.24 – 0.57) | 0.43 |
| **Parity** | | | | 0.11 | (-0.05 – 0.27) | 0.19 | | | | 0.06 | (-0.10 – 0.21) | 0.49 |
| **Maternal education (yrs.)** | | | | -0.02 | (0.07 – 0.03) | 0.48 | | | | -0.003 | (-0.05 – 0.05) | 0.91 |

*P- value = <0.05

## Supplemental Table 6.1

Differences in birth, maternal and household characteristics between children with complete measurements vs. missing body composition at follow-up from the POSGRAD cohort.

| | **Included** | **Excluded** | **p-value[a]** |
|---|---|---|---|
| | **Mean (SD)** | | |
| | **N = 536** | **N=510** | |
| **Child Characteristics** | | | |
| ***Birth weight (kg)*** | 3.22 (0.47) | 3.17 (0.47) | 0.04 |
| ***Birth height (cm)*** | 50.37 (2.39) | 50.15 (2.65) | 0.18 |
| ***Parity*** | 2.00 (1.04) | 1.98 (1.04) | 0.76 |
| | | | |
| **Maternal Characteristics** | | | |
| ***Age(yrs.)*** | 26.67 (4.71) | 25.80 (5.66) | 0.01 |
| ***Schooling (yrs.)*** | 12.98 (3.53) | 11.93 (3.54) | 0.83 |
| | | | |
| **Household Characteristics** | | | |
| **SES** | N (%) | | |
| ***1 Lowest*** | 158 (29) | 196 (35) | 0.08 |
| ***2*** | 179 (34) | 176 (33) | |
| ***3 Highest*** | 199 (37) | 179 (32) | |

[a] Differences between included vs. excluded were assessed by using Student's t-test or ANOVA.

## Supplemental Table 6.2

Fit Statistics for the Candidate Latent Class Growth Height and Weight Models, by Sex, in the DHA cohort in Mexico.

| | Height | | | | | |
|---|---|---|---|---|---|---|
| | Girls ($n$ = 255) | | | Boys ($n$ = 281) | | |
| Fit Statistics | 2 Class | 3 Class | 4 Class | 2 Class | 3 Class | 4 Class |
| Log likelihood | -7,095 | -6,983 | -6,933 | -7,685 | -7,600 | -7,557 |
| BIC | 14,279 | 14,070 | 13,987 | 15,460 | 15,307 | 15,239 |
| Entropy | 0.79 | 0.86 | 0.86 | 0.82 | 0.83 | 0.84 |
| LMR test | 406.9 | 212.6 | 94.1 | 469.7 | 160.6 | 80.3 |
| LMR, *P* value | 0.02 | 0.11 | 0.19 | 0.0003 | 0.02 | 0.12 |
| BLRT test | -7,310 | -7,095 | -6,982 | -7,933 | -7,684 | -7600 |
| BLRT, *P* value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: BIC, Bayesian Information Criterion; LMR, Lo-Mendell-Rubin Likelihood Ratio Test; BLRT, Bootstrap Likelihood Ratio Test.

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# 6 APPENDIX

## 6.1 Sample Data Collection Form for 9 year old children

"EXPOSICIÓN PRENATAL A DISRUPTORES ENDOCRINOS Y EL RIESGO DE SOBREPESO, OBESIDAD Y PUBERTAD TEMPRANA EN POBLACIÓN ESCOLAR MEXICANA: UN ESTUDIO DE COHORTE"

**MEDICIÓN DE COMPOSICIÓN CORPORAL A LOS 9 AÑOS**

Ayuno para muestra de sangre/ Ayuno 4 hr niños sin muestra de sangre

| | |
|---|---|
| 1. Número de formulario | 9 8 3 |
| 2. Número de folio del participante | 1 |
| 3. Numero de contacto | 1 7 |
| 4. Fecha de la entrevista | __ __ / __ __ / __ __ (D D / M M / A A) |
| 5. Fecha de nacimiento del niño(a) | __ __ / __ __ / __ __ (D D / M M / A A) |
| 6. Código del encuestador | |
| 7. Edad del niño(a) *(ejemplo 9 años y 4 meses anotar en Fracción 3)*<br>**Fracción:** Menos de un mes = **0** 1 mes = **1** 2 meses = **2**<br>3 meses = **3** 4 meses =**3** 5 meses = **4**<br>6 meses = **5** 7 meses = **6** 8 meses = **7**<br>9 meses = **8** 10 meses = **8** 11 meses = **9** | 9 . Edad Fracción |
| 8. Hora de la última comida del niño(a)<br>***(horas y minutos, utiliza horario 24 hrs)*** | : |
| 9. Hora de la prueba del niño(a)<br>***(horas y minutos, utiliza horario 24 hrs)*** | : |
| 10. Hora en que tomo agua por última vez del niño(a)<br>**(horas y minutos, utiliza horario 24 hrs)** | : |
| 11. Peso (kg/gr) | . |
| 12. Talla (cm / mm) | . |
| 13. Circunferencia de abdomen | . |
| 14. Circunferencia de cadera | . |
| 15. Sexo **1** = M **2** = F | |
| 16. ¿Se realizo la prueba? 1 = Si 2 = No<br>***2 =No se realizo la prueba anotar en observaciones la razón*** | |
| 17. FFM . Kg | . % |

20 nov 2014

"EXPOSICIÓN PRENATAL A DISRUPTORES ENDOCRINOS Y EL RIESGO DE SOBREPESO, OBESIDAD Y PUBERTAD TEMPRANA EN POBLACIÓN ESCOLAR MEXICANA: UN ESTUDIO DE COHORTE"

**MEDICIÓN DE COMPOSICIÓN CORPORAL A LOS 9 AÑOS**

Ayuno para muestra de sangre/ Ayuno 4 hr niños sin muestra de sangre

| | | |
|---|---|---|
| 18. FM | □□.□ Kg | □□□.□ % |
| 19. TBW | □□.□ L | □□□.□ % |
| 20. ICW | □□.□ L | □□□.□ % |
| 21. ECW | □□.□ L | □□□.□ % |

| | | |
|---|---|---|
| 22. Impedancia (Z=) | □□□□,□ | □□□□,□ |
| 23. Fase (Ph =) | □□,□ | □□,□ |
| 24. Resistencia (R=) | □□□□,□ | □□□□,□ |
| 25. Reactancia (Xc=) | □□,□ | □□,□ |

**Observaciones :**

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CODIGO DEL SUPERVISOR: □□□

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**Firma del supervisor** **Fecha**

20 nov 2014

6.2 SES variable details

Socio Economic Status (SES) was developed using principal components analysis (PCA)

Variables include in the analysis were:

- Number or rooms in the house
- Number of houses
- Type of floor
- Type of wall
- Type of ceiling
- Water availability
- Toilet availability
- Ownership:
  - TV
  - VCR
  - DVD
  - Refrigerator
  - Microwave
  - Washer
  - Dryer
  - Car
  - Motorcycle
  - Stereo
  - Computer