CHARACTERIZATION OF EARLY LIFE GROWTH: IMPLICATIONS FOR LIFELONG HEALTH

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ABSTRACT

MEGHAN M. SLINING: Characterization of early life growth: implications for lifelong health. (Under the direction of Linda S. Adair, PhD)

Evidence that early life experiences play an important role in the long-term health of individuals holds promise for the identification of public health strategies to modify prenatal and perinatal determinants of adverse adult health outcomes. Although plausible mechanisms for the role of early life experiences in the development of adult health and disease exist, methodological limitations in human epidemiological studies need to be addressed before this field can adequately inform policy recommendations. Our research specifically addressed two such methodological challenges: how best to estimate the effect of growth in one period while appropriately accounting for final attained size, and how to evaluate the impact of overall patterns of growth on later disease. Our specific aims were to: 1) Assess the relationship between infant weight velocity and adult insulin resistance, specifically evaluating whether adult whether adult body mass index (BMI) and waist circumference (WC) mediate the association, and 2) Assess the relationship between trajectories of early life growth and adult anthropometric measures of body composition.

We used over 22 years of follow-up data from The Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based cohort study of children born from 1982-1983 in a metropolitan region of the Philippines. We found minimal associations between immediate postnatal weight velocity and adult insulin resistance and no associations between accelerated BMI gain in early infancy and anthropometric indicators of adult body composition. After controlling for BMI at two years of age, infant BMI trajectory classes were associated with anthropometric measures of body composition in adulthood, suggesting that overall patterns of BMI change in infancy have long-term implications for the development of body composition. Taken together, these results suggest that in this cohort early postnatal growth is not necessarily pathological and that growth patterns over the entire infancy period are important for the development of body composition.

DEDICATION

To my parents, Tom and Suzy Slining.

In loving memory of my grandma Peg.

ACKNOWLEDGEMENTS

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I am also privileged to have had the opportunity to receive guidance from an interdisciplinary committee of scholars. Dr. Julie Daniels provided honest and open critique and guidance, both academically and personally. Dr. Elizabeth Mayer-Davis always encouraged me to take the extra step to present my work in the most accessible and applicable manner. Dr. Amy Herring shared my trajectory enthusiasm from the start and showed immense patience while later helping me to fully understand them. Dr. Barry Popkin helped me to understand my research in a broader global context and to present my work in a policy relevant manner. Finally, to my School of Public Health friends and colleagues, it is an honor to have been part of such a remarkable group of individuals. Without this group my work would not have been as academically rigorous and this experience would not have been nearly as much fun.

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LIST OF ABBREVIATIONS

BIC	Bayesian Information Criterion
BMI	Body Mass Index. Calculated by weight (in kilograms) divided by height (in meters) squared (i.e., BMI = kg/m^2).
CLHNS	Cebu Longitudinal Health and Nutrition Survey
cm	Centimeters
CVD	Cardiovascular Disease
DOHaD	Developmental Origins of Health and Disease
DXA	Dual x-ray absorptiometry
FMI	Fat Mass Index
HOMA-IR	Homeostatic Model Assessment - Insulin Resistance
kg	Kilogram = 1,000 grams
LCGA	Latent Class Growth Curve Analysis
LMI	Lean Mass Index
SGA	Small-for-Gestational Age
SES	Socioeconomic Status
SK	Skinfolds
T2D	Type 2 Diabetes
UNC-CH	University of North Carolina at Chapel Hill
WC	Waist Circumference
WHO	World Health Organization

1. INTRODUCTION

A. Background

Evidence that early life experiences play an important role in the long-term health of individuals holds promise for the identification of public health strategies to modify prenatal and perinatal determinants of adverse adult health outcomes. These are the goals of the field of study known as the Developmental Origins of Health and Disease (DOHaD), which proposes that prenatal and early postpartum nutritional status programs metabolic responses that affect current and later health and physiology.

Although plausible mechanisms for the role of early life experiences in the development of adult health and disease exist, methodological limitations in human epidemiological studies need to be addressed before this field can adequately inform policy recommendations. Our research specifically addresses two such methodological challenges: how best to estimate the effect of growth in one period while appropriately accounting for final attained size, and how to evaluate the impact of overall patterns of growth on later disease.

A challenge in the DOHaD literature is how best to estimate the effect of growth in one period (e.g. infancy, childhood) independent of final attained size. Most studies simply adjust for final attained size, while others have questioned this approach, suggesting that it results in the statistical paradoxes known as “Simpson’s paradox,” “Lord’s paradox” and “suppression,” whereby the association between two variables can be reversed, diminished or enhanced when another variable is statistically controlled for (Tu, Gunnell, & Gilthorpe, 2008). Mediation analysis is a methodological approach that emphasizes the temporal and causal relationships among variables while appropriately accounting for adult size.

A second challenge is how to evaluate the impact of overall patterns of growth on later disease. Most epidemiological studies examining the relationship between early life growth and adult health outcomes have focused on ***tempo*** of growth, ***timing*** of accelerated or decelerated growth or magnitude of ***size*** at a specific time point. These methods do not adequately capture the complex interplay of tempo, timing and size in the development of overall growth patterns. Growth trajectories, identified through latent class growth curve analysis (LCGA), represent a comprehensive statistical model that describes growth over the entire first two years of life, capturing biologically relevant differences in tempo, timing and size.

For the proposed research, we addressed these two methodological challenges using a unique birth cohort study with over 20 years of repeated measures of psychosocial and biological exposures.

B. Research Aims

The overarching goal of this research was to improve our understanding of the relationship between early life growth and the development of adult body composition and insulin resistance. To address our research aims, we used data from The Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based cohort study of children born from 1982-1983 in a metropolitan region of the Philippines. Using these data our specific aims were to:

1) Assess the relationship between infant weight velocity and adult insulin resistance, specifically evaluating whether adult whether adult body mass index (BMI) and waist circumference (WC) mediate the association. We used a combination of linear regression and bootstrapping techniques to separately evaluate the total, direct and indirect effects of infant weight velocity on adult insulin resistance through adult BMI and WC. To clarify the importance of weight velocity at different ages, we calculated weight velocity in both the immediate postnatal period (0-4 months) and during infancy and childhood (0-2 years).

2) Assess the relationship between trajectories of early life growth and adult anthropometric measures of body composition. We used latent class growth analysis (LCGA) to characterize trajectories of early life growth from 0-24 months (assessed with bimonthly anthropometrics) and then examined whether identified trajectories were associated with adult anthropometric measures of body composition. We compare identified growth trajectories with two conventional analytic approaches: (1) accelerated growth between two time points, and (2) tracking of size assessed at one time point.

2. LITERATURE REVIEW

A. Early life experiences play an important role in the long-term health of individuals

A substantial body of literature now provides evidence that early life experiences play an important role in the long-term health of individuals. Initial studies emphasized the associations between birth weight as a proxy for fetal nutrition and risk for chronic conditions later in life including central obesity, the metabolic syndrome, stroke, hypertension, cardiovascular disease (CVD), and type 2 diabetes mellitus (T2D) (D. Barker, 1998; D. J. Barker, Eriksson, Forsen, & Osmond, 2002). Subsequent work shows that early postnatal size and growth are also associated with long-term health outcomes, including risk of obesity (Monteiro & Victora, 2005; Ong & Loos, 2006), risk of type 1 diabetes (T1D) (DiLiberti et al., 2002; EURODIAB, 2002; Fisher et al., 2006; Hypoponen, Kenward, & Virtanen, 1999; Hypoponen, Virtanen, Kenward, Knip, & Akerblom, 2000; Johansson, Samuelsson, & Ludvigsson, 1994), increased blood pressure (L. S. Adair & Cole, 2003) and metabolic risk (Ekelund et al., 2007) in later life.

The importance of early growth for later health outcomes is suggested in the concept of programming, 'the idea that stimuli or insults during critical or sensitive periods in early life can have lifetime consequences (Lucas, Fewtrell, & Cole, 1999).' McCance and Widdowson first showed that early undernutrition had a permanent effect on the subsequent growth of rats, whereas later undernutrition only had a temporary effect (McCance & Widdowson, 1974). This early work emphasized the existence of critical periods during which influences can have long-term consequences for growth and metabolism. Subsequently, numerous animal studies have shown that nutrition in infancy or fetal life can stimulate lifetime effects on metabolism and growth as well as on

major disease processes such as hypertension, diabetes and atherosclerosis (Lucas et al., 1999). Less is known about whether similar phenomena apply in humans. Some evidence suggests it does.

1. Early life and the development of obesity and central adiposity in adult life

A number of epidemiologic studies have shown a positive relationship between birth weight and later BMI (Gillman, Rifas-Shiman, Berkey, Field, & Colditz, 2003; Parsons, Power, & Manor, 2001; Sorensen et al., 1997) suggesting that in utero determinants of birth weight may program the fetus for increased risk of later obesity. A good deal of evidence for human programming of obesity comes from studies of children of mothers with diabetes (Dabelea & Pettitt, 2001; Oken E, 2003). Despite the fact that maternal glucose is transferred to the fetus openly, maternal insulin does not cross the placenta (Freinkel, 1980). It is suggested that the developing fetal pancreas therefore responds to a glucose load by producing insulin which may both stimulate growth (insulin is a growth hormone) and produce hypoglycemic effects. Such a "hyperglycemia-hyperinsulinism" pathway has been suggested to explain the observation that the offspring of diabetic mothers present relatively higher birth weights (Pederson, 1954). It follows that such intrauterine exposures may have lasting influence by means of determining body composition through fat cell size or number. Additionally, evidence in cases of maternal *insufficiency* also suggests that fetal growth experiences may affect obesity through alterations in fat patterning, increasing deposition of central fat (Law, Barker, Osmond, Fall, & Simmonds, 1992; Loos, Beunen, Fagard, Derom, & Vlietinck, 2002; Oken E, 2003; Singhal, Wells, Cole, Fewtrell, & Lucas, 2003). For example, results from the Pune Maternal Nutrition Study indicate that adaptive fetal responses to maternal undernutrition resulted in substantial deficits in abdominal viscera and muscle, while subcutaneous fat was preserved (Yajnik et al., 2003).

Studies are also generally consistent in demonstrating a positive relationship between faster postnatal growth and later BMI or skinfold thickness (Monteiro & Victora, 2005; Ong & Loos, 2006; Stettler, Kumanyika, Katz, Zemel, & Stallings, 2003; Stettler et al., 2005). The shift in the target of weight gain from lean mass to fat mass is proposed as a mechanism for this association (Wells, Chomtho, & Fewtrell, 2007), however the nutritional status of the population under consideration may have a strong influence on the target of weight gain. In developing countries, faster infant weight gain

has been associated with adult lean mass but only moderately or not significantly associated with adult fat mass (Corvalan, Gregory, Ramirez-Zea, Martorell, & Stein, 2007; Sachdev et al., 2005; Wells, Hallal, Wright, Singhal, & Victora, 2005). In contrast, in developed countries faster infant weight gain has been associated with both greater adult lean and adult fat mass (Chomtho et al., 2008; Euser et al., 2005) as well as increased risk of adult obesity (Stettler et al., 2005). In such settings, faster postnatal growth is more likely to be catch-up growth as a result of intrauterine growth retardation. This catch-up growth is characterized by a disproportionately faster rate of body fat gain than lean tissue gain (A. G. Dulloo, Jacquet, & Montani, 2002), a phenomenon described as 'catch-up fat (A. Dulloo, Jacquet, Seydoux, & Montani, 2006).' Some of the earliest realizations of excessive fat deposition during catch-up growth in humans were noted in the commentaries of Widdowson and Shaw regarding nutritional rehabilitation studies in Jamaica (Widdowson & Shaw, 1973). Since these studies in the 1960's it has been shown that gains in body weight following nutritional insufficiency throughout the life cycle are largely due to gain in fat, with increases in body mass lagging behind (A. Dulloo et al., 2006). Evidence also suggests postnatal growth is not only associated with preferential fat deposition, but is also associated with fat patterning. Finally, a *deficiency* in postnatal linear growth is associated with central adiposity in Brazilian, Chinese (Popkin, Richards, & Montiero, 1996), and Hispanic-American (Martorell, Mendoza, Castillo, Pawson, & Budge, 1987) children.

Taken together, these findings support the existence of an important role for both prenatal and postnatal growth in the development of obesity and central adiposity in later life.

2. Early life and the development of insulin resistance, impaired glucose tolerance and diabetes in adult life

A number of epidemiological studies have shown a relationship between thinness at birth and low birthweight on insulin resistance and T2D, suggesting that in utero determinants of birth weight may program the fetus for increased risk of later insulin resistance (D. J. Barker et al., 1993; Bhargava et al., 2004; Eriksson, Forsen, Osmond, & Barker, 2003; Eriksson, Osmond, Kajantie,

Forsen, & Barker, 2006; Hales et al., 1991; Jaquet et al., 2005; Newsome et al., 2003). These findings have been interpreted as support for the 'thrifty phenotype' hypothesis which suggests that poor nutrition in early life produces physiological and metabolic adaptations to ensure adequate nutrient supply to essential vital organs such as the brain at the expense of peripheral organs like the pancreas (Hales & Barker, 2001). Such adaptations during critical developmental periods can lead to lasting changes in structures and functions of tissues (namely in pancreatic β cells, muscle, adipocytes, kidney and liver) and in the resetting of major neuroendrocrine systems in order to enhance the fetus' chances of survival in what it expects to be a poor nutritional environment (Fernandez-Twinn & Ozanne, 2006). It follows that such changes have permanent affects on glucose and insulin metabolism including reduced capacity for insulin secretion and insulin resistance (Hales & Barker, 2001).

Postnatal growth and body composition have also been recognized as important indicators of risk for later impaired glucose tolerance, insulin resistance and T2D (Bhargava et al., 2004; Eriksson et al., 2006; Hales et al., 1991). Evidence suggests that those who were born small or whose growth faltered during infancy but who subsequently exhibited rapid growth (catch-up growth) have increased susceptibility for the development of insulin resistance (D. J. Barker, Osmond, Forsen, Kajantie, & Eriksson, 2005; Cianfarani et al., 2001). Interestingly, in a longitudinal analysis of BMI from birth through 11 years of age, insulin resistance risk was more strongly related to the tempo of childhood gain in BMI than to the BMI attained at any particular age (D. J. Barker et al., 2005), thus emphasizing the importance of the dynamic aspects of catch-up growth on later insulin resistance. It has been suggested that the dynamic phase of catch-up growth itself is a state of insulin resistance. Catch-up growth has been associated with a higher plasma insulin response to a glucose load both in infants born small-for-gestational age (SGA) (Colle, Schiff, Andrew, Bauer, & Fitzhardinge, 1976) and in infants born thin who grow later grow rapidly (Ong & Dunger, 2004).

Taken together, these findings support the existence of an important role for both prenatal and postnatal growth in the development of insulin resistance in later life.

3. Mechanisms linking obesity and insulin resistance

Although epidemiologic data support a relationship between early growth and later insulin resistance, the underlying biologic mechanisms are still poorly understood. While early growth may have irreversible effects on insulin and glucose metabolism, it is also known to influence the development of obesity (Ong & Loos, 2006), which itself is associated with insulin resistance. Obesity affects both insulin sensitivity and insulin secretion (Felber & Golay, 2002; Kahn, Hull, & Utzschneider, 2006). In an obese state, adipose tissue releases increased amounts of non-esterified fatty acids, hormones, pro-inflammatory cytokines and other factors. The increased circulation of these factors limits the amount of glucose uptake by muscles, thus decreasing insulin sensitivity. Thus an understanding of the relationships between early life experiences and later obesity and insulin resistance requires an appreciation of the pathways from obesity to insulin resistance.

4. The catch-up growth dilemma

In developing countries, infants may experience catch-up growth (as a result of intrauterine growth retardation), a type of rapid early growth that can benefit the child, by improving his or her nutritional status, resistance to infection, and survival (Victora, Barros, Horta, & Martorell, 2001; Weaver, 2006). Current practice recommends promotion of compensatory growth of low birth weight infants, aiming to reduce morbidity and mortality rates and to protect neurocognitive aspects. However, for the reasons discussed above it has also been proposed that rapid weight gain (catch-up growth) may be associated with increased obesity and insulin resistance in maturity. Evidence reveals a dilemma whereby under-nutrition and slower early life growth are associated with infant morbidity, mortality and neurodevelopmental deficits while accelerated early life (catch-up) growth is associated with cardiovascular morbidities later in life.

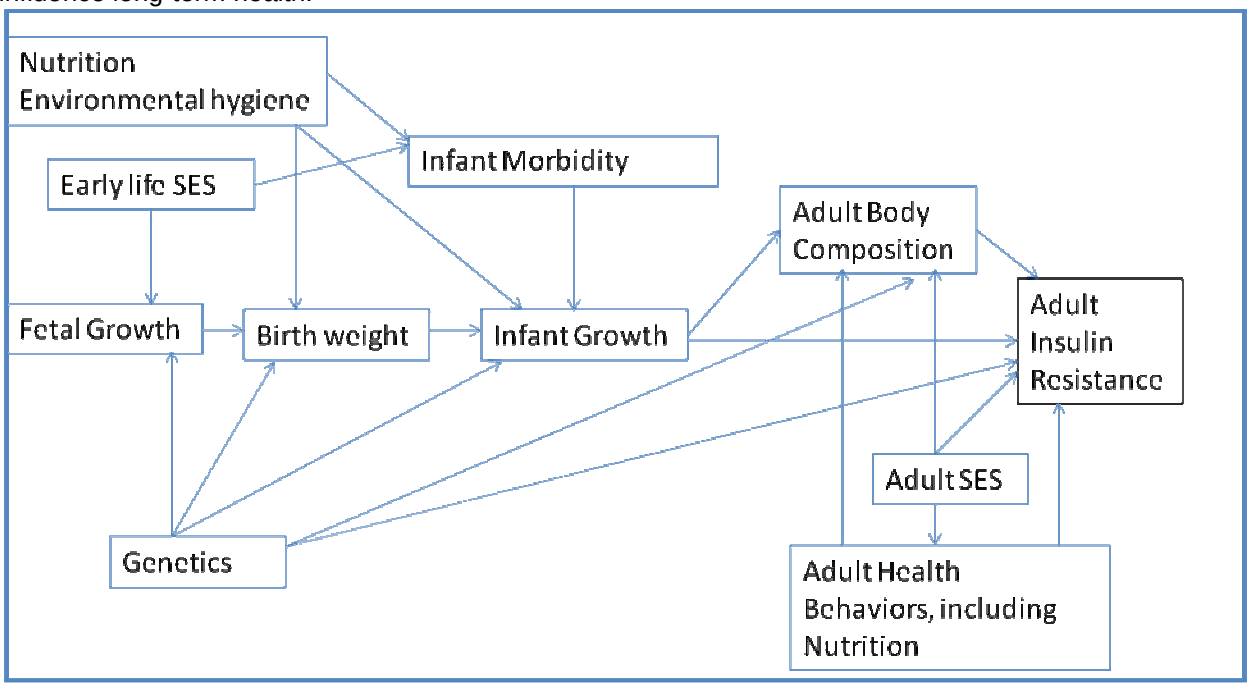
B. Methodological Research Gaps

Epidemiologic research on the relationship between early life growth and later health and disease requires the development and utilization of statistical methods that accurately reflect

biologically based conceptual models. There is still debate in the DOHaD literature over which statistical methods are most appropriate.

Figure 1 illustrates some of the biological and psychosocial factors that may influence both early life growth and adult body composition and insulin resistance. Such a model emphasizes the complex inter-relationships between biological and social mechanisms and further acknowledges that the effects of fetal growth and birth weight, as well as the effects of postnatal growth, depend on environmental influences and paths of development that precede and follow them. The model also demonstrates that fetal and postnatal growth and body composition are both outcomes of early environmental exposures and mediators of their effects on adult outcomes. Growth and body composition are in the pathway and therefore statistical models that examine these relationships must account for this biological complexity.

Figure 1. Potential biological and psychosocial exposures acting across the life course that may influence long-term health.



Our research specifically addresses two methodological challenges: how best to estimate the effect of growth in one period while appropriately accounting for final attained size, and how to evaluate the impact of overall patterns of pre and postnatal growth on later disease.

1. Mediation analysis

While alterations in fetal and postnatal growth may 'program' an individual for increased risk of insulin resistance *independent* of weight status, obesity itself is strongly associated with increased risk of insulin resistance. As such, an important issue which has yet to be fully resolved in the DOHaD literature is how best to account for current size and body composition when modeling the relationship between early life growth and adult outcomes. While most studies have simply adjusted for adult size, others have questioned this approach, suggesting that it results in the statistical paradoxes known as “Simpson’s paradox,” “Lord’s paradox” and “suppression,” whereby the association between two variables can be reversed, diminished or enhanced when another variable is statistically controlled for (Tu et al., 2008).

Deepening our understanding of the relationship between infant weight gain and insulin resistance requires greater knowledge of the pathways linking early growth with adult insulin resistance. In a recent article, Hafeman and Schwartz suggest that by using mediation analysis, epidemiologists can better describe the underlying mechanisms of observed associations and that causal inference can be improved (Hafeman & Schwartz, 2009).

Few studies have explicitly tested the pathways linking early infant weight gain with insulin resistance in young adulthood. The analytic approach used in this study accounts for current size by explicitly modeling the hypothesized pathways linking early growth with insulin resistance *through* adult size rather than *adjusting for* adult size.

2. Trajectories of infant growth

Most epidemiologic research that examines the associations between early life growth and adult health and disease outcomes focus on three important issues: ***tempo*** of growth, ***timing*** of accelerated or decelerated growth and magnitude of ***size*** at a specific time point.

To capture important differences in ***tempo*** and ***timing*** of early life growth researcher's focus on the role of rapid growth, characterized as faster weight or length gain measured over different duration intervals (e.g. birth-4 months, birth-6 months). Much literature links early rapid growth with adult obesity (Monteiro & Victora, 2005; Ong & Loos, 2006). This literature attempts to isolate time periods believed to be critical for the development of chronic diseases. However, most observational studies with long follow-up are limited by data collected for purposes other than investigating the early life origins of adult health and disease. As a result the focus on critical time periods is often based more on data availability and less on *a priori* hypotheses regarding specific sensitive periods.

Alternatively, to examine the associations between early life **size** and adult health and disease, researchers focus on 'tracking,' the persistence or relative stability of overweight over time. 'Tracking' studies consistently report an increased risk of overweight and obese youth becoming overweight adults (Abraham & Nordsieck, 1960; Nader et al., 2006; Singh, Mulder, Twisk, van Mechelen, & Chinapaw, 2008; Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). However, methodological weaknesses have been noted with such studies, including difficulty in evaluating the magnitude and significance of the tracking coefficient as well as accounting for chance and/or measurement error (Twisk, 2003; Wang & Wang, 2003).

Most of our current analytic approaches for understanding early life growth are too simplistic. An implicit assumption is that variation in a single aspect of growth (tempo, timing or size) explains variation in adult health and disease. Any single aspect of early life growth, however, does not tell the whole story. Not all children who experience rapid growth in the first months of life continue to grow rapidly throughout infancy. Moreover, not all children who experience rapid growth do so for the same reasons. Finally, children of the same size at a specific age may have attained that size in

meaningfully different ways. Unraveling the growth pathways that lead to adult chronic disease will require greater understanding of such biologic heterogeneity.

Repeated measures of early life exposures are a challenge to model. Highly correlated exposures are ever-present in epidemiologic research. Kuh and Ben-Shlomo (Kuh & Ben-Shlomo, 1997) assert that one of the critical needs in life course epidemiology is methodology that goes beyond repeated measures to understand trajectories. A promising approach to deal with complex repeated measures is to simplify the exposure profile, reducing it to a number of trajectory classes. Latent growth mixture models (LGMM), which have been used extensively in criminology and psychology, empirically identify latent trajectory classes (Nagin, 1999). This process fits curves for every individual in a sample and then identifies distinct patterns within the sample. These models are able to pick up important differences in tempo, timing and magnitude of early life growth that are not captured simultaneously by other methods of early life growth analysis. An important strength of these models is that the parameters defining the shape of each trajectory are allowed to differ across groups. This flexibility is crucial as it allows identification of differences in both size at a given age as well as in its development over time. This is in contrast to conventional growth modeling which assumes that a single growth trajectory can adequately approximate an entire population. A recent commentary by Pickles concludes that this 'novel method of analysis (LGMM) would appear to achieve a number of practical goals required by life course researchers (Pickles, 2007).'

C. Conclusion

Although plausible mechanisms for the role of early life experiences in the development of adult health and disease exist, more epidemiologic research is needed. Unfortunately there is little consensus on which statistical methods should be used to estimate associations between patterns of early growth on later disease. The use of mediation analysis and infant growth trajectories is an important innovation that addresses two challenges of epidemiologic modeling of DOHaD research questions. Mediation, or path analysis, emphasizes the temporal and causal relationships among variables while appropriately accounting for adult size. Growth trajectories represent a

comprehensive statistical model that describes growth over the entire first two years of life, capturing biologically relevant differences in tempo, timing and size.

3. METHODS

A. Description of the study site and sample

1. Study site

Metro Cebu (pop 1.9 million), on the east coast of Cebu Island in the central Philippines, comprises three cities and seven municipalities in surrounding peri-urban and rural areas. Metro Cebu includes 270 administrative units, or barangays (average area 2km^2). The study area is ecologically diverse, with densely populated cities, less dense peri-urban areas, rural towns, and more isolated mountain and island rural areas.

2. Study sample

A single stage cluster sampling procedure was used to randomly select 17 urban and 16 rural Metro Cebu barangays, which included about 28,000 households. Surveys in 1982-3 located all pregnant women, and those who gave birth between May 1, 1983, and April 30, 1984, were recruited for the sample. More than 90% of women identified agreed to participate in the survey. A baseline interview was conducted among 3,327 women during their 6th or 7th month of pregnancy. Subsequent surveys took place immediately after birth, then bimonthly for 24 months. From the baseline sample, there were 3,080 singleton live births which will make up the sample analyzed in the proposed research. Seven follow-up surveys were conducted in 1991-2, 1994, 1998, 2002, 2005, 2007 and 2009. The sample size for each follow-up survey is shown in Error! Reference source not found.Error! Reference source not found. below.

B. Data and analysis variables

CLHNS data are collected during in-home interviews using structured questionnaires. Quality control measures include extensive training and periodic inter-observer reliability assessments.

Completed questionnaires are reviewed for consistency, and data entry includes range checks. Interviewers return to the respondent's household if questionable responses are noted. All surveys include core modules to collect comparable socioeconomic, demographic, environmental, diet, and anthropometric data.

1. Infant variables

Infant assessments at birth: Infants born at home (62%) were weighed by birth attendants who were provided with and trained in the use of Salter, dial faced hanging scales. The remainder, born at hospitals or maternity clinics were weighed on hospital or clinic scales. Length and weight were subsequently measured by trained CLHNS project interviewers. Length at birth and throughout the first 2 years was measured using locally made length boards; weight was measured on Salter scales. Gestational age was estimated from the date of the mother's last menstrual period (LMP) recorded at the baseline survey. Trained nurses performed Ballard clinical assessments (Ballard JL, 1979) if pregnancy complications occurred or if the infant birth weight was <2.5 kg. Valid Ballard scores, (taken within 120 hours of birth) are used for 614 infants, while all other gestational age assessments are based on LMP. While small-for-gestational age (SGA) is typically defined as birthweight below the 10^{th} centile for gestational age using population based standards, this definition includes both growth restricted as well as constitutionally small infants. To improve the distinction between constitutional and pathological smallness, we calculated individually customized birthweight centiles adjusting for maternal and pregnancy variables (maternal height, arm fatness, parity, and the infant's gender). SGA was defined as a birthweight below the 10^{th} customized centile. Customization was performed according to the methodology described by Gardosi (Gardosi, 2006).

Infant growth: Infant weight and length were measured bimonthly from birth to age 2. We use BMI as a measure of relative weight which is uncorrelated with length in infancy. Sex and age-specific weight, length, weight-for-length and BMI Z-scores were calculated from the WHO child growth standards reference data (WHO, 2006).

Infant feeding: Detailed infant feeding data were collected at each visit using questions about breast-feeding and intake patterns of other foods and liquids in the past 7 days. A 24-hour dietary recall allowed for quantification of energy and nutrient intakes from food sources exclusive of breast milk.

Infant morbidity: Infectious disease morbidity was assessed by mothers' reports of symptoms of diarrhea, respiratory infections, and fever during the week preceding each longitudinal survey. The diarrhea morbidity variable was measured with a high degree of reliability, occurs with sufficient frequency in the sample, and is commonly used in the literature.

2. Young adult variables

Anthropometry and body composition: 2005 survey anthropometrics include height, weight, waist circumference, and skinfold thicknesses at the triceps and subscapular sites. We used the Durnin and Womersley equations, (Durnin & Womersley, 1974) validated for Southeast Asian populations by Deurenberg (Deurenberg-Yap, Schmidt, van Staveren, & Deurenberg, 2000) to estimate percent body fat from skinfolds.

Pregnancy and lactation history: Complete reproductive histories were collected once the sample reached reproductive age. For women who were pregnant in the 2005 survey but not pregnant in the 2002 survey (n=68), we used anthropometric measures collected in the 2002 survey.

Measures of insulin sensitivity and resistance: All respondents to the 2005 survey were asked to fast overnight and blood samples were collected by venipuncture the following morning using EDTA-coated tubes. After mixing to inhibit clotting, a sterile disposable pipette was used to remove several drops of blood for immediate photometric measurement of glucose based on a glucose dehydrogenase method. We used the One Touch Ultra Blood Glucose Monitoring System (Lifescan Johnson and Johnson). After separation, plasma samples were frozen and shipped on dry ice to the clinical laboratory facility at Northwestern University Hospital (Evanston, IL, USA) for analysis of

insulin using a commercially available enzyme immunoassay protocol (DY1065, R&D Systems, Minneapolis, MN).

We calculated homeostatic model assessment insulin resistance (HOMA-IR) as 22.5/(insulin x glucose) (Haffner, Miettinen, & Stern, 1997). HOMA-IR has been used as a measure of insulin sensitivity in numerous population based studies (Haffner, Kennedy, Gonzalez, Stern, & Miettinen, 1996), and is considered the preferred method in large epidemiological studies where more invasive and costly clinic-based assessments are not feasible (Matthews et al., 1985). HOMA-IR was modeled as both a continuous variables (Haffner et al., 1997) and as a dichotomous variable to represent insulin resistance (HOMA-IR>4.65) (Stern et al., 2005).

Socioeconomic Status: Household data include data on household assets, expenditures on food and other commodities, and the highest attained education level, labor force participation and earnings of each household member. SES was represented by a summary index derived from these data and found to be predictive of outcomes such as child growth in prior studies (Eckhardt, Suchindran, Gordon-Larsen, & Adair, 2005).

Urbanization: We created a time-varying multicomponent urbanicity index from community surveys (Dahly & Adair, 2007) that is a better measure of urbanicity than the traditionally used urban-rural dichotomy. This index reflects population size and density, presence of various communication modes, density of paved roads and availability of public transportation, presence of educational institutions, presence of health services and the quantity of diverse types of markets.

4. INFANT WEIGHT VELOCITY AND INSULIN RESISTANCE IN YOUNG ADULTHOOD: BIRTH COHORT STUDY FROM THE PHILIPPINES.

A. Abstract

Background: Recent research suggests that infant weight gain is associated with changes in body composition and insulin resistance in later life. Our objective was to assess the relationship between infant weight velocity and adult insulin resistance, and to evaluate whether changes in adult size and body fat distribution mediate the association.

Methods: Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), which follows a birth cohort to age 22 years (n=1,409). Insulin resistance was measured using homeostatic model assessment insulin resistance (HOMA-IR). Weight velocity (g/month) from 0-4 and 0-24 months was assessed. Multivariable linear regression models were used to examine direct and total associations between early growth and adult HOMA-IR and a nonparametric bootstrapping procedure was used to test indirect effects of early growth on adult HOMA-IR through adult body mass index (BMI) and waist circumference (WC).

Results: Weight velocity (both 0-4 and 0-24 months) was positively associated with adult BMI and WC which also predicted higher HOMA-IR. There were no total or direct effects of immediate postnatal weight velocity (0-4 months) on adult HOMA-IR although indirect effects through adult BMI and WC were significant. Weight velocity from 0-24 months positively predicted HOMA-IR among males only while indirect effects through BMI and WC were significant in both sexes.

Conclusions: In a relatively lean sample of young adults from a population with rising rates of diabetes and cardiovascular disease, we find evidence for small indirect effects of infant weight velocity on adult insulin resistance through adult BMI and WC.

B. Introduction

Longitudinal studies show that insulin resistance is strongly predictive of the development of Type 2 diabetes (T2D) (Lillioja et al., 1993). Small birth size and growth in infancy and childhood are associated with insulin resistance and T2D (D. J. Barker et al., 1993; Crowther, Cameron, Trusler, & Gray, 1998; Eriksson et al., 2003; Eriksson et al., 2006; Fall et al., 2008; Jaquet et al., 2005; Newsome et al., 2003; Ong & Dunger, 2004; Ravelli et al., 1998). These findings have been interpreted as support for the 'thrifty phenotype' hypothesis which suggests that poor nutrition in early life produces physiological and metabolic adaptations to ensure adequate nutrient supply to essential organs such as the brain at the expense of peripheral organs like the pancreas (Hales & Barker, 2001). Such changes during critical developmental periods are proposed to have permanent affects on insulin-glucose metabolism.

Although epidemiologic data support a relationship between early growth and later insulin resistance, the underlying biologic mechanisms are still poorly understood. While early growth may have irreversible effects on insulin-glucose metabolism, it is also known to influence the development of obesity (Ong & Loos, 2006), which itself is associated with insulin resistance (Felber & Golay, 2002; Kahn et al., 2006). As such, it is difficult to determine whether early growth affects later insulin resistance directly as a result of 'programming' of insulin-glucose metabolism, and/or indirectly through its influence on adult body composition. Recently, Hafeman and Schwartz suggested that through mediation analysis, which allows partitioning of relationships into direct and indirect pathways, epidemiologists may better describe the underlying mechanisms of observed associations (Hafeman & Schwartz, 2009).

Our objective was to use a mediation approach to assess the relationship between infant weight velocity and adult insulin resistance, specifically evaluating whether adult body mass index (BMI) and

waist circumference (WC) mediate the association. We use data from a large birth cohort of Filipinos who have been followed into young adulthood. Prior research in this sample has documented associations between birth size and blood pressure, lipid profiles and inflammatory status, establishing a likely link between early nutrition or growth and adult cardiovascular disease risk (L. Adair, Kuzawa, & Borja, 2001; Kuzawa & Adair, 2003; McDade, Rutherford, LS, & Kuzawa, 2010). Here we extend these analyses by modeling the role of early weight velocity as a predictor of adult insulin resistance using methods capable of distinguishing the role of body composition and fat patterning as possible mediating influences. To clarify the importance of weight velocity at different ages, we calculated weight velocity in both the immediate postnatal period (0-4 months) and during infancy and early childhood (0-2 years).

C. Methods

1. Study population

Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based cohort study of infants born in 1983-1984 in Metro Cebu, the second-largest metropolitan area in the Philippines. In 1983-1984 the Metro Cebu area was comprised of 243 administrative units; 33 (17 rural and 16 urban) were randomly selected. All pregnant women residing in these communities, and who gave birth in a 1 year period from 1983 to 1984 were invited to participate (n=3327). The resulting child sample (n=3080) is representative of singleton births in Metro Cebu. Data were collected during the last trimester of pregnancy, immediately following birth, then bimonthly for 2 years. Seven follow-up surveys were conducted in 1991-2, 1994, 1998, 2002, 2005, 2007 and 2009. In 2005, biomarkers were collected in the full sample. The present analysis used data from the longitudinal survey (0-2 years) and the 2005 follow-up survey.

Of the 616 participants lost to follow-up from 0-24 months, 155 died (25%), while the remainder were not found or were no longer living in the study area. Of the 552 participants lost to follow-up between 24 months of age and the 2005 follow-up, 55 died (10%). The remaining losses were predominantly due to migration outside of the study area.

Because prematurity may influence insulin sensitivity the analytic sample excluded preterm births (n=119). We also excluded women who were pregnant at the 2005 survey (n=81). We compared baseline characteristics of the analytic sample with subjects who were in the sample at baseline. Birth weight and length did not differ between the two groups. Those lost to follow-up were more likely to be urban residents and to have more highly educated mothers, but there were no significant differences in household assets, maternal height, age, or parity. Weight velocity from 0-4 months was greater in those retained in the sample which may reflect slower growth among those who subsequently died during infancy.

2. Infant anthropometric measures

Infant weight was measured using Salter hanging scales. Weight velocity from 0-4 and 0-24 months (kilograms/month) was calculated as the change in weight (kilograms) between two measurements divided by the time interval (months) between those measurements. We chose the 0-4 month interval in an effort to capture the first months of life, a period hypothesized to be critical for the development of obesity (Gillman, 2008). We chose the 0-2 year interval for comparability with other studies.

3. Adult anthropometric measures

BMI was calculated from measured weight and height in 2005. WC was measured at the midpoint between the bottom of the ribs and the top of the iliac crest. BMI and WC were log-transformed; geometric means (mean (SD)) are therefore presented for these variables.

4. Laboratory analyses

Participants were asked to fast overnight and blood samples were collected by venipuncture the following morning using EDTA-coated tubes. After mixing to inhibit clotting, a sterile disposable pipette was used to remove several drops of blood for immediate photometric measurement of glucose based on a glucose dehydrogenase method. We used the One Touch Ultra Blood Glucose

Monitoring System (Lifescan Johnson and Johnson). After separation, plasma samples were frozen and shipped on dry ice to the clinical laboratory facility at Northwestern University Hospital (Evanston, IL, USA) for analysis of insulin using a commercially available enzyme immunoassay protocol (DY1065, R&D Systems, Minneapolis, MN). We calculated homeostatic model assessment insulin resistance (HOMA-IR) as 22.5/(insulin x glucose) (Haffner et al., 1997). Fasting insulin and HOMA-IR were log-transformed; geometric means (mean (SD)) are therefore presented for these variables.

5. Covariates

Gestational age was estimated from the mother's report of the date of her last menstrual period. In cases where this date was unknown, when pregnancy complications occurred, or when the infant weighed <2.5 kg at birth, gestational age was determined by nurses using the Ballard method (Ballard JL, 1979). Small-for-gestational age (SGA) was defined as birthweight below the 10th centile of individually customized birthweight centiles adjusting for maternal and pregnancy variables. Customization was performed according to the methodology described by Gardosi (Gardosi, 2006).

Low birthweight was defined as <2500g. Maternal height (cm) was selected to represent the child's genetic size potential. Parity was reported by mothers at baseline. A multicomponent urbanicity scale (Dahly & Adair, 2007) was chosen as an indicator of the community environment in which the child was raised. Socioeconomic status was represented by a summary assets score including 10 key assets.

All data were collected by project staff during in-home interviews. Quality control measures included extensive training and periodic inter-observer reliability assessments. All procedures were reviewed and approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

6. Statistical analysis

Statistical analyses were performed using Stata, version 11.0 (StataCorps LP, College Station, TX) and SPSS 17.0 for Windows (SPPS, Inc. Chicago, IL). Given the known sex differences in early growth and in the development of insulin resistance, all models were sex-stratified (Regitz-Zagrosek, Lehmkuhl, & Mahmoodzadeh, 2007). While our focus was on weight velocity in the first months of life (0-4 months), we also examined weight velocity from 0-2 years for comparability with other work examining longer intervals.

We used the INDIRECT macro in SPSS (Preacher & Hayes, 2008) to test the mediation hypotheses. The macro combines linear regression models with a bootstrapping method (Preacher & Hayes, 2008) to calculate indirect effects. Weight velocity, HOMA-IR, BMI and WC were modeled as continuous variables. Potential mediators were examined in separate models.

The conceptual model for the mediation analysis is illustrated in **Figure 2**. The INDIRECT macro incorporates several regression equations to obtain path coefficients for each relationship. Linear regression was used to examine the relationships between infant weight velocity and adult BMI and WC (path a), between adult BMI and WC and adult HOMA-IR (path b) and between infant weight velocity and adult HOMA-IR (path c', the direct effect). The total effect (path c) is the association of infant weight velocity with adult HOMA-IR without mediators in the model.

The indirect effect was quantified using a bootstrapping method (with n=5000 bootstrap resamples) recommended by MacKinnon (MacKinnon, 2000) and further elaborated by Preacher and Hayes (Preacher & Hayes, 2008). Theirs is a nonparametric approach to effect-size estimation and hypothesis testing that makes no assumptions about the shape of the distributions of the variables or the sampling distribution of the statistic. We computed bias-corrected and accelerated confidence intervals (Efron, 1987) and considered point estimates of indirect effects significant if zero was not contained in the confidence intervals.

Non-linear associations were tested by producing tertiles of infant weight velocity which were compared with respect to adult HOMA-IR, BMI and WC. For all models, we separately tested interactions between infant weight velocity with SGA and low birthweight status. Since none were found, these interactions terms were not included in final models.

Covariates hypothesized to be confounders of the relationship between infant weight velocity and adult insulin resistance and between adult BMI and WC and adult insulin resistance included age, mother's height, parity, urbanicity and socioeconomic status (**Figure 2**). These same factors, along with SGA status, were considered as confounders of the relationship between infant weight velocity and adult BMI and WC.

D. Results

In infancy the sample was generally undernourished. The prevalence of underweight (weight-for-age z-score <-2) at birth was 10% for males and 6% for females and substantially increased with age, such that by two years of age, 35% of sample infants were underweight (**Table 1**). The sample was relatively young and lean in adulthood (**Table 1**).

Table 3 presents results from regression models of infant weight velocity (0-4 and 0-24 months) on adult BMI and WC (the 'a' path, **Figure 2**). Weight velocity positively predicted adult BMI and WC. Adult BMI and WC were positively associated with adult HOMA-IR (b path) (**Table 3**). Total and direct effects of infant weight velocity on adult HOMA-IR (paths c and c') are shown in **Table 4**. In the models without mediators (c path, total effect) weight velocity from 0-4 months was not associated with adult HOMA-IR while weight velocity from 0-24 months was positively associated with HOMA-IR among males only. In the models with mediators (c' path, direct effects) weight velocity was not associated with HOMA-IR.

Table 5 shows the indirect effects of infant weight velocity on HOMA-IR through adult BMI and WC. The point estimates represent the product of coefficients (paths a*b), which is the amount we expect HOMA-IR to change for a 1 kg/month increase in weight velocity, indirectly through BMI or WC. Overall, all models revealed significant, positive indirect effects of infant weight velocity on HOMA-IR through adult BMI and WC. Indirect effects were slightly stronger via WC than BMI, and among males as compared to females.

E. Discussion

We examined the association between infant weight velocity and young adult insulin resistance. To our knowledge this is the first study to explicitly examine specific components of body composition as potential mediators of the infant weight gain-adult HOMA-IR relationship in a young adult population with a low prevalence of overweight and obesity. Weight velocity in both intervals was positively associated with adult BMI and WC, which both predicted higher HOMA-IR. There were no total or direct effects of immediate postnatal weight velocity (0-4 months) on young adult HOMA-IR. Indirect effects of immediate postnatal weight velocity on HOMA-IR through adult BMI and WC were significant though small. Weight velocity over a longer interval (0-24 months) positively predicted HOMA-IR among males only (c' path, total effects) and indirect effects through adult BMI and WC were significant in both males and females.

Consistent with previous studies, infant weight gain was positively associated with adult BMI (Monteiro & Victora, 2005; Ong, 2006) and WC (Corvalan et al., 2007; Euser et al., 2005; Fall et al., 2008; Gonzalez, Nazmi, & Victora). Understanding the relationship between postnatal weight gain and adult BMI and WC is important given the well-recognized relationships between central obesity and insulin resistance (Felber & Golay, 2002; Kahn et al., 2006). As expected, adult BMI and WC were both positively associated with adult HOMA-IR.

Although immediate postnatal weight velocity (0-4 months) was positively associated with adult size, there were no total effects on adult HOMA-IR (c paths). In the DOHaD literature a number of

studies have reported statistically significant associations between early life size and adult outcomes only after adjusting for current body size (Huxley, Neil, & Collins, 2002). As we hypothesized that adult size is in the causal pathway from infant weight velocity to adult HOMA-IR we examined the indirect effects of weight velocity (0-4 months) on adult HOMA-IR *through* adult BMI and WC. We established significant, though small, positive indirect effects of immediate postnatal weight velocity on HOMA-IR through adult BMI and WC. For example, for a one standard deviation increase in weight velocity from 0-4 months (170 g/month for males and 160 g/month for females), we expect HOMA-IR to increase 3.4% and 3.2% among males and females, indirectly through WC. Increases in HOMA-IR of this magnitude would only increase the percentage of insulin resistant (HOMA-IR>4.65) adult males and females in our sample from 5.15% to 5.89% (0.74 percentage points) and from 7.75% to 7.81% (0.06 percentage points), respectively.

It is important to note that overweight and insulin resistance were still relatively rare in our young adult sample. It is possible that the long-term effects of infant weight velocity on insulin-glucose metabolism are not yet evident. Future research conducted as the population ages may reveal a strengthening of the effects documented here, or perhaps long-term effects not yet apparent.

Of note, while not statistically significant, direct effects (c' paths) were all negative. Negative direct effects may explain our findings of significant indirect effects in the absence of total effects, suggesting masking of the total effect estimate by opposing direct and indirect effects of early growth. Negative direct effects are biologically plausible. Immediate postnatal weight gain may have greater effects on lean as compared to fat mass (Sachdev et al., 2005) which would be expected to improve insulin sensitivity.

Our finding of total effects of weight velocity over a longer duration of postnatal growth (0-24 months) on adult HOMA-IR in males is consistent with previous studies demonstrating a positive relationship between infant and early childhood growth with insulin resistance in childhood (Crowther et al., 2008; Ong et al., 2004) as well as adulthood (Fall et al., 2008). In our sample males, for a one

standard deviation increase in weight velocity from 0-24 months (42.77 g/month), we expect HOMA-IR to increase 6% (total effect, without potential mediators). Interpreting the indirect effects for a one standard deviation increase in weight velocity from 0-24 months, we expect HOMA-IR to increase 7.3%, indirectly through WC. Increases in HOMA-IR of this magnitude would only increase the percentage of insulin resistant (HOMA-IR>4.65) adult males in our sample from 5.15% to 6.67% (1.52 percentage points). Many previous studies pooled male and female data. An important addition to the literature is our finding that among females weight velocity in the first 2 years was not directly associated with HOMA-IR.

Associations were larger in males than females. The gender differences that we document are not surprising given that sex hormones may have important influences on early life growth and the development of body composition (Lampl, Thompson, & Frongillo, 2005) as well as the risk of T2D (Ding, Song, Malik, & Liu, 2006). In addition, prior work in this sample has found that birth weight is inversely related to blood pressure and adverse lipid profiles measured in adolescence, with effects stronger or in some instances only present in males (L. Adair et al., 2001 ; Kuzawa & Adair, 2003). The present findings extend evidence for gender differences in long-term health effects in the CLHNS sample to the outcome of insulin resistance in early adulthood.

A focus of the critiques of mediation analysis by epidemiologists is the potential for biased estimates of the direct and indirect effects if confounding of the mediator-disease relationship is not adjusted for (Cole & Hernan, 2002; Robins & Greenland, 1992). The CLHNS includes a breadth of measurements that allowed for inclusion of covariates known to be confounders of the mediator-disease relationship, representing a major strength of the study. However, while we included many known confounders of the adult size-HOMA-IR relationship, we cannot rule out the possibility of residual confounding of these factors, or other unmeasured confounders which might create "collider bias" and inflate our estimates of the indirect effects (Hafeman, 2008).

This analysis is important to the ongoing debate in the DOHaD literature regarding how best to account for current size when modeling the relationship between early growth and adult outcomes. While most studies have simply adjusted for adult size, others have questioned this approach, suggesting that it results in the statistical paradoxes known as “Simpson’s paradox,” “Lord’s paradox” and “suppression,” whereby the association between two variables can be reversed, diminished or enhanced when another variable is statistically controlled for (Tu et al., 2008). The analytic approach used in our study accounts for current size by explicitly modeling the hypothesized pathways linking early growth with insulin resistance *through* adult size rather than *adjusting for* adult size.

In our sample, there were no total or direct effects of faster immediate postnatal weight velocity on adult HOMA-IR. There were only small indirect effects. Notably, we did not find an interaction between infant weight velocity and SGA status, indicating faster postnatal growth has similar effects in those born SGA and those who were not. These results suggest that in lower-income contexts where undernutrition and small birth size are common, the promotion of compensatory growth will not have substantial long-term negative consequences for insulin resistance if excess development of body fat and central obesity can be prevented. Faster weight gain in later childhood and adolescence has been more clearly associated with increased adult adiposity and central adiposity as well as an increased risk of impaired glucose tolerance and T2D (Bhargava et al., 2004; Sachdev et al., 2005). In making recommendations about early growth we must consider both the short- and long-term consequences. It should be emphasized that in infancy our sample was generally undernourished and the prevalence of underweight increased with the introduction of complementary foods when exposure to pathogens and diarrheal illness was more common (Popkin et al., 1990). Past work in this sample suggests that improving infant nutrition would likely reduce short-term morbidity and increase infant survival (Martorell et al., 2010; Mendez & Adair, 1999) while having positive effects on adult human capital (Victora et al., 2008). The present finding of minimal associations between immediate postnatal weight velocity and adult insulin resistance suggests that any deleterious long-term consequences of improved early life nutrition on adult diabetes risk might be comparatively small.

F. Key Messages

1) Few studies have explicitly tested the pathways linking early infant weight gain with insulin resistance in young adulthood.

2) In this study, weight velocity in the first months of life was not directly associated with markers of insulin resistance in young adulthood, however significant indirect effects through adult fatness and central adiposity were found.

3) Our findings suggest that SGA babies do not suffer disproportionate long-term health effects of rapid weight gain in our sample.

Figure 2. Conceptual model for the mediation analysis

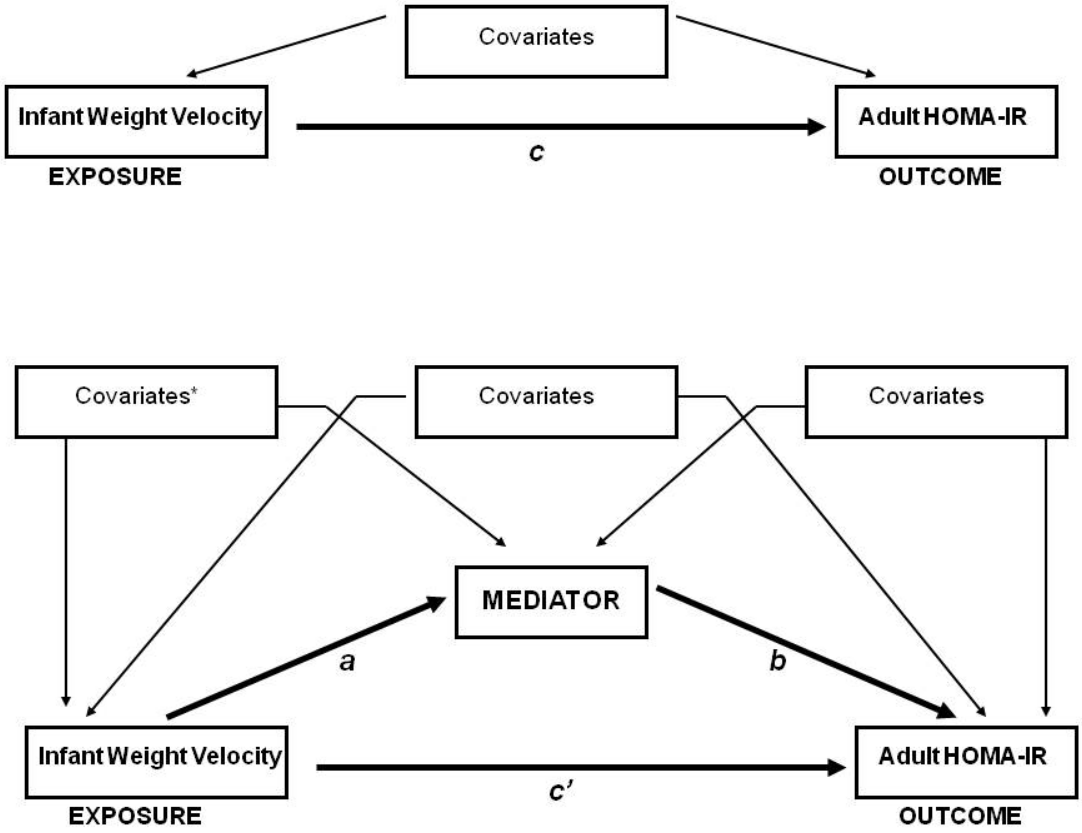


Figure 1: Conceptual model for the mediation analysis. Linear regression was used to examine the relationship between infant weight velocity and adult BMI and WC (path a), the relationships between BMI and WC and HOMA-IR (path b) and between infant weight velocity and adult HOMA-IR (path c', the direct effect). Path c (the total effect) is the path from infant weight velocity to adult HOMA-IR in a model with no mediator. * Covariates include age, small-for-gestational age status, mother's height, parity, urbanicity and socioeconomic status.

Table 1. Selected characteristics of participants included in the analyses

Measurement	n missing (n=1409)	Males (*n*=777) Mean	SD	Females (*n*=632) Mean	SD	*p* value*
Infant Characteristics						
Weight (kg)						
0 months	0	3.04	0.41	2.97	0.40	<0.01
4 months	0	6.39	0.76	5.91	0.69	<0.001
2 years	54	10.09	1.11	9.47	1.09	<0.001
Weight-for-age z-score (WAZ)†						
0 months	0	-0.82	0.88	-0.68	0.85	<0.01
4 months	0	-0.88	1.04	-0.77	0.97	0.03
2 years	54	-1.69	0.97	-1.67	0.99	0.73
Weight velocity (kg/month)						
0-4 mo	0	0.86	0.17	0.75	0.16	<0.001
0-24 mo	54	0.29	0.01	0.27	0.01	<0.001
Percent underweight (WAZ<-2)						
0 months	0	9.91		6.33		0.02
4 months	0	13.51		8.86		<0.01
2 years	54	35.33		34.71		0.81
Gestational age	0	39.12	1.61	39.32	1.69	0.02
Household Assets	0	5.21	2.05	5.33	1.92	0.25
Household Urbanicity	0	40.90	13.62	41.10	13.03	0.79
Mother's Education	0	7.47	3.67	7.38	3.64	0.67
Mother's Age at Child's Birth	0	26.50	5.94	26.68	5.88	0.55
Mother's Height	0	150.61	4.94	150.51	5.01	0.72
Parity	0	2.25	2.22	2.25	2.16	0.99
Adult Characteristics						
Age (years)	0	21.47	0.30	21.46	0.31	0.61
Height (cm)	0	163.00	5.70	151.15	5.32	<0.001
Weight (kg)	0	55.79	8.89	46.46	8.13	<0.001
BMI (kg/m^2) ‡	0	20.78	0.10	20.09	0.12	<0.001
Percent overweight §	0	18.79		15.66		0.12
Waist circumference ‡	0	71.70	0.25	67.65	0.28	<0.001
Fasting Insulin (ug/ml) ‡	0	6.47	0.13	8.21	0.19	<0.001
HOMA-IR ‡	0	1.62	0.03	2.01	0.05	<0.001
Percent Insulin Resistant **	0	5.15		7.75		<0.05

* *p* value for comparison between sexes.
† Calculated from WHO growth standards
‡ Geometric means and SDs
§ BMI<23 (WHO recommended cut-point for Asian populations)
** HOMA-IR<4.65

Table 2. Regression coefficients from separate adjusted* regression models of infant weight velocity on adult body mass index (BMI), and waist circumference (WC).

	Males			Females		
	n	Coeff	95% CI	n	Coeff	95% CI
Weight velocity 0-4 months						
Adult BMI †	777	**0.15**	**0.09, 0.20**	632	**0.10**	**0.02, 0.17**
Adult WC †	777	**0.11**	**0.07, 0.15**	632	**0.07**	**0.02, 0.12**
Weight velocity 0-24 months						
Adult BMI †	750	**1.01**	**0.79, 1.23**	605	**0.64**	**0.33, 0.94**
Adult WC †	750	**0.71**	**0.55, 0.87**	605	**0.45**	**0.24, 0.67**

Bold values are for coefficients with *p*-value <0.05.

* Models adjusted for age, small-for-gestational age status, parity, mother's height, urbanicity and socioeconomic status.

† Variables are log-transformed.

Table 3. Regression coefficients from separate adjusted* regression models of HOMA-IR† as the dependent variable and body mass index (BMI) and waist circumference (WC) as independent variables.

	Males, n=777		Females, n=632	
	Coeff	95% CI	Coeff	95% CI
Adult BMI †	**1.50**	**1.20, 2.51**	**1.63**	**1.34, 2.77**
Adult WC †	**2.28**	**1.87, 3.87**	**2.49**	**2.08, 4.29**

Bold values are for coefficients with *p*-value <0.05.

* Models adjusted for age, parity, mother's height, urbanicity and socioeconomic status.
† Variables are log-transformed.

Table 4. Regression coefficients for total* and direct† effects of infant weight velocity (kg/month) on adult HOMA-IR‡.

	Males			Females		
	n	Coeff	95% CI	n	Coeff	95% CI
Weight velocity 0-4 months						
Total effect	777	0.12	-0.13, 0.37	632	-0.002	-0.30, 0.30
Direct effect (including BMI)	777	-0.11	-0.35, 0.13	632	-0.17	-0.44, 0.10
Direct effect (including WC)	777	-0.12	-0.36, 0.11	632	-0.16	-0.43, 0.12
Weight velocity 0-24 months						
Total effect	750	**1.41**	**0.38, 2.45**	605	0.76	-1.50, 0.74
Direct effect (including BMI)	750	-0.05	-1.09, 0.99	605	-0.38	-1.50, 0.74
Direct effect (including WC)	750	-0.18	-1.20, 0.83	605	-0.30	-1.44, 0.83

Bold values are for coefficients with *p*-value <0.05.

* The total effect (path c) is the association of infant weight velocity with adult HOMA-IR with no mediators in the model.

† The direct effect (path c') is the association of infant weight velocity with adult HOMA-IR with mediators in the model.

‡ Variable is log-transformed.

All models are adjusted for age, small for gestational age status, parity, mother's height, urbanicity and socioeconomic status.

Table 5. Indirect effects of infant weight velocity (kg/month) on adult HOMA-IR through adult Body Mass Index (BMI) and Waist Circumference (WC), (5000 bootstrap samples).*

	Males				Females			
		Point	Bca† 95% CI			Point	Bca† 95% CI	
	n	Estimate	Lower	Upper	n	Estimate	Lower	Upper
Indirect Effects of weight velocity (0-4 months)								
Body Mass Index	777	0.23	0.14	0.35	632	0.16	0.29	0.31
Waist Circumference	777	0.24	0.14	0.37	632	0.17	0.05	0.31
Indirect Effects of weight velocity (0-24 months)								
Body Mass Index	750	1.46	1.03	2.10	605	1.06	0.57	1.67
Waist Circumference	750	1.60	1.13	2.28	605	1.15	0.63	1.75

* All models controlled for age, small for gestational age status, parity, mother's height, urbanicity and socioeconomic status.

† Bca=bias corrected and accelerated bootstrapping confidence intervals that include corrections for both median bias and skew (Efron and Tibshirani). Confidence intervals containing zero are interpreted as not significant.

The point estimates are the amount we expect HOMA-IR to change for a 1 kg increase of infant weight velocity, indirectly through BMI or WC.

5. INFANT BMI TRAJECTORIES ARE ASSOCIATED WITH YOUNG ADULT BODY COMPOSITION

A. Abstract

Background: The dynamic aspect of early life growth is not fully captured by typical analyses, which focus on one specific time period. To better understand the role of early growth in the development of adult body composition, we focus on infant growth trajectories.

Objective: We aimed to characterize trajectories of early growth using latent class growth analysis (LCGA) and to evaluate the impact of trajectories infant growth on adult body composition.

Design: Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), which follows a birth cohort to age 22 years (n=1,749). Latent class growth analysis (LCGA) was used to identify subgroups of respondents with similar body mass index (BMI) trajectories from 0-24 months (assessed with bimonthly anthropometrics). We then assessed how these patterns relate to anthropometric indicators of body composition in young adulthood. Finally we assessed whether trajectories provided more information than two conventional approaches: (1) accelerated growth between two time points (0-4 mos), and (2) BMI measured at one time point (24 mos).

Results: Seven distinct BMI trajectories were identified. Groups are distinguished by age-specific differences in tempo and timing of BMI gain in infancy. In predicting young adult anthropometric measures of body composition, infant BMI trajectories were more predictive than accelerated BMI gain between 0-4 months. After controlling for BMI at age 2, infant BMI trajectories still explained variation in adult body composition.

Conclusions: Using unique longitudinal data and methods, we find that distinct infant BMI trajectories have long-term implications for the development of body composition.

B. Introduction

An extensive literature shows that undernutrition in infancy and childhood is related to an increased risk of morbidity, mortality and poor developmental outcomes in childhood (Black et al., 2008; Mendez & Adair, 1999). Undernutrition in early life also has long-term consequences (Victora et al., 2008). Recent analyses using pooled data from five birth cohorts in low- and middle-income countries demonstrate that stunting in the first 2 years of life relates to shorter adult height, lower attained schooling and decreased offspring birth weight (Victora et al., 2008). As a result of such findings, the promotion of compensatory growth, especially in lower-income settings, has been strongly endorsed (Victora & Barros, 2001).

Recently, however, concern has been raised about the potential long-term adverse consequences of rapid or accelerated child growth, including increased risk of overweight and obesity as well as chronic disease risk factors (Fisher et al., 2006; Ong & Loos, 2006). Rapid weight gain is particularly relevant in low- and middle-income countries undergoing the nutrition transition and facing the dual burden of under and overweight (Popkin, 2001). Specifically, the risk of cardiovascular and metabolic disease may be highest in children who are undernourished in infancy but subsequently put on weight rapidly (D. J. Barker et al., 2005; Bhargava et al., 2004; Lawlor, Leon, & Rasmussen, 2007), suggesting that overall patterns of growth are important.

Researchers assessing the relationship between early growth and adult outcomes have typically represented growth as size at one time point (e.g. birth weight) or simple increments (e.g. weight gain from birth to 6 months), with or without adjusting for subsequent growth. Such methods do not adequately capture the interdependence of growth measures at different ages. Sophisticated methods have been utilized to model population growth curves as outcomes. However, these methods estimate an average trajectory for the entire sample, failing to capture potentially important

heterogeneity in patterns of growth.

In this paper we extend the large body of literature on the consequences of infant growth by analyzing data from a Filipino birth cohort undergoing the nutrition transition. The aim of the current study is to characterize trajectories of body mass index (BMI) over the first two years of life using latent class growth analysis (LCGA). Specifically we are interested in identifying distinct groups of infants with different shaped trajectories. We then examine whether identified trajectories are associated with adult anthropometric measures of body composition. Finally, to assess whether the LCGA approach adds to our understanding of the relationship between early life growth and adult outcomes, we compare identified trajectories with two conventional analytic approaches: (1) accelerated growth between two time points (0-4 months), and (2) size measured at one time point (24 mos).

C. Subjects and Methods

1. Study population

We used data from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based cohort study of infants born in 1983-1984 in Metro Cebu, the second-largest metropolitan area in the Philippines. In 1983-1984 the Metro Cebu area was comprised of 243 administrative units; 33 (17 rural and 16 urban) were randomly selected. All pregnant women residing in these communities and who gave birth in a 1 year period from 1983 to 1984 were invited to participate (n=3327). The resulting child sample (n=3080 singleton live births) is representative of singleton births in Metropolitan Cebu. Data were collected during the last trimester of pregnancy, immediately following birth, and then bimonthly for 2 years. Full follow-up surveys were conducted in 1991-2, 1994, 1998, 2002 and 2005. All surveys included core modules to collect comparable socioeconomic, demographic, environmental, diet, and anthropometric data. The present analysis used data from the first 2 years and the 2002 and 2005 follow-up surveys. For women who were pregnant during the 2005 follow-up but not pregnant in the 2002 follow-up (n=68), we used anthropometric measures collected in 2002. The final analytic sample included 1749 participants (**Figure 3**).

We compared baseline characteristics of the analytic sample with subjects who were in the sample at baseline (single live births). Birth weight and length did not differ significantly between the 2 groups. The subjects lost to follow-up were more likely than those retained in the sample to be urban residents and to have more highly educated mothers, but there were no significant differences in household assets or in maternal height, age, or parity. Weight velocity from 0-4 months was greater in those retained in the sample, which may reflect decelerated growth among those who died during infancy.

2. Infant anthropometric measures

Infant recumbent length was measured by research staff using custom-designed length boards and infant weight was measured with Saltar hanging-type scales. Measured length and weight were used to construct measures of Body Mass Index (BMI; in kg/m^2) at each age. Body BMI was used to define infant growth trajectory classes. Measures were also converted into z-scores (weight-for-age, length-for-age, BMI-for-age) using the WHO Growth Standards (M. G. R. S. G. WHO, 2006). Accelerated BMI gain from 0-4 months was calculated as a >0.67 change in BMI-zscore from 0-4 months (Monteiro & Victora, 2005). We chose the 0-4 month interval in an effort to capture the first months of life, a period hypothesized to be critical for the development of obesity (Gillman, 2008). We also examine attained BMI at two years of age because of the importance of the first 2 years of life as a window of opportunity for growth promotion (Martorell, 1995; Uauy, Kain, Mericq, Rojas, & Corvalan, 2008; Victora, de Onis, Hallal, Blossner, & Shrimpton).

3. Adult anthropometric measures

BMI (kg/m^2) was calculated from measured weight and height in 2005 (or 2002 for those pregnant in 2005). WC was measured at the midpoint between the bottom of the ribs and the top of the iliac crest. Waist-to-height ratio (WHR) was calculated from WC and height. Triceps and subscapular skinfold thickenesses (SF) represent the mean of three consecutive Harpenden caliper measurements. We calculated percent body fat from SF equations based on published conversion

tables (Durnin & Womersley, 1974) validated for Asian populations (Deurenberg & Deurenberg-Yap, 2002). Fat mass (FM; kg) was calculated as percentage body fat x weight, and lean mass (LM; kg) was calculated as adult weight minus fat mass. Fat mass and lean mass were adjusted for height according to sample-specific coefficients calculated from allometric models using the approach suggested by Heymsfield (Heymsfield, Gallagher, Mayer, Beetsch, & Pietrobelli, 2007) (FMI = FM/height$^{3.3}$ (males) FM/height$^{2.3}$ (females); LMI = LM/ height$^{2.1}$ (males) LM/ height$^{1.8}$ (females)). BMI, FMI, LMI, WC and WHR were log-transformed; geometric means (mean (SE)) are therefore presented for these variables.

4. Covariates

Gestational age was estimated from the mother's report of the date of her last menstrual period. In cases where this date was unknown, when pregnancy complications occurred, or when the infant weighed <2.5 kg at birth, gestational age was determined by nurses using the Ballard method (Ballard JL, 1979). Small-for-gestational age (SGA) was defined as birthweight below the 10th centile of individually customized birthweight centiles adjusting for maternal and pregnancy variables (maternal height, arm fatness, parity, and the infant's gender). Customization was performed according to the methodology described by Gardosi (Gardosi, 2006).

Information on infant feeding included frequency and predominance of breast-feeding, given in the past 24 h and general feeding pattern 7 days prior to the survey. Time predominantly breastfed was defined as the number of months the infant was fed breast milk and no other nutritive foods or liquids. Morbidity data reflected the maternal report of the number of episodes of diarrhea and severe respiratory symptoms experienced by the infant in the past week.

Maternal height (cm) was selected to represent the index child's genetic potential for size both as an infant and as an adult. Parity was reported by mothers at baseline. Socioeconomic status at baseline (1983-1984) was represented by a summary asset score derived from information on 10 key assets. Socioeconomic status in young adulthood (2005) was represented by total household

income. A multicomponent urbanicity scale calculated at baseline (Dahly D.L, 2007) was chosen as an indicator of the urban nature of the community environment in which the child was raised. A hygiene index calculated at baseline represented the overall cleanliness of the environment within and surrounding the house, including cleanliness of food preparation areas, toilet type, presence of visible excreta around the house, and availability of garbage collection services.

All data were collected by project staff during in-home interviews. Quality control measures included extensive training and periodic inter-observer reliability assessments. All procedures were reviewed and approved by the Institutional Review Boards at the University of North Carolina at Chapel Hill.

5. Statistical analysis

We used latent class growth curve analysis (LCGA) (Jones, Nagin, & Roeder, 2001; Nagin, 1999) implemented in Mplus (version 5.2) to identify BMI trajectories from 0-24 months of life. LCGA identifies distinct groups (latent classes) of infants who share similar trajectories. This approach is different from conventional latent growth curve modeling which assumes that all individuals are drawn from a single population and that a single growth trajectory can adequately approximate the entire population. While conventional latent growth curve models allow individual differences in development over time captured by random slopes and random intercepts, individuals are assumed to vary around a single mean growth curve. In contrast, the LCGA group-based method used in the current analysis relaxes the single population assumption to allow for parameter differences across unobserved subpopulations. LCGA assumes a number of discrete classes, each having a specific functional form. We used BMI measured at birth and bimonthly until 24 months (13 time points) to define a latent class model in which the latent classes correspond to different growth curve shapes.

We estimated a freed-loading model (Bollen & Curran, 2006) that effectively estimates the functional form of the BMI trajectory without any *a priori* assumptions about its shape. We allowed for differences in the unconditional means of the growth parameters across trajectory classes but did not

allow the growth factor variances or covariances to differ across classes. Our specification allowed the functional form of BMI trajectories between groups to be different.

We estimated a series of models with progressively greater numbers of trajectory classes. To avoid the problem of nonconvergence and local solutions common in the estimation of finite mixture models, we specified 1000 initial stage starts, 100 final stage starts and 10 initial stage iterations for each model estimated.

LCGA modeling produces several possible solutions varying in both growth parameters and the number of trajectory classes. We evaluated model fit using the following criteria: (i) sample size-adjusted Bayesian Information Criterion (lowest adjusted Bayesian Information Criterion is preferred solution)(Schwarz, 1978), (ii) separation of the latent classes summarized using an entropy measure based on the posterior class membership probabilities (a higher entropy—closer to 1—is preferred) (Wedel & Kamakura, 2000), (iii) the shape of the growth trajectories to assess face validity and biological plausibility of the solution (e.g. is it consistent with theory and observed individual growth trajectories) and to identify differences in functional form (e.g. nonparallel trajectories), and (iv) interpretability and clinical relevance of trajectory groups. Model selection in LCGA models is an active research area, and no single criterion has been shown to be superior in general settings.

Given the substantial gender differences in early life growth, all models were sex-stratified. Individuals were assigned to the BMI trajectory class for which they had the highest probability of membership. Once individuals were assigned to a trajectory class, we used Stata version 11.0 (StataCorp LP, College Station, TX) to calculate descriptive statistics by trajectory class and to examine associations between class membership and a number of covariates previously shown to affect growth. A likelihood ratio chi squared test for each variable tested differences among trajectory classes. Multivariate linear regression was used to examine associations between BMI trajectory class with adult BMI, FMI, LMI, WC, WHR and height, controlling for age and household income.

To compare BMI trajectories with conventional approaches, we present the F-value and adjusted R squared values from unadjusted linear regression models separately examining associations between (1) BMI trajectory class, (2) rapid BMI gain from 0-4 months, and (3) BMI at two years of age with adult BMI, FMI, LMI, WC, WHR and height. The F-test value assesses the overall statistical significance of the unadjusted regression model. The adjusted R-squared describes the proportion of the total variance that is explained by the exposure measure and is adjusted for the number of parameters in the model, allowing comparisons between models with different degrees of freedom.

Finally, to assess whether trajectory class is important independent of attained BMI in late infancy, we additionally controlled for BMI at two years of age in multivariate linear regression models examining associations of BMI trajectory class with adult outcomes.

D. Results

Descriptive statistics of the study sample are presented in **Table 6.** The prevalence of underweight (weight-for-age z-score <-2) at birth was 10% for males and 7% for females and substantially increased with age, such that by two years of age, 35% of sample infants were underweight (Table 1). The sample was young and lean in adulthood (Table 1). According to the cutpoints proposed for Asians by the WHO Asia Pacific guidelines (WHO, 2000) 17% of the sample was overweight (BMI ≥ 23) and 4% had high abdominal adiposity (WC≥90 cm for men, WC≥80 cm for women). Underweight (BMI<18.5) prevalence (22%) was higher than either overweight or high abdominal adiposity. The top panels of **Figures 2 and 3** present the single population BMI curves from 0-24 months for males and females. The median values from the WHO BMI standards are included for reference. Among both males and females, the CLHNS mean BMI curves fall below the WHO median curves at all time points except at 24 months, when the curves converge.

Table 7 presents the model fit statistics for the LCGA models assessed. Among both males and females, differences in the functional forms of identified classes became apparent starting with

the 5-class model. Solutions with a lower number of classes identified parallel trajectories that shared a common functional form. We favored the 7-class solution in males and females based on the Bayesian information criteria, entropy values, and considerations regarding the interpretability of solutions with a higher number of groups.

The bottom panels of **Figure 4 and Figure 5** present the 7-class solutions for BMI trajectories among males and females, including the median values from the WHO BMI standards. Classes are nominal; class number does not correspond to rank order. The single population curves in Figures 4(a) and 5(a) do not capture the visible differences in the shapes of BMI trajectories in Figures 5(b) and 5(b).

To assess whether the shapes of the identified trajectories correspond with factors known to influence infant growth, we examine characteristics of trajectory classes (Error! Reference source not found.Error! Reference source not found. **and Table 9).** For example, we expect a higher growth potential for infants with taller mothers, greater weight gain among infants who are breastfed and growth faltering among infants with more diarrhea and severe respiratory infections. Among males, the groups differed as expected in maternal height and BMI, household hygiene index, duration of predominant breastfeeding, SGA status, prevalence of rapid weight gain and infant weight, length, wasting and stunting indicators. There were no overall differences among the groups in diarrhea, severe respiratory infections, first born status, household assets or level of urbanicity. Among females, the groups differed as expected in maternal height and BMI, severe respiratory infections, duration of predominant breastfeeding, SGA status, prevalence of rapid weight gain and infant weight, length, wasting and stunting indicators. There were no overall differences in diarrhea, first born status, household assets, household hygiene index or level of urbanicity.

Error! Reference source not found.Error! Reference source not found. **and Table 11** present associations between BMI trajectory classes and adult outcomes adjusted for adult age and household income. The referent group is the largest class and the one that most closely

approximates the WHO median. Trajectory classes in tables 11 and 12 are presented in rank order according to BMI at 24 months (largest to smallest). Among both males and females, BMI trajectories predicted adult BMI, FMI, LMI, and WC. Trajectories predicted adult WHR in males only and adult height in females only. For all adult anthropometric indicators except height, rank order was generally maintained from age 24 months to approximately 22 years. These results are graphically portrayed in Figure 6 and **Figure 7,** which present age and income-adjusted means for each adult measure by BMI trajectory class. To facilitate comparison across measures with different units, graphs were scaled so that the y-axis represents a range equivalent to the difference between the 25th and 75th percentile of each measure.

Table 12 and Table 13 present model summary statistics from unadjusted regression models separately examining associations between (1) BMI trajectory class, (2) accelerated BMI gain from 0-4 months, and (3) BMI at two years of age with adult BMI, FMI, LMI, WC, WHR and height. Early accelerated BMI gain was not a significant predictor of any of the adult measures, while BMI trajectory classes and BMI at age two did significantly predict adult measures.

A key question we address is whether these trajectories add to the literature that uses BMI at age 2 to predict adult anthropometric outcomes. After controlling for BMI at age two years, among both males and females, trajectory classes were still statistically significant and provided additional explanation of variation in adult anthropometry (Tables 9 and 10).

E. Discussion

This study explores the development of anthropometric measures of body composition in a young, lean Filipino population undergoing the nutrition transition. We used a data-driven latent class growth curve analysis (LCGA) to explore distinct patterns of BMI change across infancy. Substantial differences among trajectory shapes suggest that a single population curve may not represent all individuals adequately. After controlling for BMI at two years of age, trajectory classes were associated with anthropometric measures of body composition in adulthood, suggesting that overall

patterns of BMI change in infancy have long-term implications for the development of body composition.

The LCGA approach used in the current study is a marked departure from conventional methods of examining growth that assume a single population curve. A number of familial and environmental factors known to influence growth were associated with trajectory class membership, suggesting that the shapes of trajectories reflect the biological and environmental characteristics of the individuals assigned to them. To illustrate, female trajectory class 5 has the highest BMI at all time points. Their mothers were the tallest with the highest BMIs and lowest parity in the sample. This class was relatively wealthy, and the infants had the lowest percentage of reported severe respiratory infections. In contrast, female trajectory class 3 had the lowest BMI at all time points. Their mothers were the shortest with the lowest BMIs and highest parity. This class was predominantly urban, and the infants had the lowest levels of early rapid weight gain and the highest levels of wasting and stunting throughout infancy.

Conventional approaches to examining the relationship between early growth and adult size focus on size in early life or accelerated growth during intervals (such as 0-6 months) hypothesized to be sensitive or critical periods for the development of obesity. A key strength of the LCGA approach is that it permits simultaneous examination of tempo, timing and magnitude of size without incorporation of *a priori* hypotheses regarding critical or sensitive periods.

Research demonstrating that accelerated growth in early infancy increases the risk of overweight later in life (Ong & Loos, 2006) has led to hypotheses that the first months of the life are critical for the development of overweight (Gillman, 2008). In this large cohort accelerated BMI gain from 0-4 months was not predictive of adult outcomes but BMI trajectories from 0-24 months were predictive of adult outcomes. These results suggest that in this cohort early postnatal growth is not necessarily pathological: our sample includes a substantial number of babies who were born small, but were subsequently exclusively breastfed and had accelerated early weight gain, likely

representing catch-up from IUGR. Our results suggest that growth patterns over the entire infancy period are important for the development of body composition.

A recent study describing worldwide growth faltering patterns demonstrated that in South Asian countries weight-for-age, length-for-age and weight-for-length z-scores faltered until two years of age and remained reasonably stable thereafter (Victora et al.), highlighting the long-term implications of attained size by age two. Consistent with this review, in our sample, BMI at two years of age predicted all adult anthropometric measures of body composition and rank order of groups by BMI at two years of age remained generally stable to approximately 22 years of age for all adult measures with the exception of height. To test whether the overall pattern of growth leading up to BMI at two years of age was important, we examined how infant BMI trajectories related to adult body composition measures, controlling for BMI at age two. Independent of BMI at age two, trajectory classes still explained variation in adult measures. Among females results for adult BMI and FMI were attenuated but remained significant, while results for LMI, WC and height were attenuated with p-values ranging from 0.05-0.20. Among males, results for adult BMI and LMI were attenuated but remained significant and results for FMI, WC and WHR were unchanged. The lack of attenuation of trajectory group coefficients after controlling for BMI at age two suggests that the trajectory groups provide important additional information not provided by a single BMI measure.

It is important to note that in young adulthood, most of our sample is still very lean with higher rates of underweight than overweight or excess abdominal adiposity. At approximately 22 years of age the sample may be just beginning the dramatic body composition transition experienced by their mothers in their late 20's to 30's (L. S. Adair, 2004), but evidence of this transition has not yet emerged. To better understand the role of infant BMI patterns in the development of overweight and obesity, similar analyses could be conducted in a population with a higher prevalence of overweight. Further, as overweight and cardiometabolic outcomes become apparent in our sample we could examine their relationships with infant BMI trajectory classes.

Infancy is a period of rapid changes in both length and weight. We chose to model BMI because we were interested in excess weight gain relative to length. However, because the nature of rapid weight gain in infancy may vary between individuals in terms of fat and fat-free mass and the relative rates of growth in weight and length may vary significantly, BMI has been shown to be less associated with fatness during infancy than other ages (Wells, 2000). Despite this limitation, BMI is still recommended as a useful way to compare relative weight between populations and within populations over time (Wells, 2000; WHO, 1995).

One of the most technically challenging issues in mixture modeling is determining the optimal number of groups to include in the model. Our final decision balanced model fit with biological relevance and interpretability of classes. While the sample-adjusted Bayesian information criteria suggested improved model fit beyond the 7-class solution, application and interpretability of higher class solutions becomes problematic, and issues with the use of the BIC in these settings are well-known (Celeux, Forbes, Robert, & Titterington, 2006; Spiegelhalter, Best, Carlin, & Linde, 2002).

A strength of the LCGA approach employed in the current study is that the forms of the identified infant BMI trajectories emerged from the data. We fit a freed-loading model that effectively estimated the functional form of the BMI trajectories without any *a priori* assumptions about their shape. Identified trajectory shapes may therefore be especially valuable in the generation of new hypotheses regarding determinants and consequences of early life growth. Future research could examine the influence of time-varying modifiable factors on trajectory class membership to identify targets for intervention.

This current study is a novel methodological approach to identifying meaningful differences in patterns of early life growth as they affect adult body composition and health. Using unique longitudinal data and methods to capture differences in tempo, timing and magnitude of growth in the first 2 years of life, we find that diverse BMI trajectories in infancy add important knowledge to traditional approaches and have long-term implications for the development of body composition.

Figure 3 Participant retention across follow-up periods for CLHNS sample.

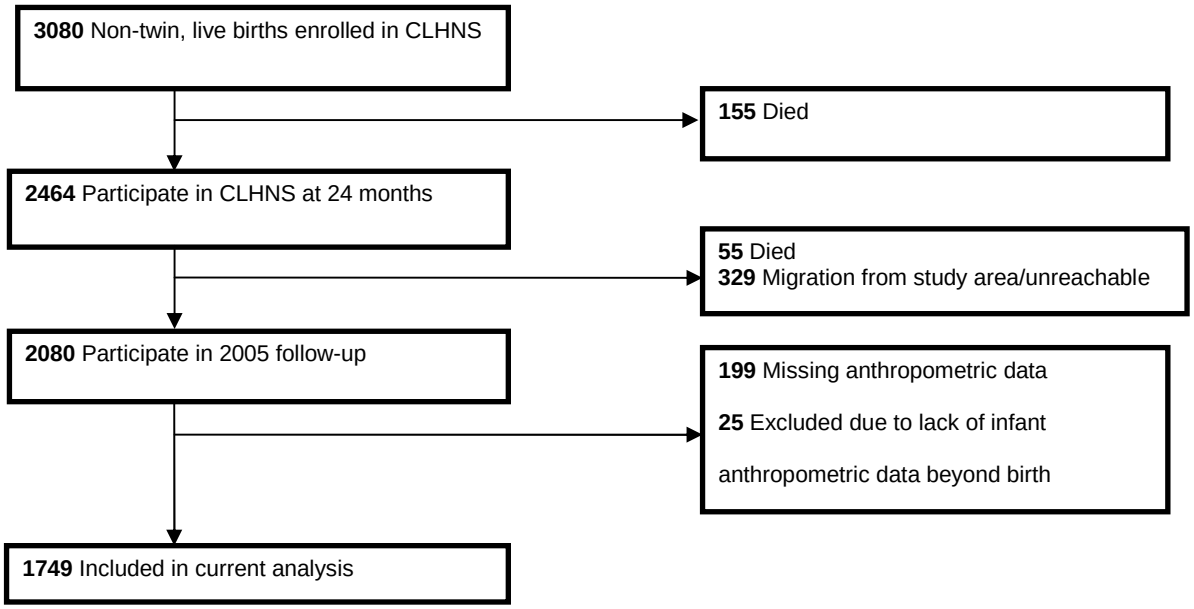
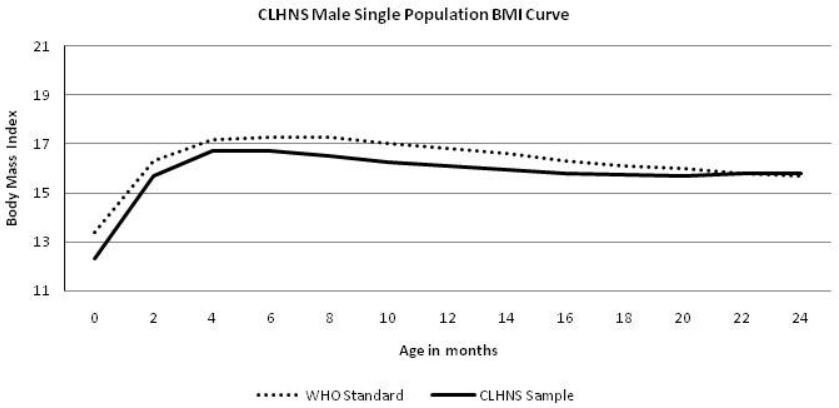


Figure 4 Male BMI Curves

(a) Median body mass index (BMI) values from 0-24 months among CLHNS sample **males** who were present in the young adult follow-up survey as compared to the WHO child growth standards. (b) 7-class freed-loading longitudinal latent class analysis model for repeated, continuous BMI measures at 13 time points (bimonthly 0-24 months) in the Cebu Longitudinal Health and Nutrition Survey (n=916).

(a)



(b)

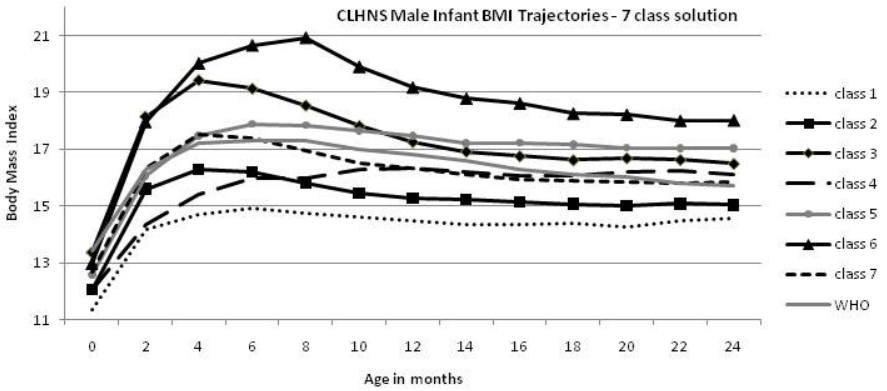
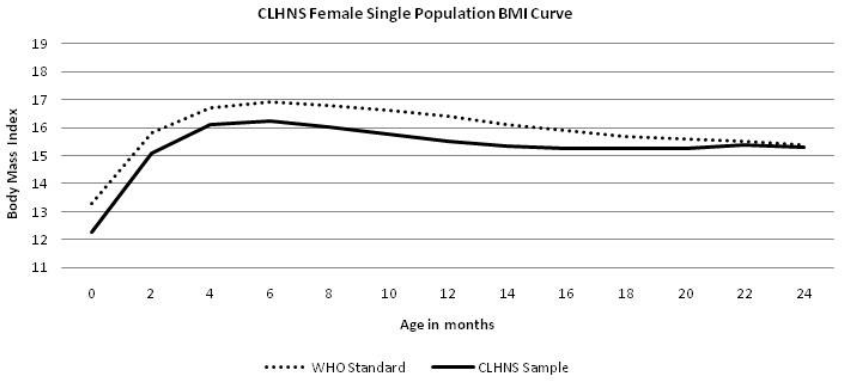


Figure 5 Female BMI Curves

(a) Median body mass index (BMI) values from 0-24 months among CLHNS sample **females** who were present in the young adult follow-up survey as compared to the WHO child growth standards. (b) 7-class freed-loading longitudinal latent class analysis model for repeated, continuous BMI measures at 13 time points (bimonthly 0-24 months) in the Cebu Longitudinal Health and Nutrition Survey (n=833).

(a)



(b)

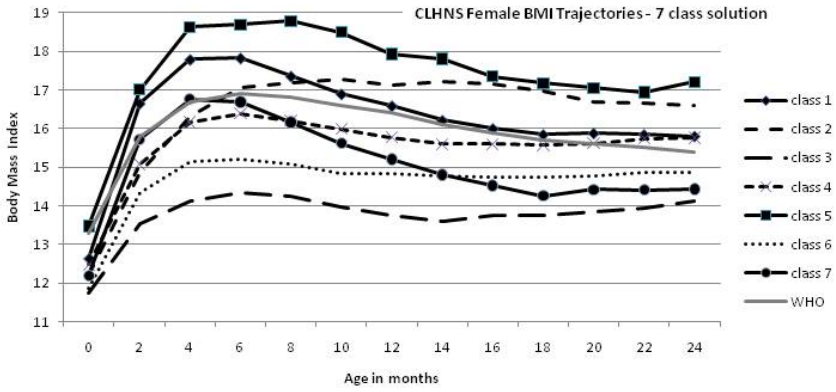


Figure 6 Age- and income-adjusted means of male adult (a) body mass index, (b) fat mass index, (c) lean mass index, (d) waist circumference, (e) waist-to-height ratio and (f) height by infant BMI trajectory class (n=916).

The y-axis for each graph represents a range equivalent to the difference between the 25th and 75th percentile of each measure.

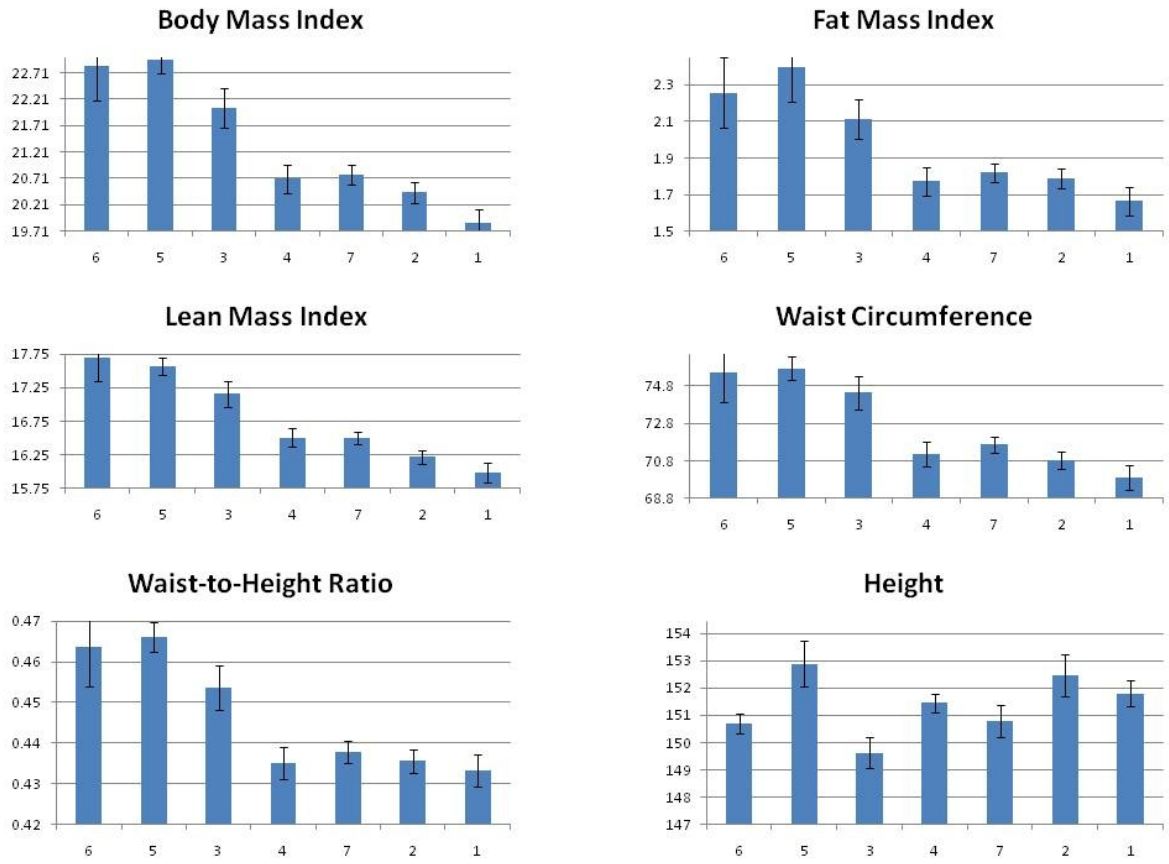


Figure 7 Age- and income-adjusted means of female adult (a) body mass index, (b) fat mass index, (c) lean mass index, (d) waist circumference, (e) waist-to-height ratio and (f) height by infant BMI trajectory class (n=833).

The y-axis for each graph represents a range equivalent to the difference between the 25th and 75th percentile of each measure.

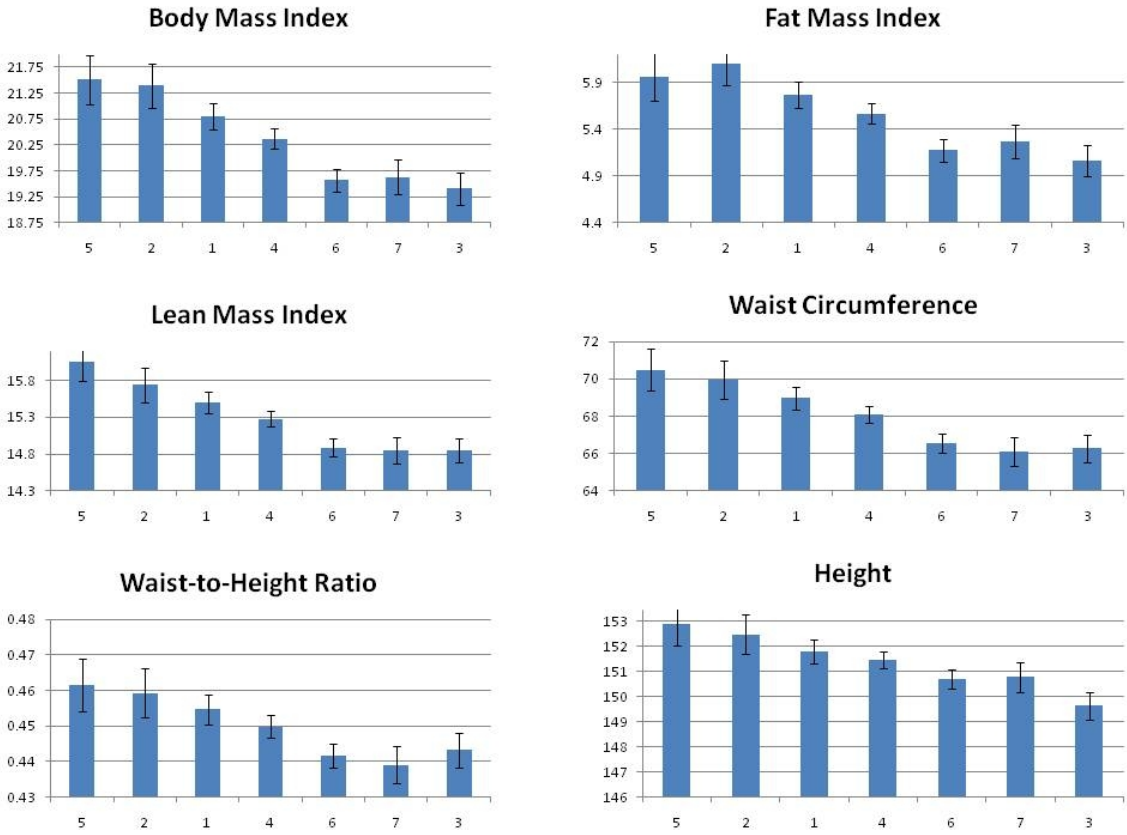


Table 6. Select characteristics of CLHNS analytic sample.

	Males		Females		p value*
	n	Mean (SD)	n	Mean (SD)	
Maternal Characteristics					
Age (years)	916	26.61 (6.07)	833	26.44 (5.92)	0.55
Years of education completed	916	7.40 (3.70)	833	7.33 (3.60)	0.65
Height	916	150.64 (4.96)	833	150.52 (4.95)	0.59
Waist circumference	853	72.03 (7.39)	721	68.02 (7.44)	<0.01
Arm Circumference	855	27.09 (2.89)	775	25.27 (3.00)	<0.01
Parity	916	2.29 (2.27)	833	2.27 (2.26)	0.81
Household Characteristics					
Assets Score	916	2.47 (1.86))	833	2.46 (1.84)	0.99
Urbanicity Score	916	29.79 (12.86)	833	29.17 (12.88)	0.31
Index Child Characteristics					
Weight (kg)					
0 months	916	3.01 (0.40)	833	2.94 (0.39)	<0.01
1 year	884	8.25 (0.99)	788	7.65 (0.95)	<0.01
2 years	331	10.11 (1.13)	788	9.45 (1.10)	<0.01
Weight-for-age z-scores (WAZ)**					
0 months	916	-0.84 (0.89)	833	-0.70 (0.87)	<0.01
1 year	884	-1.49 (1.08)	788	-1.38 (1.06)	<0.05
2 years	881	-1.67 (0.97)	788	-1.69 (1.00)	0.65
Percentage underweight (WAZ<-2)					
0 months	916	9.83	883	6.96	<0.05
1 year	884	31.11	788	27.41	0.1
2 years	881	34.96	788	36.42	0.53
Length (cm)					
0 months	916	49.38 (1.99)	832	48.91 (1.97)	<0.01
1 year	883	71.49 (2.80)	788	69.96 (2.77)	<0.01
2 years	879	79.98 (3.42)	789	78.39 (3.53)	<0.01
Length-for-age z-scores (LAZ)**					
0 months	916	-0.61 (1.03)	832	-0.45 (1.03)	<0.01
1 year	882	1.82 (1.17)	788	-1.60 (1.07)	<0.01
2 years	877	-2.41 (1.11)	788	-2.35 (1.09)	0.26

(continued next page)

Table 6. continued

	Males		Females		p value*
	n	Mean (SD)	n	Mean (SD)	
Percentage stunted (LAZ<-2)					
0 months	916	9.17	832	6.97	0.09
1 year	882	41.95	788	32.61	<0.01
2 years	877	63.06	788	60.03	0.2
BMI (kg/m^2)					
0 months	916	12.30 (1.20)	832	12.28 (1.15)	0.69
1 year	883	16.11 (1.28)	788	15.59 (1.29)	<0.01
2 years	878	15.77 (1.19)	786	15.35 (1.12)	<0.01
Weight in adulthood †	916	55.22 (0.29)	833	45.57 (0.25)	<0.01
Height in adulthood †	916	162.91(0.19)	832	151.09 (0.19)	<0.01
Body mass index (BMI) in adulthood †	916	20.81 (0.09)	832	19.97 (0.10)	<0.01
Fat mass index (FMI) in adulthood †	914	1.73 (0.02)	832	5.24 (0.05)	<0.01
Lean mass index (LMI) in adulthood †	914	16.51 (0.05)	382	15.10 (0.06)	<0.01
Waist circumference in adulthood †	914	71.66 (0.23)	833	67.33 (0.23)	<0.01
Waist -to-Height ratio in adulthood †	914	0.44 (0.00)	832	0.45 (0.45)	<0.01
Percentage overweight (BMI≥23)	916	19.43	832	14.3	<0.01
Percentage underweight (BMI<18.5)	916	15.39	832	29.57	<0.01
Percentage high WC (WC≥90 cm for men, WC≥80 cm for women)	914	3.06	833	5.76	<0.01

* p value for comparison between sexes.

** Calculated from WHO growth standards

† geometric mean (SE)

Table 7. Model fit criteria

	MALES		FEMALES	
	Sample Adjusted BIC	Entropy	Sample Adjusted BIC	Entropy
1 Class	39398.558	NA	34643.765	NA
2 Class	35488.24	0.884	30975.24	0.883
3 Class	34054.32	0.89	29794.17	0.871
4 Class	33489.38	0.878	29285.13	0.884
5 Class	33090.08	0.859	29053.93	0.839
6 Class	32758.98	0.861	28834.26	0.841
7 Class	32493.73	0.868	28641.43	0.856
8 Class	32315.179	0.871	28495.186	0.843
9 Class*	32184.217	0.875	28399.922	0.851

BIC, Bayesian Information Criteria

NA, Not applicable

* Although the 9-group model had lower sample adjusted BIC, it did not terminate normally and contained an exceptionally small class (<1% of sample).

Table 8. Selected characteristics in 7 BMI trajectories from 0-24 months of life. MALES

Measurement	Class 1 n=118 Mean (SD)	Class 2 n=226 Mean (SD)	Class 3 n=61 Mean (SD)	Class 4 n=116 Mean (SD)	Class 5 n=130 Mean (SD)	Class 6 n=19 Mean (SD)	Class 7 n=246 Mean (SD)	LR chi2[1]	*P* Value
Infant									
Weight (kg)									
0 months	2.70 (0.40)	2.94 (0.37)	3.32 (0.37)	2.96 (0.36)	3.09 (0.39)	3.16 (0.39)	3.11 (0.36)	119.93	<0.01
12 months	7.10 (0.73)	7.80 (0.65)	9.11 (0.70)	8.22 (0.81)	9.01 (0.81)	10.33 (0.84)	8.46 (0.69)	278.04	<0.01
24 months	8.87 (0.85)	9.57 (0.80)	10.93 (0.82)	10.31 (0.91)	11.06 (1.05)	12.02 (0.94)	10.24 (0.79)	258.55	<0.01
Length (cm)									
0 months	48.67 (2.09)	49.30 (1.97)	49.79 (1.58)	49.54 (2.04)	49.55 (1.98)	49.35 (2.05)	49.53 (1.96)	20.39	<0.01
12 months	69.94 (3.07)	71.40 (2.63)	72.65 (2.43)	70.91 (3.02)	71.75 (2.71)	73.37 (2.44)	72.00 (2.49)	62.28	<0.01
24 months	78.03 (3.91)	79.78 (3.28)	81.41 (2.84)	79.89 (3.51)	80.51 (3.38)	81.68 (2.98)	80.36 (3.04)	53.75	<0.01
Percent underweight (WAZ<-2)									
0 months	30.51	11.5	0	10.34	4.62	0	4.07	79.64	<0.01
12 months	83.33	48.87	3.39	31.19	4.72	0	12.77	285.49	<0.01
24 months	84.96	56.68	5.36	23.01	6.3	0	22.03	271.37	<0.01
Percent stunted (LAZ<-2)									
0 months	16.95	11.06	1.64	11.21	5.38	15.79	6.1	20.3	<0.01
12 months	61.06	45	25.42	52.29	37.8	15.79	33.62	42.14	<0.01
24 months	78.18	67.74	41.07	63.39	57.14	36.84	62.03	32.08	<0.01
Percent rapid BMI gain 0-4 months[2]	34.75	45.29	61.67	14.04	41.73	68.42	46.89	57.58	<0.01

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Table 8. continued Measurement	Class 1 n=118 Mean (SD)	Class 2 n=226 Mean (SD)	Class 3 n=61 Mean (SD)	Class 4 n=116 Mean (SD)	Class 5 n=130 Mean (SD)	Class 6 n=19 Mean (SD)	Class 7 n=246 Mean (SD)	LR chi2[1]	*P* Value
Percent Small for Gestational Age[3]	22.22	7.73	1.67	7.83	8.46	0	5.35	32.79	<0.01
Months predominantly breastfed	2.41 (1.71)	2.70 (1.66)	3.15 (1.79)	1.81 (1.61)	1.99 (1.63)	2.91 (1.81)	2.75 (1.67)	46.06	<0.01
Percent of infant surveys with reported diarrea	22.41 (18.53)	19.76 (15.18)	18.37 (18.02)	20.85 (15.53)	18.27 (14.27)	15.94 (12.0)	21.44 (15.84)	8.08	0.23
Percent of infant surveys with reported severe respiratory infections	19.18 (14.75)	18.27 (13.33)	15.15 (11.61)	17.73 (12.78)	14.57 (12.12)	14.62 (9.06)	17.54 (14.76)	11.05	0.09
Maternal									
Parity	2.71 (2.84)	2.39 (2.16)	1.87 (2.09)	2.25 (2.30)	2.19 (2.42)	2.47 (2.22)	2.17 (2.00)	7.61	0.27
Height (cm)	148.97 (5.18)	150.54 (4.93)	151.21 (5.32)	150.98 (4.40)	151.72 (4.94)	149.41 (3.52)	150.76 (4.95)	21.77	<0.01
Body mass index (BMI)	19.97 (2.21)	20.10 (2.39)	21.39 (2.44)	20.56 (2.07)	21.85 (2.75)	21.29 (2.46)	20.64 (1.84)	52.76	<0.01

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Table 8. continued Measurement	Class 1 n=118 Mean (SD)	Class 2 n=226 Mean (SD)	Class 3 n=61 Mean (SD)	Class 4 n=116 Mean (SD)	Class 5 n=130 Mean (SD)	Class 6 n=19 Mean (SD)	Class 7 n=246 Mean (SD)	LR chi2[1]	*P* Value
Household & Community									
Household assets[4]	2.28 (1.75)	2.30 (1.77)	2.46 (1.84)	2.63 (1.82)	2.86 (2.10)	3.16 (2.06)	2.37 (1.84)	12.74	<0.05
Urbanicity Index[5]	30.65 (12.96)	29.36 (13.66)	31.10 (11.73)	28.48 (11.46)	30.6 (12.61)	25.11 (13.91)	30.01 (13.01)	5.64	0.46
Household hygiene index	4.71 (1.97)	5.24 (1.94)	5.57 (1.98)	5.15 (2.04)	5.58 (2.14)	5.89 (1.82)	5.29 (1.91)	15.87	0.01

[1]Comparisons in means and prevalences between classes were performed using likelihood ratio chi-square tests for equality of means and proportions across classes.

[2] Change in BMI z-score >0.67 from 0-4 months.

[3] birthweight <10th centile of individually customized birthweight centiles (Gardosi methods employed)

[4] Summary of 10 key assets

[5] Multicomponent urbanicity index

Table 9. Selected characteristics in 7 BMI trajectories from 0-24 months of life. FEMALES

Measurement	Class 1 n=131 Mean (SD)	Class 2 n=48 Mean (SD)	Class 3 n=93 Mean (SD)	Class 4 n=238 Mean (SD)	Class 5 n=40 Mean (SD)	Class 6 n=200 Mean (SD)	Class 7 n=83 Mean (SD)	LR chi2[1]	*P* Value
Infant									
Weight (kg)									
0 months	3.06 (0.38)	3.02 (0.39)	2.76 (0.36)	2.98 (0.36)	3.35 (0.45)	2.83 (0.36)	2.89 (0.34)	103.36	<0.01
12 months	8.33 (0.70)	8.56 (0.74)	6.46 (0.80)	7.77 (0.61)	9.20 (0.74)	7.15 (0.62)	7.43 (0.63)	575.73	<0.01
24 months	9.96 (0.89)	10.57 (0.86)	8.20 (0.89)	9.75 (0.83)	10.98 (0.66)	9.01 (0.81)	8.85 (0.87)	429.55	<0.01
Length (cm)									
0 months	49.13 (1.75)	49.71 (2.69)	48.45 (1.86)	48.86 (1.85)	49.78 (2.07)	48.78 (2.07)	48.60 (1.73)	25.63	<0.01
12 months	70.82 (2.52)	70.66 (2.58)	68.39 (3.45)	70.15 (2.49)	71.61 (2.42)	69.39 (2.64)	69.87 (2.52)	68.96	<0.01
24 months	79.32 (3.12)	79.81 (2.95)	76.21 (4.37)	78.60 (3.18)	80.17 (3.21)	77.84 (3.36)	78.33 (3.61)	66.54	<0.01
% underweight (WAZ<-2)									
0 months	3.05	6.25	15.05	3.78	2.5	11	6.02	21.58	<0.01
12 months	1.63	2.13	78.16	12.11	0	49.47	31.25	279.57	<0.01
24 months	14.06	2.13	86.21	19.27	0	55.21	56.96	264.37	<0.01
% stunted (LAZ<-2)									
0 months	3.82	8.33	9.68	6.75	7.5	7	8.43	3.75	0.71
12 months	21.95	17.02	50.57	29.15	10	43.09	35	46.4	<0.01
24 months	50	36.17	76.74	58.99	42.11	68.23	63.75	37.93	<0.01

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Table 9. continued

Measurement	Class 1 n=131 Mean (SD)	Class 2 n=48 Mean (SD)	Class 3 n=93 Mean (SD)	Class 4 n=238 Mean (SD)	Class 5 n=40 Mean (SD)	Class 6 n=200 Mean (SD)	Class 7 n=83 Mean (SD)	LR chi2[1]	*P* Value
% reported severe respiratory infections in the previous week	14.90 (12.52)	16.78 (14.23)	17.79 (12.29)	13.46 (12.31)	12.45 (12.54)	18.20 (14.89)	18.74 (14.39)	23.45	<0.01
Maternal									
Parity	2.11 (2.03)	2.21 (2.25)	2.78 (2.54)	2.26 (2.40)	2 (2.14)	2.16 (2.17)	2.37 (2.12)	6.39	0.38
Height (cm)	150.12 (4.94)	151.62 (4.67)	149.55 (4.86)	150.82 (4.66)	152.77 (3.94)	150.29 (5.35)	150.18 (5.10)	16.59	0.01
Body mass index (BMI)	21.15 (2.26)	21.71 (2.61)	20.16 (2.38)	20.64 (92.9)	21.53 (2.41)	20.16 (2.49)	20.34 (2.977)	31.09	<0.01
Household & Community									
Household assets [4]	2.19 (1.74)	2.88 (2.16)	2.26 (1.80)	2.45 (1.82)	2.78 (2.06)	2.62 (1.82)	2.40 (1.77)	9.18	0.16
Urbanicity Index [5]	30.06 (12.83)	29.96 (11.24)	31.03 (12.78)	28.41 (13.31)	26.63 (13.17)	28.84 (12.65)	29.37 (13.15)	5.31	0.5
Household hygiene index	5.16 (1.87)	5.77 (2.14)	5.65 (1.75)	5.16 (1.93)	5.33 (2.18)	5.33 (1.99)	5.24 (1.70)	8.11	0.23

[1]Comparisons in means and prevalences between classes were performed using likelihood ratio chi-square tests for equality of means and proportions across classes.

[2]Change in BMI z-score >0.67 from 0-4 months.

[3] birthweight <10th centile of individually customized birthweight centiles (Gardosi methods employed)

[4] Summary of 10 key assets

[5] Multicomponent urbanicity index

Table 10. Multivariable linear regression models of association between Male infant BMI trajectories and anthropometric measures of adult body composition.

Independent Variables	Log BMI Coef.	Log BMI 95% CI	Log FMI Coef.	Log FMI 95% CI	Log LMI Coef.	Log LMI 95% CI
Class 6[1]	**0.09** [3]	**(0.03, 0.15)**	0.18	(-0.01, 0.37)	**0.07** [4]	**(0.02, 0.11)**
Class 5[1]	**0.09** [3]	**(0.07, 0.12)**	**0.25** [2]	**(0.17, 0.34)**	**0.06** [3]	**(0.04, 0.08)**
Class 3[1]	**0.06** [2]	**(0.02, 0.09)**	**0.14** [2]	**(0.03, 0.25)**	**0.04** [2]	**(0.01, 0.06)**
Class 4[1]	-0.01	(-0.03, 0.02)	-0.02	(-0.11, 0.07)	-0.01	(-0.02, 0.02)
Class 2[1]	-0.02	(-0.04, 0.01)	-0.02	(-0.10, 0.05)	**-0.02** [5]	**(-0.03, -0.001)**
Class 1[1]	**-0.05**[3]	**(-0.08, -0.02)**	**-0.13** [2]	**(-0.22, -0.04)**	**-0.03** [4]	**(-0.05, -0.01)**
Age	-0.01	(-0.03, 0.02)	-0.10	(-0.14, 0.03)	0.01	(-0.01, 0.03)
Household Income	**0.00**	**(0,0)**	**0.00**	**(0,0)**	**0.00**	**(0,0)**

Bold values are p<0.05

[1]Reference group is Group 7

[2] After adjustment for BMI at 2 years, results unchanged.

[3] After adjustment for BMI at 2 years, coefficient was attenuated but remained signficant.

[4] After adjustment for BMI at 2 years, coefficient was attenuated and p-value was 0.05-0.15

[5] After adjustment for BMI at 2 years, coefficient was attenuated and p-value > 0.20.

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Table 10. continued

Independent Variables	Log WC		Log WHR		Height (cm)	
	Coef.	95% CI	Coef.	95% CI	Coef.	95% CI
Class 6[1]	**0.05** [2]	**(0.01, 0.09)**	**0.06** [2]	**(0.01, 0.10)**	-0.07	(-1.45, 1.31)
Class 5[1]	**0.05** [2]	**(0.03, 0.07)**	**0.06** [2]	**(0.04, 0.08)**	2.12	(0.08, 4.15)
Class 3[1]	**0.04** [2]	**(0.01, 0.06)**	**0.03** [2]	**(0.01, 0.06)**	-1.14	(-2.73, 0.46)
Class 4[1]	-0.01	(-0.03, 0.01)	-0.01	(-0.03, 0.01)	0.68	-0.67, 2.03)
Class 2[1]	-0.01	(-0.03, 0.01)	-0.01	(-0.02, 0.01)	1.7	(-0.21, 3.62)
Class 1[1]	**-0.03** [2]	**(-0.05, -0.01)**	-0.01	(-0.03, 0.01)	1.03	(-0.45, 2.51)
Age	0.01	(-0.01, 0.03)	0.01	(-0.02, 0.02)	0.28	(-0.001, 0.73)
Household Income	**0.00**	**(0,0)**	**0.00**	**(0,0)**	**0.00**	**(0,0)**

Bold values are p<0.05

[1]Reference group is Group 7

[2] After adjustment for BMI at 2 years, results unchanged.

[3] After adjustment for BMI at 2 years, coefficient was attenuated but remained signficant.

[4] After adjustment for BMI at 2 years, coefficient was attenuated and p-value was 0.05-0.15

[5] After adjustment for BMI at 2 years, coefficient was attenuated and p-value > 0.20.

Table 11. Multivariable linear regression models of association between Female infant BMI trajectories and anthropometric measures of adult body composition.

Independent variables	Log BMI		Log FMI		Log LMI	
	Coef.	95% CI	Coef.	95% CI	Coef.	95% CI
Class 5[1]	**0.06** [3]	**(0.01, 0.10)**	0.07	(-0.02, 0.17)	**0.05** [3]	**(0.02, 0.09)**
Class 2[1]	0.04	(-0.01, 0.09)	0.08	(-0.01, 0.17)	0.03	('-0.01, 0.06)
Class 1[1]	0.02	(-0.01, 0.05)	0.03	(-0.03, 0.09)	0.02	(-0.01, 0.04)
Class 6[1]	**-0.04** [2]	**(-0.07, -0.01)**	**-0.08** [2]	**(-0.13, -0.03)**	**-0.03** [3]	**(-0.05, -0.01)**
Class 7[1]	**-0.04** [3]	**(-0.07, -0.01)**	-0.05	('0.13, 0.02)	**-0.03** [3]	**(-0.06, -0.01)**
Class 3[1]	**-0.01** [3]	**(-0.03, -0.02)**	**-0.11** [3]	**(-0.18, -0.04)**	**-0.03** [4]	**(-0.05, '-0.01)**
Age	-0.01	(-0.01, 0.01)	0.04	(0.01, 0.06)	-0.02	(-0.03, -0.01)
Income	0.00	(0,0)	0.00	(0,0)	0.00	(0,0)

Bold values are coeffients with p<0.05

[1] Reference group is Group 4 -- WHO Median

[2] After adjustment for BMI at 2 years, coefficient was attenuated but remained signficant.

[3] After adjustment for BMI at 2 years, coefficient was attenuated and p-value was 0.05-0.20

[4] After adjustment for BMI at 2 years, coefficient was attenuated and p-value > 0.20.

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Table 11. continued

Independent variables	Log WC		Log WHR		Height (cm)	
	Coef.	95% CI	Coef.	95% CI	Coef.	95% CI
Class 5[1]	**0.04** [b]	**(0.01, 0.07)**	0.03	(0.01, 0.06)	1.43	(-0.37, 3.24)
Class 2[1]	0.02	(-0.01, 0.05)	0.02	(-0.01, 0.05)	1.02	(-0.65, 2.69)
Class 1[1]	0.01	(-0.01, 0.03)	0.01	(-0.01, 0.03)	0.35	(-0.80, 1.50)
Class 6[1]	**-0.02** [3]	**(-0.04, -0.01)**	-0.02	(-0.04, 0.001)	-0.75	(-1.77, 0.26)
Class 7[1]	**-0.03** [3]	**(-0.05, -0.01)**	-0.02	(-0.05, 0.001)	-0.68	(-2.03, 0.67)
Class 3[1]	**-0.03** [3]	**(-0.05, -0.01)**	-0.02	(-0.04, 0.01)	**-1.82** [3]	**(-3.11, -0.53)**
Age	0.01	(-0.01, 0.01)	0.003	(-0.01, 0.01)	0.28	(-0.17, 0.73)
Income	0.00	(0,0)	0.00	(0,0)	0.00	(0,0)

Bold values are coeffients with p<0.05

[1] Reference group is Group 4 -- WHO Median

[2] After adjustment for BMI at 2 years, coefficient was attenuated but remained signficant.

[3] After adjustment for BMI at 2 years, coefficient was attenuated and p-value was 0.05-0.20

[4] After adjustment for BMI at 2 years, coefficient was attenuated and p-value > 0.20.

Table 12. Unadjusted linear regression models of associations between different measures of infant growth and size and anthropometric measures of adult body composition (MALES).

	Infant BMI Trajectory Class n=916 (df=6)		Accelerated BMI gain 0-4 mos [1] n=878 (df=1)		BMI at 2 years n=876 (df=1)	
	F value [2]	Adjusted R-squared	*F* value [2]	Adjusted R-squared	*F* value [2]	Adjusted R-squared
Body Mass Index (kg/m^2)	19.21 [5]	0.11	0.81	<0.01	66.75 [5]	0.07
Fat Mass Index (kg/cm$^{3.3}$)	12.62 [5]	0.07	2.24	<0.01	31.04 [5]	0.03
Lean Mass Index (kg/ cm$^{2.1}$)	17.30 [5]	0.1	0.34	<0.01	77.10 [5]	0.08
Waist Circumference (cm)	12.20 [5]*	0.07	0.47	<0.01	28.09 [5]	0.03
Waist-to-Height Ratio (cm)	11.85 [4]	0.07	1.28	<0.01	28.39 [5]	0.03
Height (cm)	3.33 [3]	0.02	1.25	<0.01	0.05	<0.01

[1] Accelerated = ΔBMI z-score >0.67 s.d.; Not Accelerated = ΔBMI z-score <=0.67 s.d.

[2] F-test value for the unadjusted model; Class 7 as referent for trajectory classes

[3] *P*<0.05

[4] P<0.01

[5] P<0.001

Table 13. Unadjusted linear regression models of associations between different measures of infant growth and size and anthropometric measures of adult body composition (FEMALES).

	Infant BMI Trajectory Class n=832 (df=6)		Accelerated BMI gain 0-4 mos [1] n=812 (df=1)		BMI at 2 years n=785 (df=1)	
	F value [2]	Adjusted R-squared	*F* value [2]	Adjusted R-squared	*F* value [2]	Adjusted R-squared
Body Mass Index (kg/m^2)	7.3 [5]	0.04	0.14	<0.01	37.32 [5]	0.04
Fat Mass Index (kg/cm$^{2.3}$)	5.79 [5]	0.03	0	<0.01	24.79 [5]	0.03
Lean Mass Index (kg/ cm$^{1.8}$)	6.03 [5]	0.04	0.42	<0.01	37.1 [5]	0.05
Waist Circumference (cm)	5.43 [5]	0.03	0.16	<0.01	18.43 [5]	0.02
Waist-to-Height Ratio (cm)	2.96 [4]	0.01	0	<0.01	11.56 [5]	0.01
Height (cm)	3.18 [3]	0.02	0.9	<0.01	5.53 [3]	0.01

[1] Accelerated = ΔBMI z-score >0.67 s.d.; Not Accelerated = ΔBMI z-score <=0.67 s.d.

[2] F-test value for the unadjusted model; Class 7 as referent for trajectory classes

[3] *P*<0.05

[4] P<0.01

[5] P<0.001

6. SYNTHESIS

A. Overview of findings

This research investigates the relationship between early life growth and the development of adult body composition and insulin resistance. Our specific aims were to: 1) Assess the relationship between infant weight velocity and adult insulin resistance, specifically evaluating whether adult body mass index (BMI) and waist circumference (WC) mediate the association, and 2) Assess the relationship between trajectories of early life growth and adult anthropometric measures of body composition.

To address our research aims, we used over 22 years of follow-up data from The Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based cohort study of children born from 1982-1983 in a metropolitan region of the Philippines.

In the following sections we briefly review our findings and their public health implications. We end with a discussion of directions for future research .

1. Indirect effects of infant weight velocity on adult insulin resistance through adult BMI and WC.

We examined the association between infant weight velocity and young adult insulin resistance and evaluated whether adult size and body fat distribution mediate the association. To our knowledge this is the first study to explicitly examine specific components of body composition as potential mediators of the infant weight gain-adult HOMA-IR relationship in a young adult population with a low prevalence of overweight and obesity.

Multivariable linear regression models were used to examine direct and total associations between early growth and adult HOMA-IR and a nonparametric bootstrapping procedure was used to test indirect effects of early growth on adult HOMA-IR through adult body mass index (BMI) and waist circumference (WC). Weight velocity from 0-4 and 0-24 months of age was positively associated with

adult BMI and WC, which both predicted higher HOMA-IR. There were no total or direct effects of immediate postnatal weight velocity (0-4 months) on young adult HOMA-IR. Indirect effects of immediate postnatal weight velocity on HOMA-IR through adult BMI and WC were significant though small. Weight velocity over a longer interval (0-24 months) positively predicted HOMA-IR among males only and indirect effects through adult BMI and WC were significant in both males and females.

This research fills important methodological and substantive gaps in the DOHaD literature. Methodologically, this analysis is important to the ongoing debate regarding how best to account for current size when modeling the relationship between early growth and adult outcomes. Through mediation analysis, which allows partitioning of relationships into direct and indirect pathways, we were able to better describe whether early growth affects later insulin resistance directly as a result of 'programming' of insulin-glucose metabolism, and/or indirectly through its influence on adult body composition. Substantively, in our sample, there were no total or direct effects of faster immediate postnatal weight velocity on adult HOMA-IR. There were only small indirect effects through adult body composition. Notably, we did not find an interaction between infant weight velocity and SGA status, indicating faster postnatal growth has similar effects in those born SGA and those who were not. Importantly, these results suggest that in lower-income contexts where undernutrition and small birth size are common, the promotion of compensatory growth will not have substantial long-term negative consequences for insulin resistance if excess development of body fat and central obesity can be prevented. The overall finding of minimal associations between immediate postnatal weight velocity and adult insulin resistance suggests that any deleterious long-term consequences of improved early life nutrition on adult diabetes risk might be comparatively small.

2. Infant BMI trajectories are associated with young adult body composition

We explored the development of anthropometric measures of body composition in a young, lean Filipino population undergoing the nutrition transition. We used a data-driven latent class growth curve analysis (LCGA) to explore distinct patterns of BMI change across infancy. Substantial differences among trajectory shapes suggest that a single population curve may not represent all

individuals adequately. After controlling for BMI at two years of age, trajectory classes were associated with anthropometric measures of body composition in adulthood, suggesting that overall patterns of BMI change in infancy have long-term implications for the development of body composition.

In this large cohort, accelerated BMI gain from 0-4 months was not predictive of adult outcomes but BMI trajectories from 0-24 months were predictive of adult outcomes. These results suggest that in this cohort faster early postnatal growth is not necessarily risky: our sample includes a substantial number of babies who were born small, but were subsequently exclusively breastfed and had accelerated early weight gain, likely representing catch-up from IUGR. Our results suggest that growth patterns over the entire infancy period are important for the development of lean and fat mass as well as fat patterning.

B. Limitations and strengths

Infancy is a period of rapid changes in both length and weight. The majority of studies examining the role of early life growth and later health outcomes have quantified infant size and growth in terms of weight. For comparability with the extant literature, in our first aim we characterized early growth in terms of weight; however exclusively examining weight is inadequate. Proportional gains in weight and length likely have different implications for the development of body composition than do excess weight gains relative to length. In our second aim we chose to model BMI because we were interested in excess weight gain relative to length. However, because the nature of rapid weight gain in infancy may vary between individuals in terms of fat and fat-free mass and the relative rates of growth in weight and length vary significantly, BMI been shown to be less associated with fatness during infancy than other ages (Wells, 2000). Despite this limitation, BMI is still recommended as a useful way to compare relative weight between populations and within populations over time (Wells, 2000) and the World Health Organization recommends the use of BMI for classifying overweight and obesity in children, adolescents and adults (WHO, 1995).

A focus of the critiques of mediation analysis by epidemiologists is the potential for biased estimates of the direct and indirect effects if confounding of the mediator-disease relationship is not adjusted for (Cole & Hernan, 2002; Robins & Greenland, 1992). The CLHNS includes a breadth of measurements that allowed for inclusion of covariates known to be confounders of the mediator-disease relationship, representing a major strength of the study. However, while we included many known confounders of the adult size-HOMA-IR relationship, we cannot rule out the possibility of residual confounding of these factors, or other unmeasured confounders which might create "collider bias" and inflate our estimates of the indirect effects (Hafeman, 2008).

Latent class growth curve analysis (LCGA) is also subject to limitations. The value of LCGAs depends on the accuracy of the model specification and determination of appropriate number of latent classes. One of the most technically challenging issues is determining the optimal number of groups to include in the model. Our final decision balanced model fit with biological relevance and interpretability of classes. While the sample-adjusted Bayesian information criteria suggested improved model fit beyond the 7-class solution, application and interpretability of higher class solutions becomes problematic, and issues with the use of the BIC in these settings are well- known (Celeux, Forbes, Robert, & Titterington, 2006; Spiegelhalter, Best, Carlin, & Linde, 2002). Though our models are more realistic in their assumptions than previous work, they remain models which by definition are approximations to reality.

Finally, the generalizability of the study population may be limited. While the dataset offers a unique opportunity to provide important information about a random sample of births from 33 randomly selected communities in Metro Cebu, there was lost to follow-up from birth to young adulthood. In prospective longitudinal studies appropriate for examining DOHaD research questions, selective loss to follow-up is of great concern. In the current research if those remaining in the sample experienced a different early life growth-adult insulin resistance and body composition relationship, bias may have resulted. We compared baseline characteristics of the analytic sample with subjects who were in the sample at baseline. Birth weight and length did not differ between the

two groups. Those lost to follow-up were more likely to be urban residents and to have more highly educated mothers, but there were no significant differences in household assets, maternal height, age, or parity and therefore it is likely that our sample is representative of births in Metro Cebu.

Despite these limitations, this body of research has many strengths. The CLHNS is particularly well suited for developmental origins research questions. Study populations from developing countries are underrepresented in existing research on the developmental origins of disease. The CLHNS is one of the few large, population-based longitudinal studies in a rapidly developing population with the data necessary to adequately account for and model the complexity of a life course approach. As the original survey was designed to model the biological and social factors influencing birth outcomes, infant feeding and growth, the available data are highly relevant to our study objectives. Furthermore, the index child sample retains over 60% of its original size even after 20+ years of follow up.

The analytic approaches employed in this research are important innovations that address major challenges of epidemiologic modeling of DOHaD research questions. First, our work is valuable to the ongoing debate regarding how best to account for current size when modeling the relationship between early growth and adult outcomes. The mediation approach used in our study accounts for current size by explicitly modeling the hypothesized pathways linking early growth with insulin resistance *through* adult size rather than *adjusting for* adult size. Second, this research is a novel application of LCGA to identify the heterogeneity of infant growth trajectories. While this method is used extensively in the developmental psychology literature, it has not yet been taken advantage of by public health researchers. Latent class analysis could be utilized by public health researchers to identify trajectories of health behaviors that vary greatly across population subgroups both in terms of the level of behavior at the outset of the measurement period and in the rate of growth and decline over time. Such a method is far more useful in understanding health behavior than the commonly utilized modeling strategy designed to identify averages and explain variability about those averages.

Finally, a strength of the particular LCGA approach employed in the current study is that the forms of the identified infant BMI trajectories emerged from the data. We fit a freed-loading model that effectively estimated the functional form of the BMI trajectories without any *a priori* assumptions about their shape. Identified trajectory shapes may therefore be especially valuable in the generation of new hypotheses regarding determinants and consequences of early life growth. Future research could examine the influence of time-varying modifiable factors on trajectory class membership to identify targets for intervention.

C. Public health significance

The Global Strategy on Diet, Physical Activity and Health presented at the 2004 World Health Assembly, stated for the first time that 'maternal health and nutrition before and during pregnancy, and early infant nutrition may be important in the prevention of non-communicable diseases through the life course' (INSERT REF http://www.who.int/dietphysicalactivity/strategy/eb11344/strategy_english_web.pdf).

CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause (WHO, 2009). Low- and middle-income countries are disproportionally affected: 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women (WHO, 2009). Both overweight and insulin resistance contribute to the development of CVD (Defronzo, 2010). The current research adds to the evidence that early life experiences play an important role in the development of CVD risk factors and emphasizes the need for the identification of public health strategies to modify prenatal and perinatal determinants of adverse adult health outcomes.

An extensive literature shows that undernutrition in infancy and childhood is related to an increased risk of morbidity, mortality and poor developmental outcomes in childhood (Black et al., 2008; Mendez & Adair, 1999). Undernutrition in early life also has long-term consequences (Victora et

al., 2008). As a result of such findings, the promotion of compensatory growth, especially in lower-income settings, has been strongly endorsed (Victora & Barros, 2001). Recently, however, concern has been raised about the potential long-term adverse consequences of rapid or accelerated child growth, including increased risk of overweight and obesity as well as chronic disease risk factors (Fisher et al., 2006; Ong & Loos, 2006). Rapid weight gain is particularly relevant in low- and middle-income countries undergoing the nutrition transition and facing the dual burden of under and overweight (Popkin, 2001).

Our results suggest that in lower-income contexts where undernutrition and small birth size are common, the promotion of compensatory growth in infancy and early childhood will not have substantial long-term negative consequences for insulin resistance if excess development of body fat and central obesity can be prevented in later childhood through adulthood. We found no total or direct effects of faster immediate postnatal weight velocity on adult HOMA-IR. There were only small indirect effects through adult body composition. Faster weight gain in later childhood and adolescence has been more clearly associated with increased adult adiposity and central adiposity as well as an increased risk of impaired glucose tolerance and T2D (Bhargava et al., 2004; Sachdev et al., 2005).

We also found that accelerated BMI gain from 0-4 months was not predictive of adult outcomes but BMI trajectories from 0-24 months were predictive of adult outcomes. These results suggest that in our sample early accelerated postnatal growth is not necessarily pathological: our sample includes a substantial number of babies who were born small, but were subsequently exclusively breastfed and had accelerated early weight gain representing catch-up from IUGR.

In making recommendations about early growth we must consider both the short- and long-term consequences. It should be emphasized that in infancy our sample was generally undernourished and the prevalence of underweight increased with the introduction of complementary foods when exposure to pathogens and diarrheal illness was more common (Popkin et al., 1990). Past work in

this sample suggests that improving infant nutrition would likely reduce short-term morbidity and increase infant survival (Martorell et al., 2010; Mendez & Adair, 1999) while having positive effects on adult human capital (Victora et al., 2008).

Taken together, our findings of no association between accelerated early BMI gain and adult body composition, and minimal associations between immediate postnatal weight velocity and adult insulin resistance suggest that any deleterious long-term consequences of improved early infancy nutrition on adult body composition and diabetes risk are comparatively small.

Our findings of consistent associations between overall patterns of growth from 0-24 months and adult body composition independent of attained BMI at age two, suggest intervention strategies to address malnutrition in transitional countries should focus on overall growth patterns throughout the first two years of life.

D. Future directions

Further investigation is needed to better understand the influence of early life growth on adult health outcomes. In the following section we discuss both natural extensions of the current research and future directions for the field in general.

1. Extensions of the current research

The current study is a novel methodological approach to identifying meaningful differences in patterns of early life growth. We characterized trajectories of BMI over the first two years of life using latent class growth analysis (LCGA). A strength of this approach is that the forms of the identified infant BMI trajectories emerged from the data without any *a priori* assumptions. Identified trajectory shapes may therefore be especially valuable in the generation of new hypotheses regarding determinants and consequences of early life growth. Future research could examine the influence of time-varying modifiable factors on trajectory class membership to identify targets for intervention. We

focused on trajectories of early life growth, but expansion of the model through adulthood would be informative and would help to address the methodological challenge of accounting for final attained size.

In young adulthood, most of our sample is still very lean with higher rates of underweight than overweight or excess abdominal adiposity. At approximately 22 years of age the sample may be just beginning the dramatic body composition transition experienced by their mothers in their late 20's to 30's (L. S. Adair, 2004), but evidence of this transition has not yet emerged. To better understand the role of infant BMI patterns in the development of overweight and obesity, similar analyses could be conducted in a population with a higher prevalence of overweight. Further, as overweight and cardiometabolic outcomes become apparent in our sample we could examine their relationships with infant BMI trajectory classes.

Finally, in LCGA, the variance and covariance estimates for the growth factors within each class are assumed to be fixed to zero. By this assumption, all individual growth trajectories within a class are homogeneous. While this assumption appears to be the most biologically relevant for our study question, future research could explicitly test this assumption. Our LCGA models should be compared with generalized growth mixture models (GGMM), which combine the features of the random effects model and LCGA by estimating both mean growth curves for each class and individual variation around these growth curves by estimating growth factor variances for each class.

2. Future directions in DOHaD

Precise measurements of infant body composition are needed. The majority of studies examine anthropometric indicators of body composition. Precise measurements of body composition would allow for the assessment of patterns of fat deposition in early life which likely have important implications for the development of later body composition and insulin resistance.

Pre and postnatal growth have different implications for the development of adverse adult health outcomes. Postnatal growth is relatively easy to characterize, while prenatal growth represents more of a challenge. Epidemiological studies have primarily characterized prenatal growth as birthweight proportions at birth such as ponderal index (thinness), abdominal circumference, etc. Birthweight is often used as a proxy for prenatal growth. In order to identify modifiable prenatal and postnatal determinants of adverse adult health outcomes methods are needed that better characterize pre and postnatal growth. This distinction between fetal growth and birthweight is difficult to make in human pregnancy, although repeated ultrasound measures of fetal size during pregnancy are beginning to assist here.

We found differences in both early life growth and adult outcomes between males and females. The gender differences that we document are not surprising given that sex hormones may have important influences on early life growth and the development of body composition (Lampl et al., 2005) as well as the risk of T2D (Ding et al., 2006). Prior work in the CLHNS sample has found that birth weight is inversely related to blood pressure and adverse lipid profiles measured in adolescence, with effects stronger or in some instances only present in males (L. Adair et al., 2001; Kuzawa & Adair, 2003). The majority of studies present sex pooled results. Consideration of sex differences in future analyses may improve our understanding of the underlying biological mechanisms.

E. Conclusions

The WHO Global Strategy on Diet, Physical Activity and Health, stated that 'maternal health and nutrition before and during pregnancy, and early infant nutrition may be important in the prevention of non-communicable diseases through the life course.' (INSERT REF http://www.who.int/dietphysicalactivity/strategy/eb11344/strategy_english_web.pdf). This study addressed two important methodological challenges to DOHaD research and provided substantive knowledge about the long-term implications of early life growth experiences.

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