

Environmental and Developmental Determinants of Obesity in Cebu, Philippines.

Darren Lawrence Dahly

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Approved by:

Linda Adair, PhD

Barry M. Popkin, PhD

Penny Gordon-Larsen, PhD

Jay Kaufman, PhD

Mike Emch, PhD

ABSTRACT

Darren Lawrence Dahly: Environmental and Developmental Determinant of Obesity in Cebu, Philippines.
(Under the direction of Linda Adair, PhD)

Obesity is now recognized as a serious challenge to global public health. Obesity is often viewed as a problem that results from a deficiency in a person's character; that obesity is the consequence of gluttony and sloth. However, obesity is impacted by a variety of factors that are largely exogenous to human choices. We investigated both how shared environment and individual level socio-economic status influence obesity risk, as well as how prenatal characteristics can increase human susceptibility to the obesogenic effects of modern environments before we are even born.

Analyses were conducted using data from the Cebu Longitudinal Health and Nutrition Survey, a community based study of a one year birth cohort (1983) followed up until young adulthood (2005). Using the spatial scan statistic we found that measures of overweight and obesity were spatially clustered in the study area Metro Cebu. The locations of these clusters coincided with the urban core of Cebu, but also extended into peri-urban and rural areas as well. Clustering in the males was largely explained by the spatial distribution of individual level socio-economic status. We then used multivariable linear models to explore the joint impact of community level urbanicity and multiple indicators of

individual level socio-economic status on multiple measures of overweight and obesity. We found that socioeconomic status was positively associated with obesity in males but not females. Lastly, we tested the mismatch hypothesis, which generally posits that maternal constraint of fetal growth can lead to developmental changes *in utero* that increase an individual's susceptibility to obesogenic environments. More specifically, we found that that the positive association between socio-economic status and central adiposity in male study participants was amplified in firstborns.

This research helps fill an important gap in understanding how socio-environmental conditions can influence obesity in a lower-income, rapidly developing context. We also provide one of the earliest explicit tests of the mismatch hypothesis with respect to birth order. The public health consequences of these associations could become critical as obesogenic environments become more common, and the proportion of lower order pregnancies among humans increases.

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Chapter 1. Introduction

A. Overview

Obesity is now recognized as a serious challenge to global public health. The prevalence of obesity has risen too rapidly over the past 30 years to be explained by changes in human biology. At its root, the obesity pandemic is instead caused by sweeping societal shifts (e.g. urbanization, globalization, modernization, etc.) that have dramatically altered the social and physical environments that humans occupy. These environmental changes have acted to limit healthy nutritional behaviors, and/or to facilitate obesogenic behaviors. Most public health obesity intervention is aimed at helping individuals change their behaviors in an uphill battle against their environments. These efforts have failed to reduce obesity prevalences at the population level. In response, researchers are now trying to better understand exactly how environment impacts obesity risk, with the ultimate goal of changing our environments in manner that facilitates healthy nutritional behaviors. We aimed to contribute to this growing body of research (aims 1 and 2) by investigating the joint impact of community-level urbanicity and multiple individual-level indicators of socioeconomic status (SES) on obesity risk in a lower-income country, the Philippines.

While a better understanding of the impact of environment on obesity risk will be crucial to public health obesity intervention, we also know that there is

significant variation in obesity outcomes among people who share an environment. Some people are clearly more susceptible to the obesogenic effects of modern environments than others. One explanation for these differences is the *mismatch hypothesis*, which falls under the broader Developmental Origins of Adult Health and Disease (DOHaD) paradigm. It posits that maternal constraint of fetal growth acts as a prediction of poor future nutritional conditions that is transmitted to the developing fetus. The hypothesized fetal response to maternal constraint is the development of a thrifty phenotype that improves fecundity and/or survival in a poor nutritional environment. If the offspring instead faces a nutritionally abundant environment, the thrifty phenotype is hypothesized to increase risk of obesity and related metabolic disorders. Testing this hypothesis was the primary goal of this research (aim 3).

Data are from Cebu Longitudinal Health and Nutrition Survey (CLHNS), which is ideally suited for this research. The sample includes a one-year birth cohort and their mothers, for whom there are detailed longitudinal data (1983-2005). By design, CLHNS participants are nested within administratively defined communities called barangays. Thus we know the approximate geographic location of each study participant in each year surveyed, and have detailed community-level data associated with those locations. Since its beginnings in 1983, the study area (Cebu, Philippines) has undergone rapid urbanization, modernization, and economic development, yet is still environmentally heterogeneous, with dense urban centers and rural, agrarian communities.

B. Specific research aims.

Aim 1

Using generalized estimating equations, with study participants nested within barangays, we explored how community-level urbanicity, and multiple individual-level indicators of SES were related to young-adult body size in the CLHNS birth cohort. Dichotomous measures of body size included, overweight and central adiposity. Our primary goal was to quantify obesogenic environments in a manner that facilitated our test of the mismatch hypothesis. However, our results also contribute to a broader body of literature on the socio-environmental determinants of obesity, which to date has largely ignored the developing country context.

Aim 2

Though linear models that account for geographic nesting of observations are a popular statistical approach for investigating the environmental determinants of health, they do not explicitly account for the spatial distribution of the barangays. Thus, to compliment our analysis from aim 1 with an explicitly spatial approach, we used the Kuldorff spatial scan statistic to test for spatial clustering of young-adult obesity outcomes in the Cebu birth cohort. Outcomes included dichotomous measures of overweight, obesity, and central adiposity. We then evaluated the degree to which obesity clusters coincided with urban areas in Cebu, and the degree to which they were explained by individual-level SES.

Aim 3.

The mismatch hypothesis posits that impact of obesogenic environments is amplified in individuals whose fetal growth was maternally constrained. We tested the hypothesized impact of this interaction on obesity and central adiposity using random effects logistic regression models. We crudely quantified obesogenic environments based on what we learned in aims 1 and 2. We considered multiple variables hypothesized to cause maternal constraint of fetal growth, including maternal age, height, arm fat area, and birth order. Interactions between environment and maternal constraint were tested using product terms.

Chapter 2. Literature Review

A. Obesity

A global public health crisis

Obesity can be crudely defined as an adverse health condition characterized by excess levels of adipose tissue. Overweight is a term typically used to describe a pre-obese state that is associated with mildly increased health risks. Adipose tissue was once viewed as a fairly inert substance whose sole function was to store excess energy for later use (Kershaw and Flier 2004). Today, we now understand that adipose tissue acts as an endocrine organ that secretes a variety of substances (e.g. hormones, cytokines, and free-fatty acids) that impact metabolism and subsequent health (Ahima and Flier 2000; Kershaw and Flier 2004). While research into the specific biological mechanisms that connect adipose tissue to human health is on-going, there is no doubt that having too much adipose tissue and/or having it located in particular areas of the body disrupts normal metabolism and leads to disease.

Innumerable epidemiological studies have illustrated this connection between adiposity and health. Obesity is clearly associated with increased all-

cause mortality (Hu 2008). Obesity and overweight have also been linked to numerous serious morbidities, including cardiovascular disease (Van Gaal, Mertens et al. 2006; Hu 2008) , osteoarthritis (Coggon, Reading et al. 2001; Lievense, Bierma-Zeinstra et al. 2002), cancer (Calle and Kaaks 2004; Hu 2008), diabetes (Hu 2008), hypertension (Rahmouni, Correia et al. 2005; Hu 2008), and other metabolic disorders (Hu 2008).

In addition to more obvious effects on health, obesity also results in a number of social and psychological consequences that are often overlooked. These include social stigma, bias, and discrimination (Puhl and Brownell 2001; Puhl and Brownell 2003) that lead to disparities and disadvantages in the workplace (Cawley 2004), health care (Brown 2006), education (Taras and Potts-Datema 2005), and personal relationships (Chen and Brown 2005). Obesity has also been associated with psychological disorders such as depression and suicide (Carpenter 2000).

While there is no doubt that obesity has a serious influence on health and well-being, to be considered a serious public health problem it must occur in a significant proportion of people. The most common way of assessing obesity and overweight at the population level is the body mass index (BMI), which is calculated as weight (kg) over height (m)². Typically, a BMI of ≥ 25 is considered overweight while a BMI ≥ 30 is considered obese. According to the most recent global figures from the World Health Organization (2005), 1.6 billion adults are overweight and 400 million are obese (WHO 2009). With the exception of some Polynesian nations (Prentice 2006), the highest prevalences of obesity are found

in high-income countries For example, in the US, current prevalences of adulthood overweight and obesity are estimated as 66.3% and 32.2% respectively (Hu 2008). Recent estimates place the prevalence of adulthood obesity at ~24% in the UK (Rennie and Jebb 2005), 15% in Canada (Belanger-Ducharme and Tremblay 2005), 21% in Australia (Cameron, Welborn et al. 2003; Thorburn 2005), and similar numbers are found in other high-income countries (Hu 2008).

Though obesity was once viewed as a problem limited to higher-income countries, it is now clear that obesity is a emergent or existing public health problem in many middle and lower-income countries as well, particularly in urban areas (James, Leach et al. 2001; Popkin 2001; Popkin and Gordon-Larsen 2004; Mendez, Monteiro et al. 2005; Nishida C. 2005; Prentice 2006). When comparing obesity prevalences in lower-income countries to those in the West, obesity may not seem like a serious public health problem in the developing world. However, most developing country contexts are still dealing with other public health crises such as infectious diseases that are no longer a serious problem in high-income countries. This problem is acutely illustrated by the coexistence of obesity and overweight with undernutrition at the national (Mendez, Monteiro et al. 2005) and even household level (Caballero 2005; Doak, Adair et al. 2005). Lastly, the societal shifts that have largely driven the obesity problem in high-income countries are occurring much more rapidly in lower-income countries (Popkin 2002), and all evidence suggests that the prevalence of overweight and obesity will continue to rapidly rise in these contexts. Thus obesity and overweight

present a serious problem in lower-income countries as policy makers must figure out how to spread their already depleted public health resources to deal with obesity and related morbidities both today and in the future.

Obesity and related disease in the Philippines

Contemporary surveys have highlighted overweight, obesity, and related health outcomes as key public health issues in the Philippines (INCLEN 1992; INCLEN 1994; Janus, Postiglione et al. 1996; FNRI 2001). The prevalence of metabolic syndrome in the Philippines was recently estimated at 12-19% depending on the definition used (Morales, Punzalan et al. 2008). Heart disease and diseases of the vascular system were the top two causes of adult mortality in 1998, accounting for 16% and 12% of deaths, respectively (FNRI 2001). Recent national survey data document a high prevalence of CVD risk factors: 16% of adult Filipinos have a total cholesterol >200 mg/dL; 22% have LDL-C >130; and 21% are hypertensive (FNRI 2001; Tanchoco, Cruz et al. 2003). Nearly 40% of adult women had a waist-to-hip ratio (WHR) >0.85, a level associated with increased risk of hypertension and diabetes. According to the WHO, estimated disability adjusted life years from heart disease are higher in the Philippines than in the US or China (Mackay J 2004). From 1993-98, the percentage of adults with a BMI>25 kg/m² increased from 17% to 20%, and overweight prevalence doubled among female adolescents. Current WHO estimates place the prevalence of obesity and overweight combined at 29% in females and 21% in males (WHO 2009). The mothers from the CLHNS have also experienced a

dramatic increase in prevalence of overweight (BMI \geq 25) , from 6% in 1983 to 42% in 2002 (Adair 2004).

B. A brief overview of the developmental origins of disease and obesity

The Barker Hypothesis

The origins of the DOHaD paradigm are generally credited to David Barker's observation that the geographical distribution of neonatal mortality in England and Wales in 1911-15 closely corresponded to CVD mortality from the same areas in 1968-78 (Barker and Osmond 1986). Because most neonatal deaths at that time were attributed to low birth weight, Barker hypothesized that poor fetal nutrition was acting to program the body's physiology in ways that adapted the offspring for a life of food insecurity while increasing "susceptibility to the effects of an affluent diet." This was originally known as the "Barker" or "fetal programming" hypothesis.

Subsequent studies conducted in a variety of European cohort studies found inverse associations between birth size and a variety of metabolic outcomes such as hypertension, stroke, insulin resistance, and type-2 diabetes (Barker and Osmond 1988; Barker, Winter et al. 1989; Osmond and Barker 2000; Gluckman and Hanson 2004). However, many of these early studies were limited in that they used recalled measures of birth size as a proxy for poor fetal nutrition, and were not able to account for confounders such as SES.

The Thrifty Phenotype Hypothesis

It was later discovered that the deleterious “effects” of low birth weight were more evident in individuals who became relatively large as adults (Hales and Barker 1992; Hales and Barker 2001). For example, using data from the birth cohort of the CLHNS, Adair and Cole (2003) found that age- and height-adjusted prevalence of high blood pressure was highest in individuals who fell in to the bottom third of the BMI distribution at birth, and the upper third of the BMI distribution at age 16. A pattern of similar observations formed the basis of the “Thrifty Phenotype” hypothesis which expanded upon the Barker hypothesis by proposing that pathological effects of poor fetal nutrition were “critically dependant” on other factors, particularly obesity (Hales and Barker 2001).

However, the manner in which the thrifty phenotype hypothesis is formulated makes it difficult to test in observational studies, particularly when birth weight is the only available measure of fetal nutrition or development. The largest challenge comes from the fact that birth weight and current weight are measurements of the same thing at different time points and mathematically coupled. Thus, when simultaneously considering the effects of birth weight and current weight or obesity, it is impossible to rule out an effect of change in weight (Lucas, Fewtrell et al. 1999). Furthermore, obesity is an independent determinant of many of the diseases studied (i.e. CVD or diabetes), and neglecting to account for it could mask true inverse associations between birth weight and disease. Lastly, there is growing evidence (summarized below) that obesity itself has developmental determinants (the focus of this research). Considering all of the

above, current weight could be acting as a modifier, a confounder, *and* a mediator of associations between birth weight and later disease outcomes. However, the closely related Mismatch (or alternately, Predictive Adaptive Response) hypothesis, recently proposed by Gluckman and Hanson, is formulated in a manner that avoids some of these complications while still capturing the nature of the thrifty phenotype hypothesis.

The Mismatch Hypothesis

Adaptation is a key characteristic of life. Furthermore, adaptation occurs at multiple time scales. At one extreme, organisms can maintain internal conditions in response to immediate environmental changes (homeostasis), while adaptation due to natural selection takes millennia. A predictive adaptive response (PAR) is an adaptive mechanism that falls somewhere between these two extremes. They occur when an environmental cue, experienced during a period of developmental plasticity, alters the developmental program in a manner that better prepares the organism for a future environment (Gluckman and Hanson 2004). Thus the environmental cue acts as a prediction of future conditions. Based on whether the prediction is correct, the predictive adaptive response is considered appropriate or inappropriate (Gluckman and Hanson 2004). Appropriate PARs confer a survival advantage, while inappropriate PARs can result in disease. Thus PARs can be broken down into four components: the environmental cue, the predicted environment (versus the realized environment); the physiological adaptation; the consequence of an inappropriate PAR.

It has been recently hypothesized that PARs may act as a mechanism which explains apparent associations between small size at birth and a variety of health outcomes studied under the Developmental Origins of Health and Disease (DOHaD) paradigm (Gluckman and Hanson 2004; Gluckman and Hanson 2004). More specifically, Gluckman and Hanson hypothesize that the environmental cue may arise from a variety of determinants of fetal growth and development (not just fetal or maternal nutrition) that lead to a future expectation of insecure nutritional environments for the developing fetus. These include maternal constraint, primiparity, and age. The fetal response to these possible signals is to alter its physiology to maximize energy conservation and storage. The PAR becomes inappropriate if the post-natal nutritional environment is instead characterized by energy abundance, and subsequently leads to pathological levels of centrally stored adipose tissue.

The developmental origins of obesity

Animal models make up the most compelling evidence for a developmental effect on later obesity. The example most relevant to the research proposed here is a rat model by Vickers, Breier et al. (2000). Rats were randomly fed *ad libitum* (AB) or were undernourished (UN) using a diet of 30% of AB intake. The offspring of UN rats were characterized by smaller birth size. At weaning both sets of offspring (AB and UN) were then randomly stratified and exposed to either a normal control diet, or a hypercaloric diet with a 30% fat composition. Food intake in the offspring of UN rats was elevated starting at an

early post-natal age and continued to increase with age relative to the offspring of AB rats. This effect was further amplified by exposure to the hypercaloric, high-fat diet. Offspring of UN rats also had larger retroperitoneal fat pads (relative to body size) than the offspring of AD rats. In later experiments (Vickers, Breier et al. 2003), using the same rat model, the investigators found that the offspring of UN rats were less active than the offspring of AD rats at the three time points measured (35, 145, and 420 days after birth). This effect was also exacerbated by post-natal exposure to the hypercaloric, high fat diet. Other rat studies in which maternal malnutrition or hormonal manipulation led to increased offspring obesity have also been reported (Anguita, Sigulem et al. 1993; Jones, Pothos et al. 1995).

A recent review of human studies of the association between birth weight and later obesity (Rogers 2003) concluded that although birth weight tends to be linearly related to later BMI, this may be largely due a positive association with lean body mass (as opposed to increased adiposity). The review also concluded that after controlling for BMI, there was consistent evidence of an inverse relationship between birth weight and central adiposity reflected by central to peripheral skin-folds ratios. These conclusions were also upheld in another recent review (Oken and Gillman 2003). It is important to note, that in all of the studies reviewed, none tested for interactions between determinants of fetal development and later environment and most suffer from the limitations we have previously described, particularly the use of birth weight as a proxy measure for fetal development.

C. Determinants of fetal growth

Traditional tests for developmental effects on later disease outcomes have focused on the “effects” of birth weight, interpreted as a proxy measure for “fetal nutrition,” a complex supply chain that delivers nutrients and oxygen to the fetus. The assumption is that larger babies are more likely to have experienced better fetal nutrition than smaller babies. However, fetal nutrition is just one factor affecting fetal growth. Maternal constraint is another. It is defined by Gluckman and Hanson (Gluckman and Hanson 2004) as a phenomenon “whereby the growth of the fetus is limited so that it cannot outgrow the mother’s reproductive tract and her capacity for vaginal delivery.” Because the influence of maternal size on birth size is inter-generational in nature (Drake and Walker 2004) it represents a particularly interesting mechanism for the transmission of developmental effects. Primiparous pregnancies, and young maternal age (Wallace, Bourke et al. 2001; Gluckman and Hanson 2004) are also associated with reduced birth size and hypothesized to affect fetal development.

A key weakness of using birth size is that does not represent a point of public health intervention since each of the above determinants of fetal development may represent different mechanisms leading to later disease. By using only birth weight as the key exposure, it is impossible to discern the specific cause of impaired fetal development that is contributing to later disease. Furthermore, Gluckman and Hanson hypothesize that the effects of fetal development on later disease may occur in individuals falling within the normal range of birth sizes. A key innovation of the research proposed here is that we

will consider multiple determinants of fetal growth and development, including maternal nutrition (such as diet and energy stores), maternal constraint (estimated by maternal height), primiparity, and maternal age. Determining which, if any, of these factors increases susceptibility to central obesity will better inform us regarding the physiological mechanisms involved.

D. Quantifying the obesogenic environment

Because the mismatch hypothesis posits an interaction between maternal constraint of fetal growth and the later nutritional environment, we must first conceptualize what constitutes this “nutritional environment.” There is a rapidly growing body of scientific literature on the effects of nutritional environments (and “health and place,” or “neighborhoods and health” in general) to which we hope to contribute. We believe that epidemiological studies of the nutritional environment can be approached from two directions. The first is a causal model based on an etiological theory that aims to elucidate the effects of specific factors within a given environment that are amenable to public health intervention.

Examples of this approach include the location of supermarkets (Morland, Wing et al. 2002; Inagami, Cohen et al. 2006; Moore and Diez Roux 2006; Morland, Diez Roux et al. 2006) and their relationships with nutritional outcomes. The second approach is to develop broader, predictive models of more general neighborhood characteristics such as land-use mix or urban form (Frank, Andresen et al. 2004; King, Belle et al. 2005; Nelson, Gordon-Larsen et al.

2006). Here the goal of the analysis is often to just illustrate the importance of “place” without trying to disentangle the effects of environmental components.

For the purpose of testing the PAR hypothesis, we are best served by using this approach, where we identify broad, up-stream, environmental predictors of obesity. This approach is appealing because this research is not concerned with specific pathways connecting the nutritional environment to central obesity, just their “crude” relationship. While the research proposed will not explicitly lead to neighborhood level, public health interventions, given the relative scarcity of published research on nutritional environments, particularly in developing countries, this research will still make an important contribution to this literature, both substantively and methodologically.

Our conceptualization of an individual’s nutritional environment is comprised of three elements: a spatial extent that adequately captures an individual’s typical geographic range; the urbanicity of that area; and the economic status of the individual.

Urbanicity and obesity

The world we live in has changed dramatically over the past 150 years. Today, for the first time in human history, half of the world’s population is living in an urban area (U.N.). This figure is remarkable - prior to 1850 not a single society on earth could be classified as predominately urban (Davis 1987). Over the past century, however, the urban environment has become the norm in the more developed regions of the world, where 75% of people live in urban areas

(U.N.). Even in the less developed regions of the world, 43% of the population is now concentrated in urban settlements (U.N.). Figure 2.1 presents urbanization trends since 1950 in the more and less developed regions of the world, as well as the annual rate of change in urbanization. Note that while the less developed regions still lag behind in terms of percent urban, the annual rate of change in percent urban is more than twice that seen in the more developed regions.

Urbanization coincides with modernization, globalization and development in most contexts. This combination of factors has led to dramatic global shifts in physical activity and dietary behaviors, often referred to as the nutrition transition (Popkin and Gordon-Larsen 2004), that are in turn driving a world-wide obesity epidemic.

Urbanization is frequently cited as a key determinant of the nutrition transition. In most contexts, urban lifestyles are associated with sedentary jobs, motorized transportation, and constant exposure to calorie rich, inexpensive foods. The world's mass media also focus on urban environments, often exposing urbanites in the developing world to western culture and corporate advertising (much of which is for food and drink). This is in contrast to rural areas where people often engage in physically active jobs, have limited resources, and are isolated from mass media influences. All of this leads to the reasonable assumption that urban areas are more obesogenic than rural ones.

However, a growing literature on diet, activity, and obesity differentials between urban and rural areas paints a more complex picture. Within a given country or region, urban populations almost always have a higher prevalence of

obesity than nearby rural populations. However, the degree of difference between urban and rural areas can vary widely from area to area (Mendez, Monteiro et al. 2005).

From these studies, investigators infer a contextual effect of urban residence on obesity risk. These studies have several limitations though. One is that they typically compare two distinct geographic and thus two distinct populations. Without controlling for compositional effects, the case for a contextual effect is much weaker. In one of the few studies that found no urban-rural difference in BMI, the ethnic and cultural make up of the two populations were very similar because researchers selected an urban area largely populated by migrants from the rural area investigated (Hussain, Rahim et al. 2005). Another typically weakness of these studies is their cross-sectional nature. Longitudinal analyses would of course be more interesting. For example, a study in Cameroon (Sobngwi, Mbanya et al. 2004) used migration records and interviews to characterize life-course exposure to urban environments. In a sample of 1726 males and females (age ≥ 25), they found a significant positive association between lifetime urban exposure and BMI in every 10 year age group. Furthermore, a small sample ($n=29$) of recent migrants to an urban area (with ≤ 2 years of urban exposure) had higher BMIs than current rural residents with more than 2 years of previous urban exposure.

A key limitation of each of these studies is their use of the urban-rural dichotomy to characterize environment. This is problematic because there is no universal definition of "urban." Vlahov and Galea (2002) illustrate this point nicely,

noting that "among 228 countries for which the United Nations has data, about half use administrative definitions of urban (e.g., living in the capital city), 51 use [population] size and density, 39 use functional characteristics (e.g., economic activity), 22 have no definition of urban, and 8 define all (e.g., Singapore) or none (e.g., Polynesian countries) of their population as urban." Not only do definitions of urban vary widely, many of the studies noted above don't explicitly state the urban definition they used, making it more difficult to meaningfully compare results.

The urban-rural dichotomy is also problematic because it fails to capture important environmental heterogeneity. In the past, urban and rural environments were more distinct, but modern "rural" areas are now experiencing factors traditionally associated with the urban environment and the result is "increased blurring of urban-rural distinctions" (Champion and Hugo 2004). Additionally, patterns of urbanization vary between regions (Kasarda and Crenshaw 1991), resulting in equally varied settlement types and a great deal of heterogeneity among urban areas across the globe and even within countries (Champion and Hugo 2004). The importance of this heterogeneity is not lost on urban health researchers, many of whom have called intra- and inter-urban health research (Yach, Mathews et al. 1990; McDade and Adair 2001; Vlahov and Galea 2002; Wharton 2002).

To more adequately represent urban heterogeneity in the CLHNS study area, we used a recently developed scale measure of urbanicity, another key innovation of the research proposed here. The details of the scale's development

can be found in (Dahly and Adair 2007). Briefly, the urbanicity scale is based on seven demographic and modernization characteristics: population size and density, health and education services, transportation, markets, and communications. It is calculated from the community level data for each survey year. The reliability and validity of the scale have been established using scale development methodology. The scale has been shown to be an improvement over the traditional urban-rural dichotomy in several ways: it is better able to measure differences in urbanicity between communities; it is better able to detect changes in urbanicity over time; and it allows for more refined analyses of the relationship between the urban environment and human health.

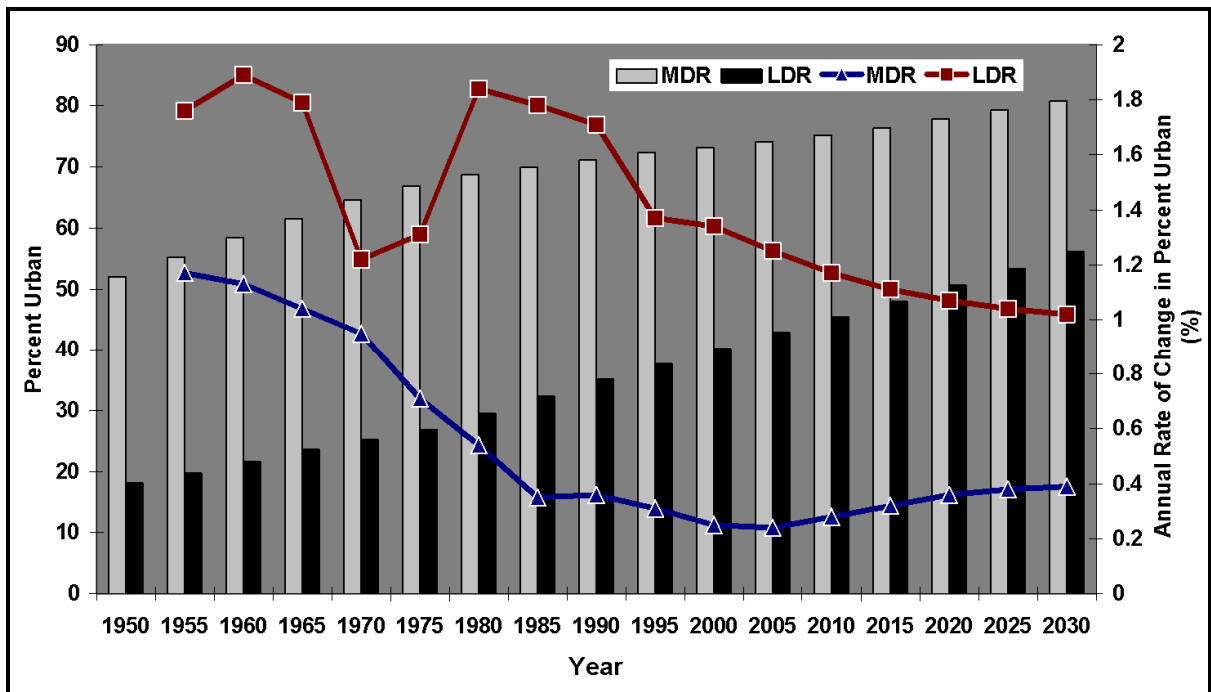
Socioeconomic status and obesity

In high-income countries, SES tends to be inversely associated with obesity, particularly in women (Sobal and Stunkard 1989). Conversely, obesity has traditionally been associated with affluence in lower-income countries (Sobal and Stunkard 1989), though recent evidence suggests that this relationship is becoming more like that seen in high-income countries (Monteiro, Conde et al. 2004; Monteiro, Moura et al. 2004; McLaren 2007). Explanations for this shift are fairly consistent across the literature, but perhaps summarized best by Monteiro et al. (2001) whom we liberally paraphrase here. At low levels of economic development, material wealth is the primary determinant of food availability, and wealthy people are much less likely to engage in jobs requiring high levels of physical activity. Affluent people will also be more likely to own TVs, labor saving

home appliances, and have increased access to Western style packaged and fast foods (which tend to be relatively expensive when first introduced and are often associated with prestige). Thus a positive SES-obesity gradient could be the result of wealth causing a positive energy balance that leads to obesity *and* wealth protecting against a negative energy balance caused by undernutrition and physical labor. However, as economies develop, barriers to food availability are reduced for the poor, particularly for staple foods, and jobs tend to require less physical activity across SES strata. At this point we would expect the positive SES-obesity gradient to start shifting towards a null relationship. Finally, at the next stage of economic development, obesity risk is reduced among high SES groups because they are better equipped to make informed food choices (by being better educated and/or because they face fewer economic and geographic barriers to healthy food), and are more likely to engage in leisure time activity. At the same time, the least expensive foods tend to be those that have little nutrient value and high energy density.

A better understanding of this emerging health disparity in lower-income contexts is critical. However, most studies illustrating these trends have focused on a single SES indicator (Monteiro, Moura et al. 2004; McLaren 2007), though it is likely that multiple aspects of SES could impact body size independently of one another.

Figure 2.1. Percent urban and change in percent urban in the more and less developed regions of the world, 1950-2030.



Chapter 3. The spatial distribution of young adult overweight, obesity, and central adiposity in Cebu, Philippines, 2005.

A. Introduction

Urbanization, modernization, and globalization have radically altered human environments, resulting in sweeping changes to the way we work, play, and eat (Popkin 2008). These changes have recently been most dramatic in the developing world, where the pace of urbanization has been especially rapid (U.N.). In the wake of these changes, obesity has emerged as a global public health problem (Popkin and Gordon-Larsen 2004; Popkin 2006), even in contexts where underweight is still prevalent (Mendez, Monteiro et al. 2005). While our physical and social environments can clearly facilitate obesogenic behaviors, we know very little about exactly *how* they do so. Accordingly, research on the environmental determinants of obesity has recently intensified (Hill and Peters 1998; French, Story et al. 2001; Macintyre, Ellaway et al. 2002; Hill, Wyatt et al. 2003; Booth, Pinkston et al. 2005; Popkin, Duffey et al. 2005; Lake and Townshend 2006; Entwisle 2007).

A variety of theoretical and methodological perspectives are needed to help identify mutable environmental determinants of obesity. For this paper, we have taken an urban health approach (Vlahov and Galea 2002) that first

considers the broad influence urban environments have on obesity risk. Many previous studies have looked at differences in prevalent obesity between “urban” and “rural” areas (e.g. Mendez, Monteiro et al. 2005). In lower-income countries like the Philippines, where our research takes place, these studies have typically found that urbanites are more likely to be obese than their rural counterparts, though the degree of difference varies widely between studies (e.g. Mendez, Monteiro et al. 2005). Our goal was to build upon these observations to paint a more refined picture of the relationship between urban environments and obesity in a lower-income, rapidly developing context.

To achieve this goal, we used the spatial scan statistic (Kulldorff 1997) to detect *spatial clusters* in our study area where the prevalence of obesity in a birth cohort of young adult Filipinos was unusually high or low . We then displayed cluster locations on urbanicity maps of the study area. We compared and contrasted two different measures of urbanicity: the traditional urban-rural dichotomy, and a continuous scale measure that captures environmental heterogeneity within “urban” and “rural” areas (Dahly and Adair 2007). Lastly, we evaluated the degree to which any clusters were explained by the spatial distribution of individual-level socioeconomic status (SES).

B. Methods

Study Design and Sample

Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community based, one-year birth cohort in Metropolitan Cebu, Philippines. A single stage cluster sampling procedure was used to randomly select 33 administratively defined communities called *barangays*. Pregnant women residing in these barangays were recruited for the study in 1982 and 1983, and those who gave birth between May 1, 1983, and April 30, 1984, were included in the sample. More than 95% of identified women agreed to participate. A baseline interview was conducted among 3,327 women during their 6th or 7th month of pregnancy. Another survey took place immediately after birth; there were 3,080 non-twin live births which make up the CLHNS birth cohort. Subsequent surveys were conducted bi-monthly to age 2, then in 1991, 1994, 1998, 2002, and 2005.

We used birth cohort data on barangay of residence and multiple adiposity measures collected in 2005 when the study participants were young adults (20-22 years of age). Women pregnant in 2005 were excluded (n=73). Anyone with missing data for barangay residence and any outcome measures were also dropped (5 males and 2 females), resulting in a sample of 988 males and 820 females. By 2005, participants were living in 161 different barangays, though most were still located in the original 33 sample barangays (77% of males and 76% of females).

Barangay level data were also collected for each round of the survey. The community surveys included information on the barangays' physical characteristics, infrastructure and utilities, social services, community

organizations, industrial and commercial establishments, labor markets, and wage rates. Data for the community surveys were obtained from barangay officials or other knowledgeable people recommended by these officials. Population sizes were taken from the most applicable Filipino census.

Study Site

Metro Cebu (pop 1.9 million), on the east coast of Cebu Island in the central Philippines, is composed of three cities and seven municipalities in surrounding peri-urban and rural areas. Metro Cebu includes 270 barangays (average area 2.65 km²) comprising a 720 km² contiguous area. Consequently, the ethnic and cultural make-up of Metro Cebu's population is fairly homogenous, while the study area is environmentally diverse, with densely populated urban centers, less dense peri-urban areas, rural towns, and more isolated mountain and island areas.

Measures

Neighborhoods. 2005 barangay of residence was used to define participant neighborhoods. The assumptions implied are: constant barangay-level effects across respondents in a given barangay; and that the barangay is a reasonable approximation of a person's "activity space," defined as the set of locations a person encounters in the course of their daily activities (Golledge and Stimpson 1987; Nemet and Bailey 2000). Similar assumptions are commonly made in health geography. Though they are administratively defined (similar to

the US census block or block group), Cebuanos very much associate themselves with the barangay they live in (unlike in the US). Barangays have their own elected officials and budgets, community centers, etc, and the vast majority of Cebuanos can easily identify their barangay of residence. Thus, barangay of residence is arguably a better measure of neighborhood (one that encompasses social factors and not just space) than the administratively defined neighborhoods used in other contexts.

Urbanicity. While most research uses the urban-rural dichotomy to describe urbanicity, our research uses a continuous measure that captures a range of variation in urbanicity across a single dimension. The starting point for this measure is a previously designed urbanicity scale (description, rationale, and validation are given in Dahly, Adair (Dahly and Adair 2007)).

Briefly, the scale is made up of seven components derived from data collected for the CLHNS barangay level surveys. The components are population size; population density; communications (availability of mail, telephone, internet, cable TV, and newspaper services); transportation (paved road density and public transportation services); markets (presence of gas stations, drug stores, grocery stores and the number of small commercial kiosks called *sari-sari* stores); educational facilities; and health services. Theoretically, the scale represents an underlying latent construct, labeled urbanicity, that is imperfectly reflected in each of these seven components.

Since publishing the details of the scale's creation, we've modified it by making the urbanicity value for a given barangay a function of its own score and

the scores of surrounding barangays. In other words, an urban barangay surrounded by other urban barangays will have a higher final score than an urban barangay with the same initial value that is bordered by more rural barangays. These values were created with the ESRI ArcMap inverse distance weighting (IDW) interpolation tool, using the default settings. For more detail on IDW, please see (Waller and Gotway 2004).

To further validate the scale, we compared its spatial distribution (in figure 3.1) across the study area to a Landsat 7 ETM+ image of the study area (<http://landsat.gsfc.nasa.gov/>), which is a false color composite that depicts vegetation as shades of red, while mixes of bare soil and impermeable land cover (buildings, roads, etc.) appear green. Areas classified as more rural by the urbanicity scale are clearly characterized by more vegetation in the Landsat image, while urban areas are characterized by more bare soil and impermeable ground cover. We also compared our image to a SRTM elevation map (<http://srtm.csi.cgiar.org/>) because mountains constrain urban development to the northwest; thus the urban core of Cebu is elongated, running southwest to northeast along the coastal low-lands. The SRTM map depicts higher elevations as darker shades of blue, and the both the Landsat image and urbanicity map confirm that the urban areas are located in the relatively low elevations between the mountains and the sea.

Anthropometrics. We used three anthropometric measures to define elevated adiposity. They were body mass index (BMI), waist circumference (WC), and percent body fat (BF%). All anthropometrics were collected by trained

field staff during in-home interviews using techniques described in Lohman et al. (1988). Weight was measured with a mechanical scale to the nearest kg, while height was measured with a folding stadiometer to the nearest tenth of a cm. BMI was calculated as measured weight (kg) divided by measured height (m) squared. While BMI is strongly correlated with both BF% and total fat mass (Hu 2008), it does not differentiate fat mass from lean mass. However, it is the standard measure of adiposity for public health research (Hall and Cole 2006), and allows the results from this study to be compared with others. WC was measured at the midpoint between the bottom of the ribs and the top of the iliac crest. WC is a measure of central obesity, which is thought to be an important driver for a number of important metabolic disorders (Alberti, Zimmet et al. 2005) compared to other patterns of fat distribution. BF% was calculated using the sum of three skin folds (triceps, subscapular, and suprailiac) as described by Durnin and Wormersley (1974). It is included as a more specific measure of overall adiposity than BMI.

All measures were dichotomized to represent individuals with relatively elevated levels of adiposity. BMI was dichotomized as overweight or obese (OW; $BMI \geq 23$) versus not OW ($BMI < 23$), or obese ($BMI \geq 25$) versus not obese ($BMI < 25$), using standard Asian cut-points (Misra 2003). Obesity was alternately defined as $WC > 85$ cm in males or > 80 cm in females (Bei-Fan 2002), or $BF\% \geq 25$ in the males, or ≥ 38 in the females (Chang, Wu et al. 2003).

Socio-economic status. In addition to investigating the spatial co-distribution of adiposity and urbanicity, we also evaluated the degree to which the

spatial distribution of adiposity was explained by individual-level SES. To capture SES, we used a continuous measure of household assets (e.g. television, land, etc.) derived from a principal components analysis (previously used in Victoria, Adair et al. 2008).

Analytical methods

A spatial cluster can be defined as a contiguous geographic space for which the value of some characteristic is unusual when compared to the space surrounding it. The characteristic we are interested in is the prevalence of elevated adiposity in our sex stratified sample. To detect clusters, we used the spatial scan statistic as implemented by the software SaTScan and employed the Bernoulli Model (Kulldorff and Nagarwalla 1995; Kulldorff 1997), which is appropriate for detecting clusters when the outcome is binary.

We started by deriving the center-point of each barangay using ArcGIS, giving a set of Cartesian coordinates (x,y) that were then associated with individuals in the sample based on their barangay of residence. The result is a set of point locations characterized by their Cartesian coordinates, the number of “cases” of each outcome (individuals with elevated adiposity), and total number of study participants at that location.

For every point location, SaTScan draws multiple scan windows, centered on that point, that steadily increase in size, the largest of which contains $\leq 50\%$ of the total study population. For each of these windows, a prevalence (p) is calculated as the number of observed cases divided by the total population

residing within the window. This is compared to the observed prevalence (q) for participants residing outside the given window, resulting in a prevalence ratio ($PR=p/q$). The null hypothesis tested for each window is $H_0: p/q=1$. In this analysis, we set out to detect clusters of higher *and* lower than expected prevalence, thus the alternate hypothesis is $H_1: p/q \neq 1$.

The goal is to detect the least likely cluster, represented by the window with a prevalence ratio that is the least likely to occur given H_0 . To do this, a likelihood is calculated for each window. For the Bernoulli model detecting both high and low prevalence clusters, the likelihood function is:

$$\left(\frac{c}{n}\right)^c \left(\frac{n-c}{n}\right)^{n-c} \left(\frac{C-c}{N-n}\right)^{C-c} \left(\frac{(N-n)-(C-c)}{N-n}\right)^{(N-n)-(C-c)}$$

where c is the number of cases in the window, C is the total number of cases in the sample, n is the number of observations in the window, and N is the total number observations in the sample (Kulldorff 1997). The likelihood function is maximized over all the windows, and the one with the maximum likelihood is identified as the cluster that is least likely to have occurred by chance. This cluster is the “primary cluster.”

To obtain a p-value, the same analysis is repeated on 999 random replications of the data generated under the null hypothesis, and the maximum likelihood from the real data is ranked (R) along with maximum likelihoods from each of these Monte Carlo simulations. The p-value of the least likely cluster is given by $R/1000$. For this analysis we have elected to report all primary clusters (regardless of p-value), and any secondary clusters, defined in this analysis as

any cluster for which H_0 can be rejected on its own strength (at $p < 0.15$) but that doesn't geographically overlap with the primary cluster.

The shape of the scan window used to detect clusters can take on a variety of forms. We chose to use an elliptical scan window (Kulldorff, Huang et al. 2006) because the urban core of Metro Cebu is elongated, running roughly southwest to northeast (see figure 3.1). By hypothesizing that adiposity clusters will geographically coincide with the most urban areas of Metro Cebu, we are, in effect, hypothesizing that the clusters will be elliptical in nature. The elliptical scan window has slightly higher power for long narrow clusters, and slightly lower power for circular or more compact clusters (Kulldorff 2006). We used a medium strength non-compactness penalty which favors less eccentric clusters (Kulldorff 2006). In practice, this penalty helps prevent the detection of long, thin clusters that are artifacts driven by high prevalences at the two ends of the ellipse.

We then repeated our analysis, adjusting for individual-level SES. The goal was to evaluate the degree to which spatial clusters of adiposity are explained by the spatial distribution of SES among study participants. In a previous analysis we found strong positive associations between adiposity and multiple indicators of SES in the males, but not in the females (Dahly 2009). The adjustment for SES was made by stratifying the samples by sex-specific tertiles of SES and using the multiple datasets option in SaTScan. More detail on how this adjustment is calculated can be found in the SaTScan users guide (Kulldorff 2006).

Clusters are displayed by outlining the barangays that make up the cluster (in red for high prevalence clusters and in blue for low prevalence clusters), then combining that information with urbanicity maps of the study area using ArcGIS. Urbanicity maps were created using the continuous urbanicity scale, or the barangays' urban-rural designations from the 2000 Philippines census. When appropriate, 95% confidence intervals for prevalence ratios are reported as (PR Estimate; 95% CI Lower Limit to Upper Limit). All reported p-values are two sided.

C. Results

A high prevalence cluster was detected for all four outcome measures in males (table 3.2). Generally, the prevalence of a given outcome among males residing within the respective cluster was more than twice that of males living outside of the cluster. The high prevalence clusters for BMI \geq 23 and BMI \geq 25 were highly unusual ($p < 0.05$) given the null hypothesis of complete spatial randomness. Conversely, the high prevalence clusters for BF% and WC $>$ 85 were not highly unusual ($p = 0.104$ and 0.108 respectively). In every instance, these high prevalence clusters were located in the urban core of Metro Cebu, with minor variations in the set of barangays contained within them (see figure 2). Furthermore, low prevalence clusters were detected in the males for each outcome except WC $>$ 85, and they occurred in the rural south or southwestern regions of Metro Cebu, though the low prevalence of BF% cluster extended into some urban areas (figure 3.2).

Like the males, a high prevalence cluster was detected for all four outcome measures in females (table 3.3), though the BMI \geq 25 and BF% clusters were not highly unusual given the null hypothesis of complete spatial randomness ($p=0.062$ and 0.125 respectively). The prevalence of a given outcome among females living in the respective cluster was generally more than twice that of females living outside the cluster, but almost four times larger for the WC $>$ 80 cluster. Each of these high prevalence clusters was located in the urban core of Metro Cebu (see figure 3.3). There were no low prevalence clusters detected among the females.

To illustrate how informative the urban-rural dichotomy would be for guiding intervention efforts, we redisplayed the male clusters on a map of Cebu barangays defined by the urban-rural dichotomy (figure 3.4). For example, though the magnitude of the prevalence ratio comparing obesity (BMI \geq 25) in urban and rural males (PR 1.80 ;95% CI 1.06 to 3.04) is similar to that found in the high prevalence obesity cluster (PR 2.33; 95% CI 1.56 to 3.47); top left, figure 3.4), if we only intervened in the urban barangays we would be ignoring 18 rural barangays included in the obesity spatial cluster, and acting in 37 urban barangays not included in the spatial cluster. Furthermore, looking at the BF% clusters (bottom right, figure 3.4), intervening to reduce obesity in urban areas would target barangays that are in fact part of a low prevalence cluster.

After adjustment for individual-level SES (table 3.4), there was no evidence of spatial clustering of BMI \geq 25, WC $>$ 85, or BF% \geq 25 in the males. There was still strong evidence of a high prevalence cluster of BMI \geq 23 in the

males, but no evidence for a low prevalence cluster of BMI \geq 23. Adjustment for SES did not appreciably impact the spatial clusters in the females.

D. Discussion

These results highlight the potential for spatial analyses to provide important etiological insights into studies of human health. Whenever disease is spatially clustered (i.e. some areas have an unusual number of cases relative to the expectation that cases are randomly distributed across space) it suggests two things: that there are environmental determinants of the outcome shared by individuals in that area (i.e. contextual effects), and/or that a disproportional number of people in that area are characterized by individual-level variables that affect the outcome (i.e. compositional effects). Overall, our results indicated strong evidence of spatial clustering in overweight, obesity, and central adiposity in a birth cohort of young adults living in Cebu, Philippines.

To better understand the degree to which the obesity clusters were due to contextual effects, we compared the locations of these clusters to urbanicity measured at the barangay level and displayed across the study area. The detected high prevalence clusters for the various adiposity measures consistently included some of the most urban areas of Cebu. However, we did not find highly localized clusters that *only* included the most urban areas. We instead found more dispersed clusters that often extended into peri-urban and even some rural areas. This dispersion suggests that activity spaces in Cebu are not limited to

neighborhood of residence, and/or that the environmental features associated with urban residence have effects that extend beyond neighborhood boundaries.

To evaluate the degree to which the clusters were explained by compositional effects, we then repeated our analysis adjusted for individual-level SES, using a continuous measure of household possessions derived from a principle components analysis (age and sex were already accounted for due to study design). We found that upon adjustment for SES, evidence for clustering of adiposity in the males was much weaker, though there was no impact of the adjustment on the female results. This finding was consistent with a large body of evidence suggesting that SES is an important determinant of obesity in males but not females in lower-income contexts (Sobal and Stunkard 1989; Monteiro, Moura et al. 2004; McLaren 2007). . However, these results should not be seen as evidence that geographic location does not matter, but rather that the spatial distribution of SES is very similar to that of urbanicity in this population.

Understanding the spatial distribution of disease can also aid public health efforts by providing the best possible information on where to focus interventions. Unfortunately, the spatial data required to detect spatial clusters of obesity are often not available. In lower-income countries, this information is typically approximated by looking at obesity outcomes between areas defined as “urban” or “rural.” As obesity intervention efforts in developing countries increase, it seems likely they will rely on these urban-rural differences to target interventions. Our results suggest that targeting obesity interventions in this manner should be done with caution. Though our study area is the second largest metropolitan area

in the Philippines, there is a great deal of environmental heterogeneity in Metro Cebu and targeting interventions at the entire area could be inappropriate. Furthermore, targeting the administratively defined urban areas within Metro Cebu also seems problematic because this descriptor does not accurately describe where the highest prevalences of obesity are. This information is valuable because lower-income countries have fewer public health resources, but must contend with a greater variety of public health problems. Thus any information that increases the efficiency of intervention efforts is especially important in these contexts.

A key strength of the study was our application of the spatial scan statistic to detect adiposity clusters. There are many ways to test for clusters, but the spatial scan statistic is ideal in that it both locates clusters and provides a statistical test of how unusual the clusters are given H_0 . Furthermore, the method accounts for multiple testing; it does not require *a priori* decisions regarding the scale of the analysis; and the clusters are robust to the spatial distribution of cases and controls within them. Another strength was our application of a previously developed scale measure of urbanicity instead of the urban-rural dichotomy to describe our study area. Other strengths of the study include the high quality of the data; an environmentally diverse study area contained in a single contiguous space that facilitated an intra-regional approach; and because the data come from a single study using two stage cluster randomization, there is no detection bias creating the clusters (Forand, Talbot et al. 2002).

This analysis was limited by its cross-sectional nature. We tried to account for the possibility of residential selection by limiting our sample to individuals who still lived in the barangay they were born in; we found that this exclusion had no impact on our results (not reported). Furthermore, we were unable to evaluate the degree to which time spent in an urban area impacts obesity risk (Sobngwi, Mbanya et al. 2004).

Another potential limitation of the study is that there are very few obese people in this sample. The sample is fairly young and childhood obesity is not yet a serious public health problem in Cebu. This is not to suggest that adulthood obesity is not a problem in Cebu (increases in childhood obesity typically follow increases in adulthood obesity as a population moves through its nutritional transition). The mothers of this birth cohort underwent a remarkable 6-fold increase in overweight and obesity prevalence (from 6% to >35%) between 1983 and 1999 (Adair 2004). While the socio-environmental determinants of obesity in the mothers have been investigated (Colchero and Bishai 2008; Colchero, Caballero et al. 2008), we have not yet applied the spatial scan statistic to that sample, though we plan to in the near future.

Given the overall leanness of this sample, we were also concerned that using BMI as a measure of adiposity would also reflect increases in lean mass associated with overall improvements in nutrition in the more developed areas of Cebu. Thus we also included an alternate measure of BF% estimated from skin folds. While we found a high prevalence cluster of BF% that was located in the same place as the high prevalence of $BMI \geq 25$, there was less evidence for the

unusualness of that cluster given the null hypothesis of complete spatial randomness. Though BF% is a more valid measure of adiposity than BMI (which also captures lean mass) it is measured less reliably due to its reliance on skin folds (versus height and weight which are measured much more accurately). Thus measurement error in BF% could have reduced our power to detect the high prevalence cluster. In addition to these measures of overall adiposity, we also used WC to define central adiposity. An interesting finding was that in males we found the weakest evidence of clustering in central adiposity, while in females, evidence of clustering was strongest for central adiposity. More research is needed to investigate the possibility that central fat distribution and total adiposity each have unique environmental determinants that vary by gender.

To date, there has been little research on the environmental determinants of obesity in the developing world. What research there is largely focuses on simple urban rural comparisons of overweight and obesity prevalences. This focus on urban and rural differences will likely be used to target future obesity interventions in these contexts. Our results suggest that care should be taken before targeting efforts at administratively defined urban areas. More etiological research is needed that considers alternate classifications of environment, multiple measures of obesity, and the importance of gender differences. More explicitly spatial analyses are also needed to help understand the roles of space and scale in the development of obesity in rapidly changing environments. Research in these contexts is critical as the emergence of obesity and related

health problems can create a double burden of disease where under-nutrition and infectious illnesses are still major public health problems. Furthermore, if we act soon, we might have a chance to stem the growing obesity problem *before* it reaches the magnitude it has in the West. Given that the rest of the world is urbanizing much more rapidly than the West did, this window to take preventive measures via environmental intervention is closing. Thus research effort aimed at informing environmental intervention efforts in developing country contexts must intensify immediately.

Table 3.1. Adiposity measures in 988 male and 820 female young adults (mean age 22 years) enrolled in the Cebu Longitudinal Health and Nutrition Survey, 2005.

	Males (n=988)			Females (n=820)		
	BMI kg/m ²	WC cm	BF%	BMI kg/m ²	WC cm	BF%
Mean	21.03	72.17	16.70	20.23	67.91	32.65
SD	3.05	7.53	5.10	3.17	7.45	4.77
Median	20.46	70.8	16.07	19.67	66.5	33.05
Maximum	40.33	112	33.59	41.17	112.2	45.56
Minimum	14.48	56.5	3.69	13.93	53.7	17.09
% Overweight ^a	19.7 (17.3 to 22.3)			15.4 (13.1 to 18.0)		
% Obese (BMI) ^b	9.4 (7.7 to 11.4)			7.8 (6.2 to 9.8)		
% Obese (BF%) ^b	6.7 (5.2 to 8.4)			12.2 (10.0 to 14.6)		
% Centrally obese ^c	6.1 (4.7 to 7.7)			6.5 (5.0 to 8.4)		

^aOverweight defined as BMI \geq 23

^bObese alternately defined as BMI \geq 25 or as BF% > 25 in males or >38 in females

^cCentrally obese defined as WC>85 in males or >80 in females

95% confidence intervals for proportions reported as Estimate (Lower Limit to Upper Limit), and calculated using the Wilson procedure (Wilson 1927; Newcombe 1998). BMI body mass index; WC waist circumference; BF% percent bodyfat.

Table 3.2. SaTScan* clusters for multiple anthropometric measures in young adult males (N=988) and females (N=820) enrolled in the CLHNS; Metropolitan Cebu, 2005.

	C	P	Cluster information						
			ID	n	c	p ^b	PR ^c	LLR	p
Males									
BMI≥25	93	0.09	1 ^o	95	0	0.00	-	9.90	0.015
			2 ^o	411	58	0.14	2.33 (1.56 to 3.47)	8.97	0.041
BMI≥23	195	0.20	1 ^o	492	134	0.27	2.21 (1.68 to 2.92)	17.74	0.001
			2 ^o	95	3	0.03	0.15 (0.05 to 0.45)	12.64	0.002
WC>85	60	0.06	1 ^o	428	41	0.10	2.82 (1.66 to 4.79)	8.12	0.104
BF%≥25	66	0.07	1 ^o	202	2	0.01	0.12 (0.03 to 0.49)	9.28	0.021
			2 ^o	478	47	0.10	2.63 (1.57 to 4.43)	7.57	0.108
Females									
BMI≥25	64	0.08	1 ^o	405	47	0.12	2.83 (1.65 to 4.84)	8.31	0.062
BMI≥23	126	0.15	1 ^o	407	85	0.21	2.10 (1.48 to 2.97)	9.96	0.020
WC>80	53	0.06	1 ^o	405	42	0.10	3.91 (2.04 to 7.49)	10.71	0.010
BF%≥38	100	0.12	1 ^o	214	43	0.20	2.13 (1.48 to 3.07)	7.72	0.125

^aSaTScan Bernoulli model; elliptical scan window; medium non-compactness penalty; maximum cluster ≤ 50% of the population; overlapping clusters not reported; p-values two sided.

^b Prevalence defined as (cases/n) within a cluster

^c Ratio of the prevalence inside a cluster to the prevalence outside of the cluster. 95% CIs reported as Estimate (Lower Limit to Upper Limit)

BMI body mass index; C total cases; c cluster cases; P total prevalence; WC waist circumference; BF% percent body fat; ID cluster identifier (1^o primary cluster; 2^o secondary cluster); PR prevalence ratio; LLR log likelihood ratio

Table 3.3. Least likely SES adjusted SaTScan* clusters for multiple anthropometric measures in young adult males (N=986) and females (N=819) enrolled in the CLHNS; Metropolitan Cebu, 2005.

	C	P	Cluster information						
			ID	n	c	P ^b	PR ^c	LLR	p
Males									
BMI≥25	93	0.09	1 ^o	402	57	0.14	2.30 (1.55 to 3.42)	7.93	0.108
BMI≥23	195	0.20	1 ^o	365	104	0.28	1.97 (1.53 to 2.53)	14.06	0.002
WC>85	60	0.06	1 ^o	355	31	0.09	1.90 (1.16 to 3.10)	5.86	0.413
BF%≥25	66	0.07	1 ^o	358	38	0.11	2.38 (1.48 to 3.81)	6.12	0.337
Females									
BMI≥25	64	0.08	1 ^o	252	34	0.13	2.55 (1.60 to 4.07)	8.87	0.038
BMI≥23	126	0.15	1 ^o	394	82	0.21	2.01 (1.43 to 2.82)	12.34	0.004
WC>80	53	0.06	1 ^o	404	42	0.10	3.92 (2.05 to 7.51)	11.88	0.003
BF%≥38	100	0.12	1 ^o	20	6	0.30	2.55 (1.27 to 5.11)	7.14	0.175

^aSaTScan Bernoulli model; elliptical scan window; medium non-compactness penalty; maximum cluster ≤ 50% of the population; overlapping clusters not reported; p-values two sided.

^b Prevalence defined as (cases/n) within a cluster

^c Ratio of the prevalence inside a cluster to the prevalence outside of the cluster. 95% CIs reported as Estimate (Lower Limit to Upper Limit)

BMI body mass index; C total cases; c cluster cases; P total prevalence; WC waist circumference; BF% percent body fat; ID cluster identifier (1^o primary cluster; 2^o secondary cluster); PR prevalence ratio; LLR log likelihood ratio

Figure 3.1. Urbanicity in Metro Cebu, 2005.

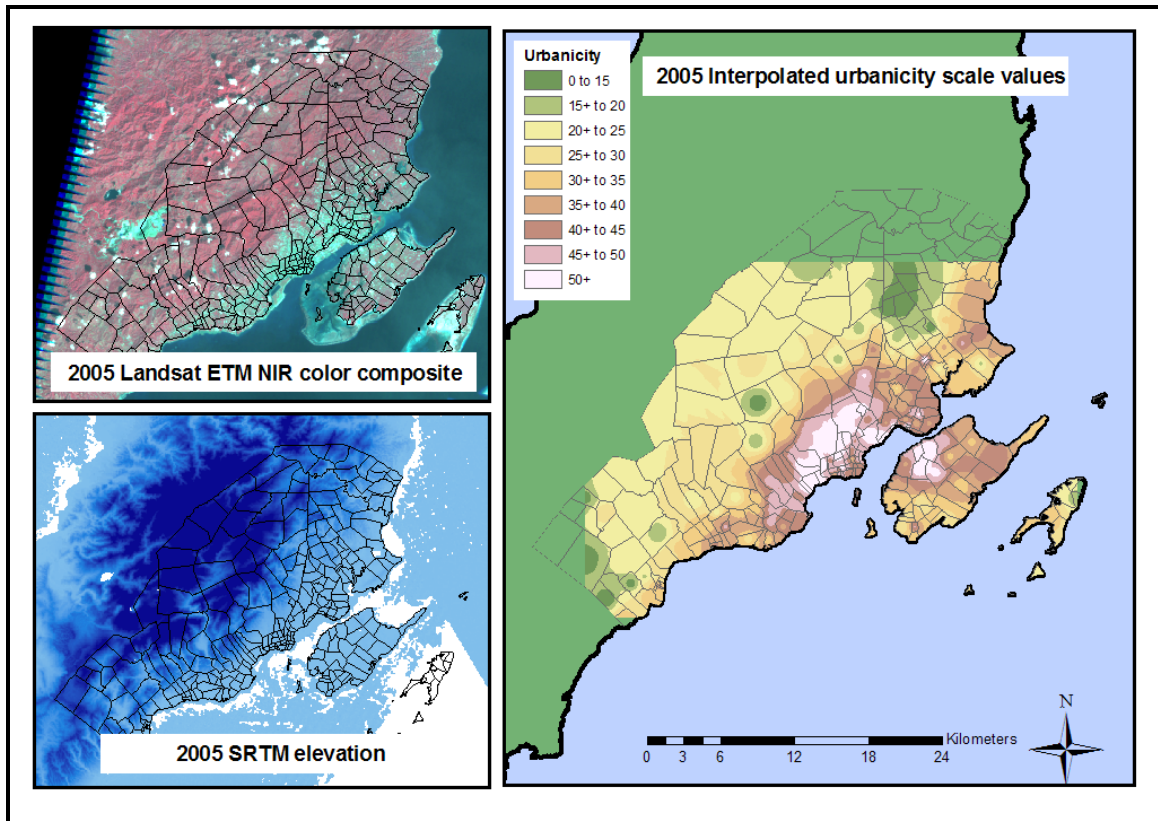
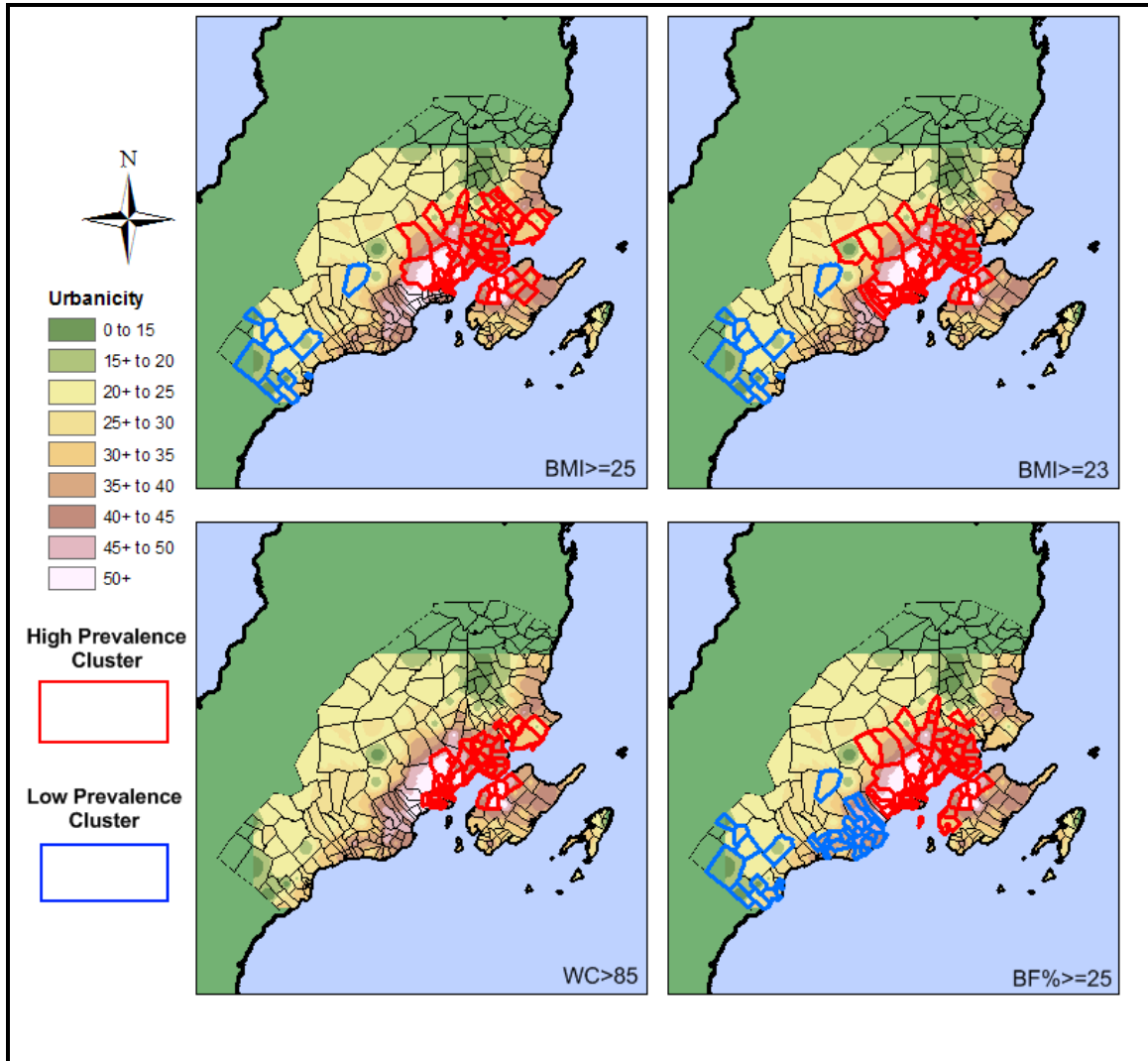
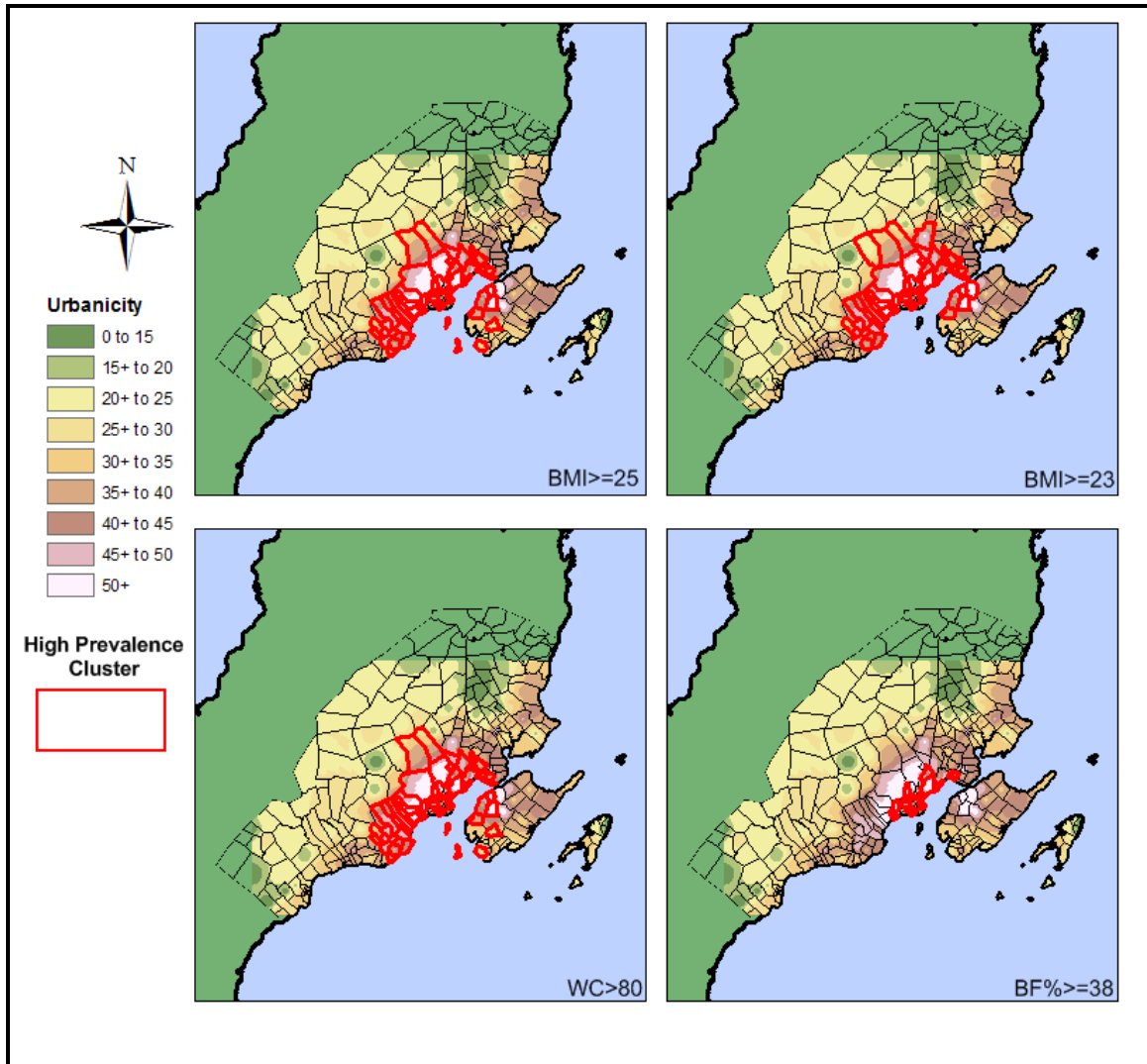


Figure 3.2. High and low prevalence obesity clusters in CLHNS males, n=988 (Cebu, Philippines, 2005).



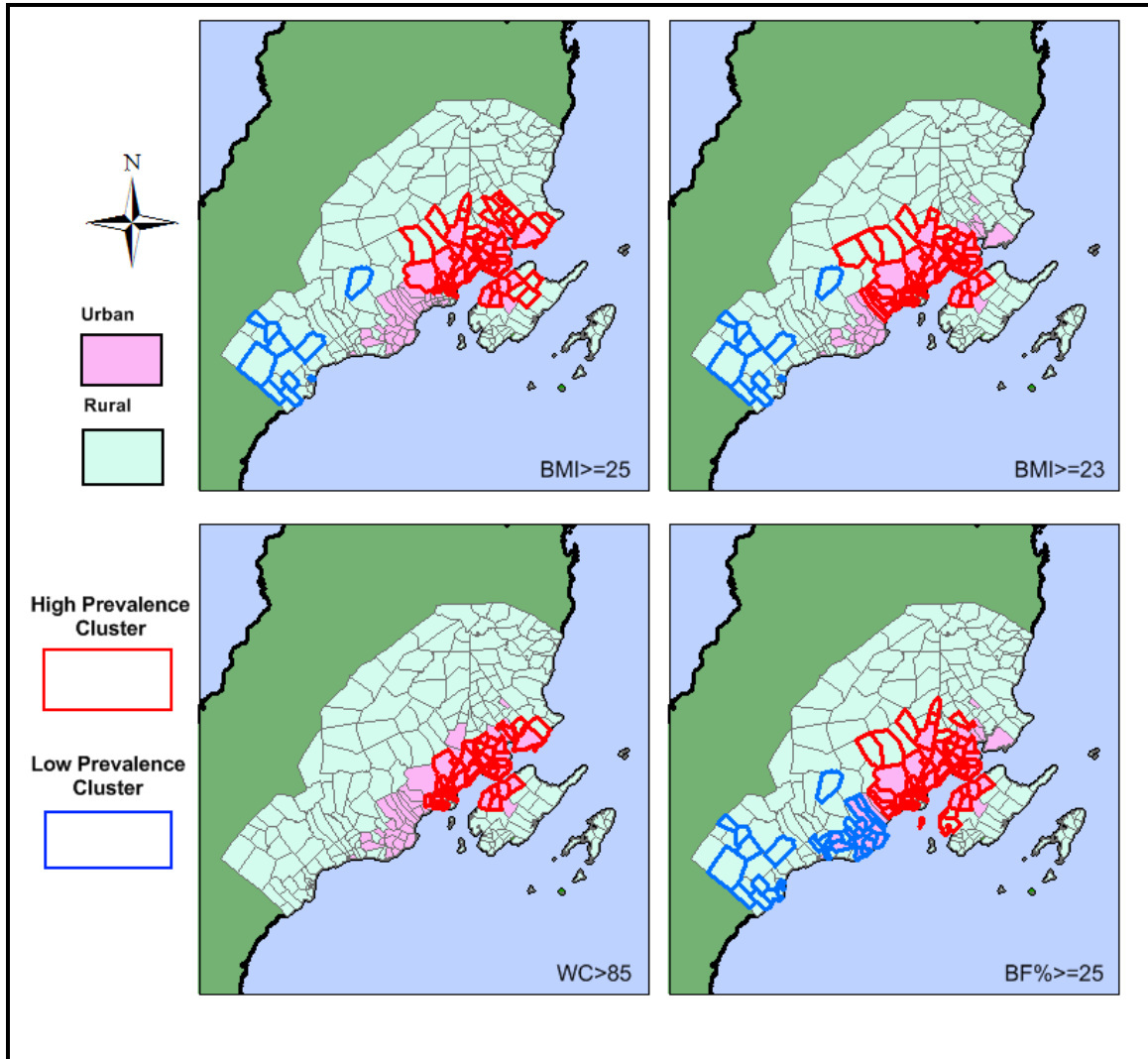
BMI body mass index; WC waist circumference; BF% percent bodyfat

Figure 3.3. High prevalence obesity clusters in CLHNS females, n=820 (Cebu, Philippines, 2005).



BMI body mass index; WC waist circumference; BF% percent bodyfat

Figure 3.4. Male obesity clusters displayed on top of barangays designated as urban or rural (Cebu, Philippines, 2005)



BMI body mass index; WC waist circumference; BF% percent bodyfat

Chapter 4. Socio-environmental determinants of obesity in young adult Filipinos.

A. Introduction

Obesity impacts human health through direct effects on well-being and as a risk factor for various diseases (WHO 2000). Once viewed as a predominantly Western problem, obesity has also emerged as a serious public health problem in many lower and middle-income countries (Popkin and Gordon-Larsen 2004; Prentice 2006; Popkin 2008). The increasing prevalence of obesity in these contexts is broadly driven by socioeconomic development, which in turn promotes obesogenic dietary and activity behaviors (Popkin 2008). Consequently, there is a substantial body of research focused on the association between socioeconomic status (SES) and obesity.

Sobal and Stunkard published the first major review of studies reporting associations between socioeconomic status (SES) and obesity (Sobal and Stunkard 1989). Their review highlighted the importance of “social research” in explaining the global rise in obesity prevalence, and provided compelling evidence for a socioeconomic disparity in obesity, particularly among women, in higher-income contexts. Conversely, their review found that obesity was largely a problem associated with affluence for both men and women in lower-income

countries. However, evidence soon emerged from Brazil which suggested that the burden of obesity was shifting towards lower SES strata, particularly in women (Monteiro, Mondini et al. 1995; Popkin, Paeratakul et al. 1995). This inverse SES-obesity relationship has now been observed in a variety of lower and middle-income contexts (Martorell, Khan et al. 1998; Martorell, Khan et al. 2000; Monteiro, Conde et al. 2004; Monteiro, Moura et al. 2004; McLaren 2007). Furthermore, evidence suggests that this shift progresses as a function of economic development and urbanization (Monteiro, Conde et al. 2004; Monteiro, Moura et al. 2004; McLaren 2007).

An important gap in this literature is that most previous studies have focused on single indicators of SES such as education or income, or composite scores that combined multiple indicators. However, some studies have found contrasting effects of individual SES indicators, such as income and education (e.g. Monteiro, Conde et al. 2001). Consequently, our interpretation of the relationship between SES and obesity in a particular context may be influenced by the SES indicator investigated. Furthermore, understanding the concurrent impact of multiple SES indicators could yield important etiological insights.

Our primary goal was to help address this gap by investigating cross-sectional associations between obesity and multiple indicators of SES in a birth cohort of young adults enrolled in the Cebu (Philippines) Longitudinal Health and Nutrition Survey (CLHNS). We also tested the hypothesis that the SES-obesity gradient would vary as a function of urban development at the intra-regional level, using a continuous scale measure that captures urban heterogeneity within

a contiguous area (Dahly and Adair 2007). This contrasts with, and compliments, previous studies which have looked at differences in the SES-obesity relationship across different levels of economic development, either by comparing countries (e.g. Monteiro, Conde et al. 2004; Monteiro, Moura et al. 2004), or distinct geographical regions within countries (e.g. Monteiro, Conde et al. 2001).

B. Methods

Study design and sample

Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community based study of a one-year birth cohort living in Metropolitan Cebu (pop 1.9 million), Philippines. The study area includes 270 administratively defined communities called *barangays* (average area 2.65 km²), comprising a 720 km² contiguous area. A single stage cluster sampling procedure was used to randomly select 33 barangays, and pregnant women residing in these barangays were recruited for the study in 1982 and 1983. Those who gave birth between May 1, 1983, and April 30, 1984, were included in the sample. More than 95% of identified women agreed to participate. A baseline interview was conducted among 3,327 women during their 6th or 7th month of pregnancy. Another survey took place immediately after birth; there were 3,080 non-twin live births which make up the CLHNS birth cohort. Subsequent surveys

were conducted bi-monthly to age 2 y, then in 1991, 1994, 1998, 2002, and 2005.

We used 2005 birth cohort data (n=1885) when the study participants were young adults (mean age 21.5 years). Women pregnant in 2005 were excluded (n=73). Anyone with missing data on variables of interest were also dropped (4 males and 2 females), resulting in a final sample of 987 males and 819 females (96% of the total 2005 sample).

The analysis sample of 1806 males and females is 59% of the original 3080 single live births recruited for the study. This is overwhelmingly due to the loss to follow-up characteristic of longitudinal studies of this length. The 1806 individuals included in this analysis sample did not differ at baseline (1983) from the 1274 single live births also recruited at baseline (by t-test or chi square, $p \leq 0.05$) in mean household income and assets; or maternal education, BMI, and height. However, the analysis sample did have slightly higher birth weights (difference 0.06 kg, 95% CI 0.03 to 0.09), and lengths (0.18 cm, 95% CI 0.03 to 0.33). The gender distribution was also different in 2005 than at baseline (45% versus 49% female).

Measures

Body size measures were collected by trained field staff during in-home interviews using techniques described in Lohman et al. (1988). Weight was measured with a mechanical scale to the nearest kg, while height was measured with a folding stadiometer to the nearest tenth of a cm. Body mass index (BMI)

was calculated as weight (kg) divided by height (m) squared. Waist circumference (WC) was measured in cm at the midpoint between the bottom of the ribs and the top of the iliac crest. BMI is a measure of weight adjusted for height. While BMI does not describe fat distribution, or differentiate fat mass from lean body mass, it is a reasonably good predictor of overall body fat (Wang, Thornton et al. 1994; Deurenberg, Yap et al. 1998). WC is a measure of centrally distributed adipose tissue, which is thought to be particularly relevant for a number of disease outcomes (Klein, Allison et al. 2007). Based on these two measures, we dichotomously defined overweight as BMI ≥ 25 , and central adiposity as a WC > 85 cm for males and a WC > 80 cm for females (Bei-Fan 2002). Though these cutpoints are fairly low, evidence suggests that cardiovascular outcomes are associated with lower levels of fatness in Asian populations than in Caucasians (Misra 2003).

In-home interviews were used to assess weekly household income, measured in Philippines pesos (PHP) and deflated to 1983 values. Housing quality and assets indicators were used to create a continuous measure of household assets derived from a principal components analysis (Victora, Adair et al. 2008). Education, based on the highest grade completed by the study participant was categorized using indicator variables as: *no schooling or any primary school; attended any secondary school; and attended any college*. Marital status was attained by asking participants whether they were living with a spouse or partner (*yes/no*).

We used one barangay-level variable, urbanicity, which refers to the urban nature of a barangay. While most researchers use the urban-rural dichotomy to describe urbanicity, we used a continuous measure that captures a range of variation in urbanicity (from rural to highly urban) across a single dimension (Dahly and Adair 2007; Dahly 2009). Briefly, the scale is made up of seven components derived from data collected for the CLHNS barangay level surveys. The components are population size; population density; communications (availability of mail, telephone, internet, cable TV, and newspaper services); transportation (paved road density and public transportation services); markets (presence of gas stations, drug stores, grocery stores and the number of small commercial kiosks); educational facilities; and health services. Theoretically, the scale represents an underlying latent construct, labeled urbanicity, that is imperfectly reflected in each of these seven components, and could be viewed as a localized proxy for economic development.

C. Analytical methods

Due to the design of the CLHNS, individuals are clustered by barangay of residence. Because social and built environments impact obesity risk (Hill and Peters 1998; Booth, Pinkston et al. 2005; Gordon-Larsen, Nelson et al. 2006), we expect individuals living in the same barangay to be more similar to each other, with respect to obesity outcomes, than they are to individuals living in other barangays (i.e. observations within barangays are statistically dependent). This dependence was confirmed in a preliminary analysis, for which we used empty

random-intercept logistic regression models to estimate the intra-class correlations (ICCs) for overweight and central adiposity in our sample. The ICCs represent the proportion of variation in the outcomes described at the barangay level, and thus the degree of dependence. In the males, the estimated ICCs for overweight and central adiposity were 0.18 (95% CI 0.06 to 0.45) and 0.10 (95% CI 0.01 to 0.46) respectively. For females the respective estimated ICCs were 0.05 (95% CI 0.01 to 0.30) and 0.18 (95% CI 0.05 to 0.46). Ignoring this statistical dependence could result in biased confidence intervals around parameter estimates. Additionally, the sample we analyzed started the study living in 33 barangays but now reside in 161 barangays, due to the 26% of this sample that has migrated within the study area between birth and young adulthood. The result is a heavily unbalanced dataset (which is problematic for a number of statistical methods) for which most barangays included in the analysis have fewer than 3 observations.

To account for these issues, we employed generalized estimation equations (GEE; Zeger, Liang et al. 1988; Hubbard, Ahern et al. 2008) with an exchangeable correlation structure to estimate the population-averaged (i.e. marginal) effects of the independent variables of interest. We began by estimating a series of gender stratified models to estimate the unadjusted effect of each SES variable and urbanicity on overweight or central adiposity, thus placing our research in the context of previous studies that investigated a single measure of SES. Nonlinearities in continuous variables were tested using quadratic terms and retained in the models when $p < 0.05$. We then estimated

multivariable models that included the four SES variables and urbanicity. We tested for multiplicative interactions among these variables, which were retained in the models when their respective Wald test p was <0.10 (or by chunk tests with $p \leq 0.10$ for interactions involving categorical variables). All continuous variables were mean centered, but left unstandardized to facilitate gender comparisons. All reported p -values are two sided.

D. Results

Sample characteristics are reported in table 4.1. Overall, the sample is young (mean age 21.5 years) and lean (mean BMI 20.2 and 21.0 for males and females respectively). Overweight and/or central adiposity were found in 11% of the total sample, compared to the 22.1% of the total sample classified as underweight (BMI <18.5). The distribution of income and assets were similar for males and females, though females were more likely to be college educated (34.3% versus 23.8%) and married (27.6% versus 19%) than males.

Results varied by gender, but were similar when comparing outcome measures within gender, so we have focused on describing the overweight (BMI ≥ 25) results. The results for males were similar to those seen in populations in other lower middle-income countries. Each of the SES indicators, as well as urbanicity, was positively related to overweight in the unadjusted models (table 4.2). In the multivariable model, only assets, marital status, and college education remained strong predictors of overweight. The relationship between assets and odds of overweight was particularly strong. A one standard deviation

increase over the mean assets score (*SD* 2.96; total range 19.4) was associated with a 64% increase in the odds of overweight (OR 1.64, 95% CI 1.26 to 2.13).

Unlike the males, marital status was the only crude predictor of overweight in the females (table 4.3). Though there was no discernable relationship between education and overweight in females (OR 0.82, 95% CI 0.27 to 2.50), it was notably the only SES indicator with a point estimate that suggested an inverse relationship.

An inhibitive interaction between urbanicity and assets emerged in the multivariable model for females (no other interactions were detected in either gender). This could be interpreted as a reduction in the positive impact of assets on overweight as urbanicity increases, or vice-versa. The difference in the estimated impact of assets on the odds of overweight at the ends of the observed urbanicity distribution was considerable. At the lowest observed level of urbanicity (8.0 points), a one point increase in assets was associated with a 29% increase in the odds of overweight (OR 1.29, 95% CI 1.01 to 1.65; figure 4.1); at the highest observed level of urbanicity (60.6 points), the same increase in assets was conversely associated with a 8% reduction in the odds of overweight (OR 0.92, 95% CI 0.76 to 1.11). The ratio of these ORs was 1.40 (95% CI 0.97 to 2.03). We also explored the nature of this interaction by looking at the prevalence of overweight in groups crudely defined by tertiles of assets and urbanicity (figure 4.2). Within the lower two tertiles of urbanicity, there is no clear relationship between assets and the prevalence of overweight. However, among women living in the most urban areas, there is an emerging trend for which the

prevalence of overweight declines with increasing assets. The lowest prevalence of overweight in the entire sample is found for highly urban women with high assets scores (<1%).

E. Discussion

We observed a pattern of relationships between SES and overweight and central adiposity that is consistent with studies from other countries with similar levels of economic development (Monteiro, Moura et al. 2004) (2005 Philippines per capita GNP was 1304 US\$). Assets, income, and college education were all crude, positive predictors of overweight and central adiposity in males from our study. In the final multivariable model, assets were the most important predictor, overshadowing the estimated impact of income. This is probably because the assets score, which is derived from a principle components analysis of interviewer observed indicators of assets and housing quality, was a more valid and/or reliable measure of wealth than income, which is based on respondent reports of multiple sources of household income. The estimated impact of college education was attenuated in the multivariable model, but still positively related to overweight and central adiposity. Conversely, in the females, only marital status was a strong predictor of overweight and central adiposity. However, the multivariable models revealed an important interaction between assets and urbanicity. Among the most rural women, assets were positively related to overweight or central adiposity, while in the more urban areas, assets were not related to overweight or central adiposity.

Studies of the relationship between SES and obesity are beginning to produce important insights into rising obesity prevalences in lower and middle-income countries. This body of research was initially focused on socioeconomic disparities in obesity. In higher income countries, SES tends to be inversely related to obesity, particularly among females (Sobal and Stunkard 1989; McLaren 2007). Conversely, in lower-income countries, it was once thought that obesity was only a problem for the affluent (Sobal and Stunkard 1989). However, evidence such as ours suggests that suggests that the SES-obesity gradient is inversely shifting, becoming more like that seen in high-income countries. Furthermore, this shift seems to be occurring in women first, and as a function of economic development (Monteiro, Conde et al. 2004; Monteiro, Moura et al. 2004).

The early focus on socioeconomic disparities in obesity was reinforced by the fact that most previous studies investigated single indicators of SES such as education or income, or composite scores that combined multiple indicators. This implies a “unitary view” (Bollen, Glanville et al. 2001) whereby SES (alternately social-class, or socio-economic position) is treated as an underlying construct that is similarly reflected in multiple, largely interchangeable, measures (e.g. wealth, education). However, other research has indicated that individual indicators of SES may have varied, or even antagonistic, effects on obesity (Popkin, Paeratakul et al. 1995). A lack of studies looking at the independent effects of multiple SES indicators was a key gap that we aimed to address.

Our results were consistent with studies that have looked at the independent effects of multiple indicators of SES, particularly income and education, in lower and middle-income countries. For example, a study of Brazilian adults living in two regions of the country that differed in their level of economic development (Monteiro, Conde et al. 2001), found that the estimated effects of income and education varied as a function of both gender and region of residence. Income was a positive predictor of obesity ($BMI \geq 30 \text{ kg/m}^2$) in males living in both regions, while education was inversely associated with obesity in the more developed region. For females, income was positively related to obesity only in the less developed region, while education was inversely related to obesity in both regions.

Given these observations from Brazil, it is notable that in our study, college education in females was the only SES indicator whose point estimate suggested an inverse relationship. Similar gender differences with regard to education have been recently reported in Asian populations in Thailand (Aekplakorn, Hogan et al. 2007), and Korea (Yoon, Oh et al. 2004). Furthermore, the interaction between assets and urbanicity in females also mimics the trend seen in Brazil, as well as the broader national level trends for which SES tends to be positively related to obesity in lower-income contexts, and inversely associated with obesity in higher-income countries (Monteiro, Conde et al. 2004; Monteiro, Moura et al. 2004). To our knowledge, our study is the first time this dynamic has been illustrated within a single contiguous study area. Our results also illustrate the importance of investigating “more carefully the extent of

interactions between characteristics of individuals and the features of places associated with varying health risks” (Cummins, Curtis et al. 2007).

Lastly, our research has helped confirm that the relationship between SES and body size is much more complicated than that suggested by previous studies which have focused on a single SES indicator. More studies of the independent effects of multiple SES indicators are needed to help improve our understanding of the etiology of obesity in a transitioning society. Our results, combined with previous research, suggest that at low levels of economic development, material wealth is the primary determinant of food availability, but that as economies develop, barriers to food availability are reduced for the poor, particularly for staple foods, and jobs tend to require less physical activity across SES strata. Eventually obesity risk is reduced among high SES groups because they are better equipped to make informed food choices (by being better educated and/or because they face fewer economic and geographic barriers to healthy food).

Individual indicators of SES tended to be positively related to overweight and central adiposity in males, and unrelated to overweight and central adiposity in females. However, once the modifying effects of urban residence were accounted for, assets were positively related to overweight and central adiposity among the most rural women, but not among more urban women. These dynamics mimic broader trends for which the relationship between SES and obesity shifts from a positive nature to an inverse one as a function of economic development, even at the intra-regional level. Furthermore, our results were consistent with previous research suggesting that this shift occurs in females

first, and that changes in the impact of education precede changes in the impact of wealth. These results have important policy implications. Though the prevalences of overweight and central adiposity are low in this sample of young adults, we observed a pattern of relationships that is consistent with countries further along in their economic transition. This strongly suggests the public health impact of obesity will increase as the Philippines continues to develop economically. Furthermore, future public health interventions aimed at preventing obesity in lower income contexts should not assume that higher SES populations are the primary target. Lastly, our results confirm that future studies of the relationship between SES and obesity should do their best to consider the independent effects of multiple SES indicators, particularly wealth and education, as well as interactions between these individual level characteristics with environmental features such as urbanicity.

Table 4.1. Sample characteristics study participants (male n=987; female n=819) enrolled in the CLHNS, 2005.

		Females	Males
Age (yrs)	Mean _(sd)	21.5 _(0.31)	21.5 _(0.30)
BMI (kg/m ²)	Mean _(sd)	20.2 _(3.2)	21.0 _(3.1) *
	% overweight	7.8	9.4
WC (cm)	Mean _(sd)	67.9 _(7.5)	72.2 _(7.5) *
	% central adiposity	6.5	6.1
Assets	Mean _(sd)	0.1 _(2.8)	0.0 _(2.9)
	Range	-3.4 to 15.7	-3.3 to 16.0
Income (100 PHP)	Mean _(sd)	5.9 _(5.9)	5.4 _(5.9)
		0 to 40	0 to 40
Education (%)	No secondary school	7.9	20.7
	Any secondary school	57.8	55.5
	Any college	34.3	23.8*
Lives with spouse (%)		27.6*	19.0*
Urbanicity	Mean	41.0	40.6
	Range	8-61	8-61
Barangay N		127	136

* Significant difference between genders assessed by t-test or chi-square with $p \leq 0.05$.

Table 4.2. Estimated impact of multiple socioeconomic indicators and urbanicity on obesity ($BMI \geq 25 \text{ kg/m}^2$) and central adiposity ($WC > 85 \text{ cm}$) in 987 Filipino young adult males.

Independent variables	Dependent variable			
	Male overweight ($BMI \geq 25$)		Male central adiposity ($WC > 85 \text{ cm}$)	
	OR (95% CI)			
	Unadjusted*	Adjusted**	Unadjusted*	Adjusted**
Urbanicity (10 pts)	1.22 (0.99 1.51)	1.06 (0.85 1.32)	1.25 (0.99 1.57)	1.06 (0.82 1.35)
Assets	1.20 (1.13 1.28)	1.19 (1.08 1.30)	1.25 (1.17 1.34)	1.22 (1.10 1.35)
Income (100 PHP)	1.05 (1.02 1.08)	1.00 (0.96 1.04)	1.07 (1.04 1.10)	1.00 (0.96 1.04)
Any secondary school	1.40 (0.71 2.75)	1.26 (0.62 2.56)	1.43 (0.59 3.51)	1.18 (0.46 2.99)
Any college	3.33 (1.66 6.69)	2.22 (0.99 5.00)	4.57 (1.88 11.11)	2.37 (0.85 6.58)
Married	1.81 (1.12 2.94)	3.04 (1.76 5.25)	1.29 (0.70 2.42)	2.52 (1.26 5.07)

* ORs from unadjusted models estimate the crude relationship between the given independent and dependent variables.

**ORs from the adjusted models estimate the relationship between the given independent and dependent variables, adjusted for all of the other independent variables.

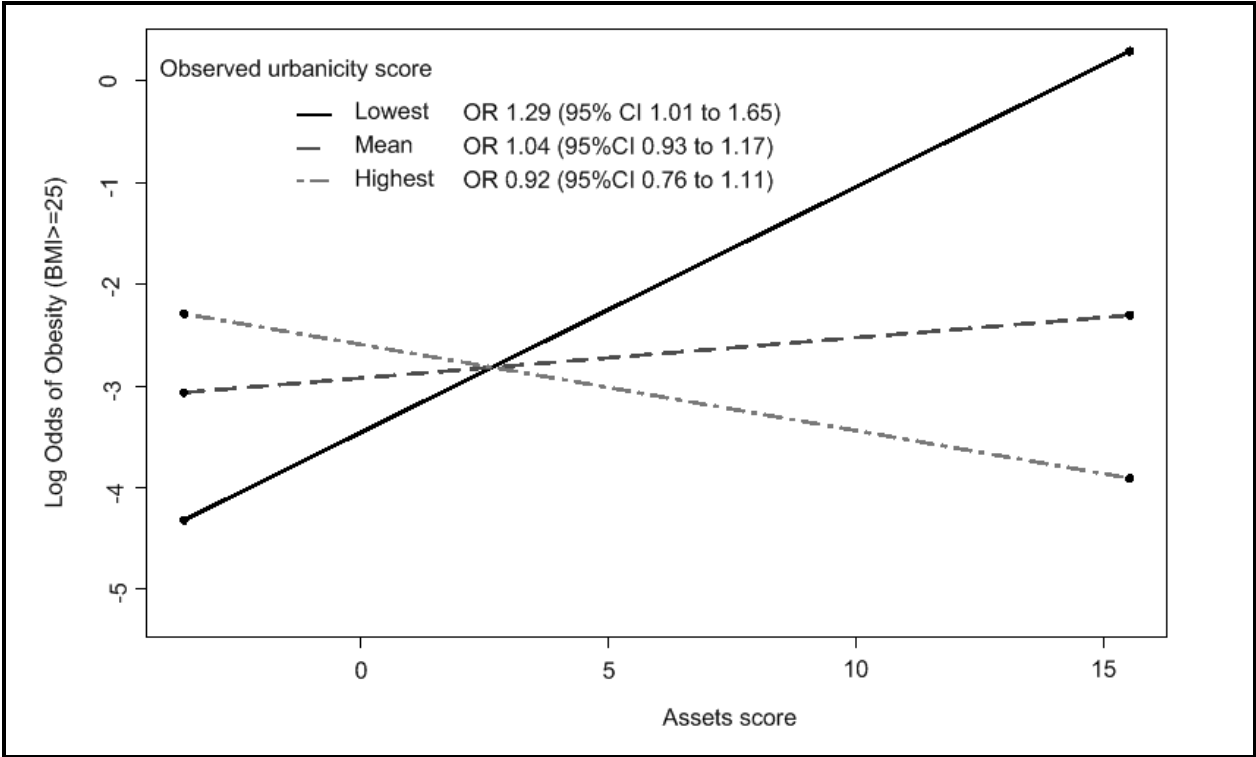
Table 4.3. Estimated impact of multiple socioeconomic indicators and urbanicity on overweight (BMI \geq 25 kg/m²) and central adiposity (WC>80 cm) in 819 Filipino young adult females.

Independent variables	Dependent variable			
	Female overweight (BMI \geq 25)		Female central adiposity (WC>80cm)	
	OR (95% CI)			
	Unadjusted*	Adjusted**	Unadjusted*	Adjusted* ^l
Urbanicity (10 pts)	1.20 (0.95 1.52)	1.19 (0.93 1.51)	1.27 (0.95 1.69)	1.28 (0.95 1.71)
Assets	0.99 (0.91 1.08)	1.04 (0.93 1.17)	1.02 (0.93 1.12)	1.10 (0.97 1.24)
Income (100 PHP)	1.01 (0.97 1.05)	1.01 (0.97 1.06)	1.02 (0.98 1.06)	1.02 (0.97 1.07)
Any secondary school	1.49 (0.53 4.21)	1.54 (0.53 4.44)	1.18 (0.42 3.32)	1.10 (0.38 3.20)
Any college	0.82 (0.27 2.50)	0.85 (0.24 2.99)	0.56 (0.18 1.78)	0.50 (0.13 1.86)
Married	2.06 (1.21 3.50)	1.94 (1.11 3.41)	2.95 (1.64 5.31)	3.01 (1.62 5.60)
Assets X Urbanicity	-	0.94 (0.87 1.01)	-	0.94 (0.87 1.01)

* ORs from unadjusted models estimate the crude relationship between the given independent and dependent variables.

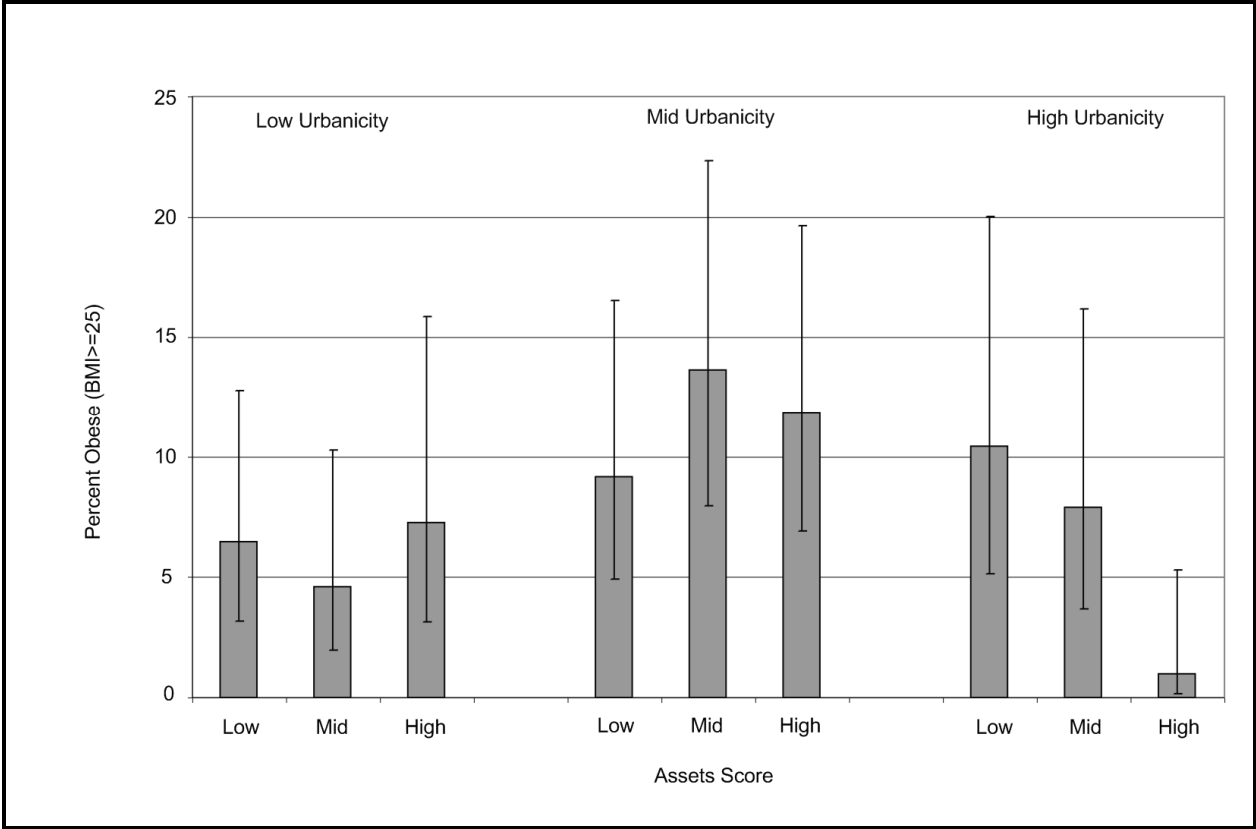
**ORs from the adjusted models estimate the relationship between the given independent and dependent variables, adjusted for all of the other independent variables.

Figure 4.1: Differential impact of assets on the log odds of overweight by level of urbanicity among 819 young adult Filipino females.



BMI – Body Mass Index; OR – Odds ratio; CI confidence interval

Figure 4.2. Prevalence of overweight (BMI \geq 25) by levels of urbanicity and household assets among 819 young adult Filipino females.



BMI – Body mass index.
 95% confidence intervals for proportions calculated using the Wilson procedure (Wilson 1927; Newcombe 1998).

Chapter 5. Lower birth order amplifies the association between high socio-economic status and central adiposity in young adult Filipino males: support for the mismatch hypothesis.

A. Introduction

Obesity is a serious challenge to global public health (WHO 2000). Public health interventions have traditionally targeted individual-level behaviors affecting dietary intake and physical activity, but these efforts have had no success at reducing obesity prevalences. Consequently, there is growing interest in how social and physical environments influence obesity risk, and efforts to identify mutable, environmental causes of obesity are underway (Hill and Peters 1998; French, Story et al. 2001; Macintyre, Ellaway et al. 2002; Hill, Wyatt et al. 2003; Booth, Pinkston et al. 2005; Popkin, Duffey et al. 2005; Lake and Townshend 2006; Entwisle 2007; Black and Macinko 2008). However, it is equally important to explain heterogeneity in adiposity among individuals that share an environment. Some people are clearly more susceptible to obesogenic environments than others, but why? One explanation is genetic variation; that some people possess *thrifty genes* that increase their susceptibility to modern, obesogenic environments (Neel 1962). However, the importance of thrifty genes

and the degree to which they could explain the modern obesity pandemic is still debated (e.g. van der Sande, Ceesay et al. 2001; Prentice, Hennig et al. 2008).

Another explanation is Gluckman and Hanson's *mismatch hypothesis* (Gluckman and Hanson 2004; Gluckman and Hanson 2004; Gluckman and Hanson 2004; Gluckman, Cutfield et al. 2005; Gluckman, Hanson et al. 2005; Gluckman and Hanson 2006; Gluckman, Hanson et al. 2007; Kuzawa, Gluckman et al. 2007; Pike, Hanson et al. 2008), which falls under the broader Developmental Origins of Health and Disease (DOHaD) paradigm (Gillman 2005). Briefly, it posits that maternal constraint of fetal growth can signal the developing fetus to prepare for a poor nutritional environment. Highlighted causes of maternal constraint include maternal body size, age, diet, and birth order (Gluckman and Hanson 2004; Gluckman and Hanson 2004). The hypothesized fetal response to these signals is an integrated set of adjustments in the way energy is handled in the body (Kuzawa, Gluckman et al. 2007). These adjustments are thought to enhance fitness via improved survival or fecundity during lean times, but could lead to obesity and related metabolic disorders in a nutritionally abundant environment. Ultimately, the mismatch hypothesis posits that prenatal influences can modify how we experience our postnatal environment, and could at least partly explain why some people are more susceptible to obesogenic environments than others.

There is substantial evidence that constraints on fetal growth are associated with offspring obesity later in life. For example, maternal exposure to famine during gestation is associated with increased risk of obesity in the adult

offspring (Ravelli, Stein et al. 1976; Ravelli, van Der Meulen et al. 1999). Other studies have found an inverse association between birth weight and central adiposity once body mass index (BMI) is accounted for, though these associations tend to be mild, and are not consistently detected (Oken and Gillman 2003). Maternal smoking has also been associated with both lower birth size and subsequent obesity later in life (Ong, Preece et al. 2002; Power and Jefferis 2002). However, most previous studies have not explicitly tested the hypothesis that obesity results from an *interaction* between the constraint of fetal growth and later environment. Instead, most studies have estimated direct associations between fetal development and later obesity, irrespective of the postnatal environment. Given the mismatch hypothesis, failure to account for this interaction could lead to underestimation of the relationship between fetal growth and obesity.

Using data from a birth cohort of young adult Filipino males, we tested the hypothesis that lower birth order modified the association between central obesity and socio-economic status (SES), a useful proxy for the obesogenic environment in this context (Dahly 2009). We also examined the influence of birth order on birth size, and explored BMI growth curves (from birth to young adulthood) in groups defined by firstborn status and SES. Although birth order is a hypothesized prenatal influence on later disease (Gluckman and Hanson 2004), and has been associated with reduced birth size (Seidman, Ever-Hadani et al. 1988; Cogswell and Yip 1995; Ong, Preece et al. 2002; Gluckman and Hanson 2004; Miller 2008) and increased risk of central adiposity (e.g. Stettler,

Tershakovec et al. 2000; Ghosh and Bandyopadhyay 2006; Wang, Sekine et al. 2007) and diabetes (Bingley, Douek et al. 2000; Stene, Magnus et al. 2001; Cardwell, Carson et al. 2005), it has not been adequately investigated in epidemiological studies.

B. Methods

Study design and sample

Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based, one-year birth cohort study in Metropolitan Cebu (pop 1.9 million), Philippines. The region includes 270 administratively defined communities called *barangays* (average area 2.65 km²) comprising a 720 km² contiguous area. A single stage cluster sampling procedure was used to randomly select 33 barangays, and pregnant women residing in these barangays were recruited for the study in 1982 and 1983. Those who gave birth between May 1, 1983, and April 30, 1984, were included in the sample. More than 95% of identified women agreed to participate. A baseline interview was conducted among 3,327 women during their 6th or 7th month of pregnancy. Another survey took place immediately after birth; there were 3,080 non-twin live births which make up the CLHNS birth cohort. Subsequent surveys were conducted bi-monthly to age 2, then in 1991, 1994, 1998, 2002, and 2005 (n=1885, 61% retention). For this analysis we used a sample of young adult males still enrolled in the CLHNS in 2005 (mean age 21.5 y) with complete case data (n=970; 98% of the 2005 sample, 59% of the original sample at birth). Males included in this

analysis sample did not differ at from the remainder of the cohort at baseline (by t-test; $p \leq 0.05$) in mean 1983 household assets, birth length, ponderal index, maternal height, maternal AFA, maternal age, or birth order. However, the analysis sample did have slightly higher birth weights (difference 0.05 kg; 95% CI 0.01 to 0.09). Because the socio-environmental determinants of obesity are more complex and poorly understood in females (Dahly 2009), we have excluded them from this analysis.

Measures

The theoretical model that describes the hypothesized relationships among variables included in this analysis is given in figure 5.1. The primary exposure, birth order, was assessed during the baseline interview (1983). Birth order is represented continuously or as firstborn status (versus all others) in our analyses.

First we estimated the impact of birth order on birth size for gestational age. Birth weights (kg) for infants born at home (62%) were measured by trained birth attendants with Salter hanging scales. The remainder, born at hospitals or clinics, were weighed on clinical scales. Lengths (cm) were measured within 6 days of birth using custom made length boards. Ponderal index is a measure of body mass independent of length (though unfortunately it can not distinguish lean mass from fat mass) and was calculated as $\text{weight kg}/\text{length m}^3$. Gestational age was estimated from the mother's self-reported date of her last menstrual period. For cases where this date was unknown, when pregnancy complications

occurred, or when the infant was born weighing less than 2.5 kg, gestational age was clinically assessed using the Ballard method (Ballard, Novak et al. 1979).

To isolate the impact of birth order on birth size, we controlled for several possible confounders. Birth order is inversely associated with maternal SES at birth due to reduced fertility in high SES mothers. SES, in turn, is positively associated with maternal age, height, and arm fat area, and inversely associated with smoking, each of which are determinants of birth size. Failure to control for these factors could obscure any relationship between birth order and birth size. We measured maternal SES at baseline using an assets-based index that reflects longer-term wealth and living standards. This SES index was calculated using a principal components analysis of data on ownership of a variety of household assets at baseline (e.g. television, land, etc) (Vyas and Kumaranayake 2006; Victora, Adair et al. 2008). Maternal height was measured with a folding stadiometer. AFA was calculated from mid-upper arm circumference and triceps skinfold thickness (Lohman, Roche et al. 1988) during the second or third trimester of pregnancy. Maternal smoking was represented dichotomously (yes/no), irrespective of the number of cigarettes smoked. Dummy variables were used to represent younger (<20 years) and older (>35 years) maternal ages, versus a reference age (20-35 years).

Then we estimated the impact of birth order on central adiposity in young adulthood. The primary outcome, waist circumference (WC), was measured by trained interviewers in 2005 at the midpoint between the bottom of the ribs and the top of the iliac crest. High WC was defined using a fairly low cut point of

WC>85 cm that may be more appropriate in Asian populations (Bei-Fan 2002). We again controlled for maternal age, height, and AFA, and smoking because each of these variables could have a developmental effect on later central adiposity. We also controlled for offspring SES in 2005, again using the same continuous index derived from a principal components analysis of 2005 household assets ownership (Vyas and Kumaranayake 2006; Victora, Adair et al. 2008).

C. Analytical methods

First we used multivariable linear models to estimate the effect of birth order and firstborn status on birth weight, length, or ponderal index. Nonlinear effects of birth order were tested using quadratic terms. We then used multivariable linear models to estimate impact of birth order or firstborn status on young adult WC, or log odds of high WC. Again, nonlinear effects of birth order were tested using quadratic terms. We report both the crude estimates and estimates adjusted for potential confounders.

We then added an interaction between birth order (or firstborn status) and 2005 SES (our proxy variable for the post-natal environment) using the appropriate product term. Under the mismatch hypothesis, our expectation was that the positive effects of SES on central adiposity would be amplified in individuals with lower birth orders. Additional interactions were tested between SES and the other prenatal variables in the model that could also moderate the effects of SES under the mismatch hypothesis (maternal age, height, AFA, and

smoking). Interactions were considered significant and reported when the corresponding $p < 0.10$.

All linear models included random intercepts to account for potential dependence among observations caused by the cluster-randomized design of the CLHNS that could lead to biased standard errors for estimated regression coefficients. Because we are not otherwise interested in interpreting estimated random effects for this analysis, we do not report them. All reported p-values are two-sided. All models were run using Stata, version 10.0 (Stata corp., College Station, Texas).

In an exploratory analysis, we evaluated the mean BMI growth curves from birth to young adulthood of four groups defined by firstborn status (versus not) and high versus low maternal SES measured at birth (defined by the median). This was to help evaluate whether firstborn status coupled with high SES was associated with a postnatal growth trajectory characterized by early catch up growth. Heights and weights were recorded bimonthly from birth to age two, and at ages 8.5y, 11.5y, 16y, 19y, and 21.5y. BMI was calculated as weight kg/height m^2 .

D. Results

Sample characteristics are reported in table 5.1. The sample in 2005 had a mean age of 21.5y. They were characterized by low mean WC (72.2 cm; *sd* 7.6) and body mass index (21.0; *sd* 3.1). Only 6% were classified as having high WC. The median birth order was 3, and ranged from 1-15. 22% were classified

as firstborn. A higher proportion of firstborns compared to higher order births were preterm (21.6% versus 15.2%, $\chi^2 p=0.027$) or small for gestational age (36.6% versus 23.5%, $\chi^2 p<0.000$).

Firstborn status was associated with reduced birth weight, length, and ponderal index, adjusted for gestational age (table 5.2). The relationship between continuously measured birth order and birth weight, length, or ponderal index, was best described by a third order polynomial model (table 5.2, figure 5.2), though the impact of birth order on length after adjustment was not significant at $p\leq 0.05$. Higher order births were increasingly larger up to the sixth born. Birth weight then decreased as birth order increased. The final upward trend was likely spurious, due to the small sample sizes at that end of the birth order distribution. The model was not altered by the exclusion of two outliers with recorded birth weights under 1 kg. Young maternal age, height and AFA were important determinants of birth length but not ponderal index; and maternal smoking, like birth order, was an important determinant of ponderal index but not length.

Firstborn status and lower birth order were associated with WC and log odds of high WC (table 5.3). The association between birth order and WC (or log odds of high WC) was linear (versus the nonlinear association we observed between birth order and birth size). After adjustment for potential confounders, this relationship was attenuated. Maternal height and AFA were consistent, positive predictors of central obesity. We failed to detect non-linearities in these variables using quadratic terms that tested the hypothesis that there was risk at

both ends of their respective distributions. Maternal smoking and age were not meaningful predictors of WC. Model results were not appreciably altered when the natural log of WC was used, nor when preterm birth (*yes/no*), small for gestational age (*yes/no*), or birth size variables were included as covariates (models not shown).

We detected a meaningful interaction between 2005 SES and birth order that was consistent with the mismatch hypothesis (table 5.4). For example, based on the estimated coefficients, a one SD increase in SES (2.9; observed range -3.4 to 16.0) would be associated with a 149% increase in odds of high WC (OR 2.49; 95% CI 1.65 to 3.76). However, the same increase in SES coupled with an increase in birth order would be associated with a 114% increase in odds of high WC (OR 2.14; 95% CI 1.58 to 2.89). The interaction could be viewed as a reduction in the positive impact of SES among individuals with higher birth orders (see figure 5.3). We found no evidence for a similar interaction between SES and the other prenatal variables (maternal age, height, AFA, smoking). We repeated our models, replacing 2005 SES with the same measure from 1983 to ascertain the relative importance of early versus later SES (model not shown). The estimated impact of early SES on central obesity was weaker than that of current SES, and there was no interaction between birth order and early SES in any model.

Mean BMI growth curves of four groups based on firstborn status and SES are displayed in figure 5.4. The high SES, firstborn group was characterized by low BMI at birth and rapid early postnatal gains in BMI. They had the largest

mean BMI by six months, though at two years they were not distinguishable from the other high SES group. However, they had the largest increase in BMI across childhood and adolescence, resulting in the highest mean BMI in young adulthood. While BMI growth curves among high SES individuals were differentiated by firstborn status, there was no apparent impact of firstborn among lower SES individuals.

E. Discussion

The DOHaD paradigm broadly posits that environmental influences on prenatal and early postnatal development can alter physiology and/or behavior in a manner that increases risk of metabolic diseases, including obesity, in adulthood (Gillman 2005). Interest in the developmental origins of disease intensified after David Barker's observation that the geographical distribution of neonatal mortality in England and Wales in 1911-15 closely corresponded to CVD mortality from the same areas in 1968-78 (Barker and Osmond 1986). Because most neonatal deaths at that time were attributed to low birth weight, Barker hypothesized that poor fetal nutrition was acting to program the body's physiology in ways that adapted the offspring for a life of food insecurity while increasing "susceptibility to the effects of an affluent diet." While the DOHaD paradigm was initially met with a great deal of skepticism (Couzin 2002), it now finds a great deal of support, and DOHaD research has intensified over the past 20 years. This support is largely based on a large body of research illustrating that birth size is associated with later disease in a variety of human cohorts

(Gillman 2005). However, it is now well understood that for the DOHaD paradigm to move forward, researchers must move beyond investigating birth size (Barker 2001; Gillman 2002; Law 2002; Langley-Evans 2007) and start testing specific hypotheses focused on upstream determinants of the fetal environment.

Our goal was to test the mismatch hypothesis, which posits that maternal constraint of fetal growth increases susceptibility to the obesogenic effects of modern environments. Maternal constraint refers to the set of normal, non-pathological factors through which the mother limits fetal growth (Gluckman and Hanson 2004). Maternal constraint of fetal growth is important to ensure that the developing fetus does not outgrow the pelvic canal of its mother (Gluckman, Hanson et al. 2005). The impact of maternal constraint was illustrated most famously by Walton and Hammond (Walton and Hammond 1938) who found that upon cross breeding large Shire horses and smaller Shetland ponies, the size of the foal at birth was primarily dependent on the size of the mare. Gluckman and Hanson's focus on maternal constraint is notable because it is a normal process that operates in all pregnancies to some degree (Gluckman and Hanson 2004). This contrasts with the idea that the influences on fetal development which lead to later disease are caused by nutritional *insults* (Hales and Barker 2001). The importance of nutritional insults has been well illustrated in studies which found that maternal exposure to the Dutch Hunger Winter (1944-45) during early pregnancy was associated with increased rates of obesity in young adult male offspring (Ravelli, Stein et al. 1976), and increased BMI and WC among 50 year old female offspring (Ravelli, van Der Meulen et al. 1999). Associations between

maternal smoking and later offspring obesity have also been reported (Power and Jefferis 2002), further illustrating the potential impact of environmental insults during fetal development on later obesity. However, the idea that maternal constraint, a normal, non-pathological influence on the fetal environment, can impact offspring obesity has not been well investigated in humans (Gluckman and Hanson 2004). There is indirect evidence in the form of studies reporting an inverse association between birth size and later central adiposity (reflected by WC or skinfold ratios) (Oken and Gillman 2003); however birth size is a non-specific indicator of the fetal environment that reflects both normal and abnormal influences.

Among the forms of maternal constraint, we chose to focus on birth order and its impact on later obesity for several reasons. First, lower birth order is associated with reduced size at birth (Cogswell and Yip 1995). We estimated associations between both firstborn status and continuously measured birth order with birth weight, length, and ponderal index. The results from our subsample of CLHNS males were consistent with earlier findings from an analysis of a larger subset of the CLHNS birth cohort: firstborns were both shorter and thinner at birth than higher order births (Miller 1993). Other cohort studies have also confirmed that firstborns are both shorter and thinner at birth (e.g. Ong, Preece et al. 2002). Our model results also indicated that the relationship between birth weight and birth order was best described by a third order polynomial relationship. While we posited that the increase in weights at the high end of the birth order distribution was likely spurious (due to small sample sizes (e.g. only

4% of males in the analysis sample were of birth order nine or above), it is worth noting that a study of sheep found a similarly unexpected increase in birth weight at a parity of nine (Gardner, Buttery et al. 2007).

Previous studies have also reported associations between firstborn status and later obesity in adulthood. For example, firstborn status was associated with a four fold increase in odds of adiposity (skinfold thickness >85th percentile) in a cohort of young adult African Americans after adjustment for other perinatal measures including maternal BMI, education, and household size (Stettler, Tershakovec et al. 2000). Ravelli and Belmont, using data from a cohort of 19 year old Dutch males, found that being an only child was associated with obesity (Ravelli and Belmont 1979), though there was no apparent association between lower birth order and obesity in larger families. We found that firstborn status, and lower birth order in general, were associated with increased risk of central adiposity reflected by WC in young adult males.

However, under the mismatch hypothesis, the effects of birth order should be more apparent if the individual has experienced a nutritionally abundant postnatal environment. In high income countries, where nutritional energy abundance seems to be the norm, this interaction is less important (i.e. most people are experiencing the environment required to express the deleterious effect of reduced fetal growth). However, in a lower-income country such as the Philippines, where there is greater variation in nutritional environments and the prevalence of underweight is still considerable, the nature of this interaction is

critical. By exploiting this environmental variation, we were able to test the mismatch hypothesis.

To test for this interaction, we used a measure of SES based on household assets in young adulthood as a crude but useful proxy measure for the obesogenic environment for males in our study. In previous analyses, we used a spatial clustering method to investigate obesogenic environments in this sample (Dahly 2009). We found that SES reflected in 2005 household assets was an important predictor of central adiposity in males that largely explained the spatial clustering (Dahly 2009) in high WC that we observed. Consequently, we concluded that the 2005 SES was a crude but useful measure to identify obesogenic environments, and took advantage of this to test the mismatch hypothesis in the CLHNS males. However, we found that the socio-environmental determinants of obesity were much more complex in the females, and at this point have not developed a useful way to estimate their exposure to obesogenic environments that would facilitate their inclusion in this analysis.

We confirmed our prediction under the mismatch hypothesis in the males: low birth order amplified the impact of SES on young adult central adiposity. While the idea that disease arises from a discordance between the pre- and postnatal nutritional environment is not a new one for DOHaD researchers, to our knowledge, only one previous study has explicitly tested for an interaction between prenatal variables and environment measured in young adulthood; Barker et al. found that the risk of coronary heart disease associated with low

social class were amplified in men who were born thin at birth (Barker, Forsen et al. 2001).

Rapid postnatal growth is also a hypothesized determinant of later obesity (Ong, Preece et al. 2002; Ong and Loos 2006). Because birth order is associated with higher maternal SES (due to reduced fertility among high SES women), our expectation was that firstborns would be more likely to experience an early postnatal environment that would promote rapid catch-up growth. This contrasts to other maternal constraints on fetal growth such as young age, or small body size, which tend to be associated with lower SES and thus a poorer postnatal environment that instead promotes growth faltering. We explored mean BMI growth curves in subgroups based on firstborn status and SES at birth, finding that being firstborn and having a high SES was associated with lower birth BMI followed by a rapid increase in BMI through early infancy. Furthermore, this group also had the largest mean BMI in young adulthood. The early trajectory was similar to that found among firstborns in the ALSPAC study who were thin at birth and also experienced rapid catch-up growth (Ong, Preece et al. 2002). However, due to the exploratory nature of this analysis, we were not able to determine whether the rapid postnatal growth we observed mediates the impact of birth order and SES on later young adult BMI, or whether rapid postnatal growth is a downstream indicator of aspects of fetal growth and development that impact later obesity risk independently of the postnatal growth pattern. We did try to test the hypothesis that early rather than later environment was a more important modifier of birth order by replacing SES in young adulthood with SES

measured at birth in our interaction models. We found that estimated impact of early SES on later central obesity was weaker than that of current SES, and there was no interaction between birth order and early SES on young adult WC in any model. However, this is an admittedly crude attempt at elucidating the nature of this timing and more research is clearly needed.

While our analysis failed to reject the mismatch hypothesis, we must interpret our results cautiously. Lower birth order is a complex exposure variable that is likely associated with a variety of pre- and postnatal factors that we were not able to account for. Birth order is linked to household size which may influence body size in adulthood. However, household size likely reflects different exposures at various points across the lifecourse and thus its inclusion in our linear models is somewhat problematic. We tried to crudely account for this influence by including a measure of household size averaged across the study period (results not reported). While this inclusion attenuated the estimated effects of birth order on WC, it did not affect the interaction between birth order and SES. In a lower income country like the Philippines where underweight is still prevalent, it is also possible that higher WC associated with lower birth order is due to improvement in overall nutrition found in higher SES individuals from smaller families. We tried to account for this by estimating the impact of birth order on both continuously measured WC and on the upper end of the WC distribution. We also looked at the joint impact of birth order and SES on young adult height (results not reported), finding that continuously measured birth order and SES affected height similarly to WC, though the joint impact of firstborn

status and SES seemed to be confined to WC. Another competing hypothesis that we did not explicitly test was the possibility that lower order births, particularly firstborns, are allocated more food during their childhood development (Horton 1986; Horton 1988). However, this mechanism predicts a strong association between lower birth order and relatively better lifecourse nutrition (usually reflected by height) in large, poorer families whose overall nutritional environment is limited. Thus it seems unlikely to account for the increased risk of central obesity that our results suggest.

More research on the underlying mechanisms explaining the relationship between birth order, fetal growth, and later disease are clearly needed. If low birth order is truly related to increased disease risk in adulthood in the manner described by the mismatch hypothesis, then a better understanding of the biological mechanisms connecting birth order and fetal growth will likely provide important insights for intervention efforts. More research is also needed to evaluate whether rapid postnatal growth is a mediator of the hypothesized impact of birth order on later obesity. This is especially important as birth order is clearly not a target for public health intervention. The interaction between pre- and post-natal nutritional environments requires more explicit testing in human populations, ideally using data from prospective longitudinal birth cohort studies. The global public health impact of the mismatch hypothesis with respect to birth order could be critical, as obesogenic environments become more common, and the proportion of lower order pregnancies among humans increases.

Table 5.1. Sample characteristics for 970 young adult Filipino males enrolled in the Cebu Longitudinal Health and Nutrition Survey

Variables		Values
Birth order	Median (Range)	3 (1 to 15)
Firstborn	%	22.2
Waist circumference (cm)	Mean _(SD) (Range)	72.2 _(7.6) (56.5 to 112)
High waist circumference (>85cm)	%	6.1
Birth weight (kg)	Mean _(SD) (Range)	3.0 _(0.43) (0.9 to 4.2)
Birth length (cm)	Mean _(SD) (Range)	49.3 _(2.0) (39.74 to 55.5)
Ponderal index (kg/m ³)	Mean _(SD) (Range)	25.2 _(3.0) (13.6 to 40.6)
Gestational age (wks)	Mean _(SD) (Range)	38.7 _(2.1) (30 to 44)
Maternal age at birth (yrs)	Mean _(SD) (Range)	26.7 _(6.0) (14.9 to 45.6)
Maternal height (cm)	Mean _(SD) (Range)	150.7 _(5.0) (136.1 to 166.1)
Maternal AFA (cm ²)	Mean _(SD) (Range)	14.8 _(5.5) (3.8 to 50.6)
Smokes	%	12.4
SES (1983)	Mean _(SD) (Range)	0 _(2.1) (-2.0 to 8.0)
SES (2005)	Mean _(SD) (Range)	0 _(2.9) (-3.4 to 16.0)

AFA arm fat area; SES socioeconomic status

Table 5.2. Multivariable linear models estimating the impact of birth order or firstborn status on birth weight, length, and ponderal index.

	Dependent Variable			
	Birth weight (g)		Birth length (cm)	
Birth order models				
Birth order	157.27	(76.82 to 237.68)	0.14	(-0.25 to 0.52)
Birth order squared	-23.12	(-38.95 to -7.66)	-0.02	(-0.09 to -0.06)
Birth order cubed	1.02	(0.20 to 1.84)	0.0003	(-0.004 to 0.004)
Gestational age (wks)	44.67	(32.50 to 56.82)	0.22	(0.16 to 0.28)
Maternal age <20 yrs	-47.15	(-131.47 to 37.17)	-0.51	(-0.91 to -0.11)
Maternal age 20-35 yrs	REF		REF	
Maternal age >35 yrs	-55.41	(-157.47 to 46.65)	-0.28	(-0.77 to 0.20)
Maternal height (cm)	11.70	(6.51 to 16.89)	0.07	(0.04 to 0.09)
Maternal AFA (cm ²)	7.12	(2.28 to 11.96)	0.04	(0.02 to 0.06)
Smokes	78.78	(-158.61 to 1.05)	0.13	(-0.25 to 0.51)
SES (1983)	6.60	(-6.29 to 19.50)	0.05	(-0.01 to 0.11)
Firstborn models				
Firstborn	-183.98	(-252.92 to -115.04)	-0.25	(-0.58 to -0.75)
Gestational age (wks)	44.74	(32.65 to 56.82)	0.22	(0.16 to 0.28)
Maternal age <20 yrs	-45.61	(-128.69 to 37.46)	-0.46	(-0.86 to -0.07)
Maternal age 20-35 yrs	REF	-	REF	
Maternal age >35 yrs	-38.66	(-124.05 to 46.74)	-0.39	(-0.80 to 0.01)
Maternal height (cm)	11.69	(6.52 to 16.86)	0.07	(0.04 to 0.09)
Maternal AFA (cm ²)	7.63	(2.81 to 12.44)	0.04	(0.02 to 0.06)
Smokes	-70.77	(-149.28 to 7.75)	0.10	(-0.27 to 0.48)
SES (1983)	7.16	(-5.58 to 19.90)	0.05	(-0.01 to 0.11)

*Coefficients reported as a change in independent variable associated with a tenth of a point change in ponderal index.

Point estimates and 95% confidence intervals reported as Estimate (Lower Limit to Upper Limit)

AFA arm fat area; REF reference category; SES socioeconomic status

Table 5.2 continued

	Ponderal index* (kg/m ³)	
Birth order models		
Birth order	11.31	(5.49 to 17.10)
Birth order squared	-1.72	(-2.85 to -0.61)
Birth order cubed	0.08	(0.02 to 0.14)
Gestational age (wks)	0.77	(-0.11 to 1.65)
Maternal age <20 yrs	3.48	(-2.64 to 9.60)
Maternal age 20-35 yrs	REF	
Maternal age >35 yrs	-1.60	(-9.00 to 5.78)
Maternal height (cm)	-0.02	(-0.39 to 0.36)
Maternal AFA (cm ²)	-0.10	(-0.45 to 0.26)
Smokes	-8.81	(-14.59 to -3.02)
SES (1983)	-0.36	(-1.31 to 0.58)
Firstborn models		
Firstborn	-11.71	(-16.71 to -6.71)
Gestational age (wks)	0.80	(-0.09 to 1.68)
Maternal age <20 yrs	0.29	(-3.13 to 8.96)
Maternal age 20-35 yrs	REF	
Maternal age >35 yrs	0.19	(-4.26 to 8.14)
Maternal height (cm)	-0.03	(-0.41 to 0.34)
Maternal AFA (cm ²)	-0.05	(-0.41 to 0.30)
Smokes	-7.54	(-13.26 to -1.82)
SES (1983)	-0.36	(-1.30 to 0.58)

Table 5.3. Unadjusted and Multivariable linear models estimating the impact of birth order or firstborn status on waist circumference or log odds of high waist circumference.

	Dependent Variable			
	WC (cm)		OR High WC (>85cm)	
<u>Unadjusted models</u>				
Birth order	-0.36	(-0.57 to -0.15)	0.76	(0.64 to 0.91)
Firstborn	1.21	(0.08 to 2.34)	1.88	(1.06 to 3.34)
<u>Adjusted birth order models</u>				
Birth order	-0.51	(-0.76 to -0.27)	0.73	(0.59 to 0.90)
SES (2005)	0.66	(0.50 to 0.82)	1.22	(1.13 to 1.32)
Maternal age <20 yrs	-1.21	(-2.58 to 0.16)	1.19	(0.52 to 2.72)
Maternal age 20-35 yrs	REF	-	REF	-
Maternal age >35 yrs	1.52	(0.18 to 3.21)	1.68	(0.55 to 5.14)
Maternal height (cm)	0.23	(0.14 to 0.32)	1.11	(1.04 to 1.18)
Maternal AFA (cm ²)	0.19	(0.11 to 0.28)	1.07	(1.03 to 1.12)
Maternal Smoking	0.79	(-0.58 to 2.16)	1.55	(0.55 to 4.33)
<u>Adjusted firstborn models</u>				
Firstborn	1.51	(0.32 to 2.70)	1.71	(0.85 to 3.42)
SES (2005)	0.67	(0.52 to 0.83)	1.22	(1.13 to 1.32)
Maternal age <20 yrs	-1.11	(-2.56 to 0.35)	1.41	(0.59 to 3.35)
Maternal age 20-35 yrs	REF	-	REF	-
Maternal age >35 yrs	-0.11	(-1.58 to 1.36)	0.85	(0.31 to 2.34)
Maternal height (cm)	0.23	(0.14 to 0.32)	1.10	(1.04 to 1.17)
Maternal AFA (10 cm ²)	0.19	(0.11 to 0.27)	1.07	(1.02 to 1.12)
Maternal smoking	0.51	(-0.85 to 1.88)	1.28	(0.47 to 3.52)

AFA arm fat area; OR odds ratio; REF reference category; SES socioeconomic status;
WC waist circumference
Point estimates and 95% confidence intervals reported as: Estimate (Lower Limit to
Upper Limit)

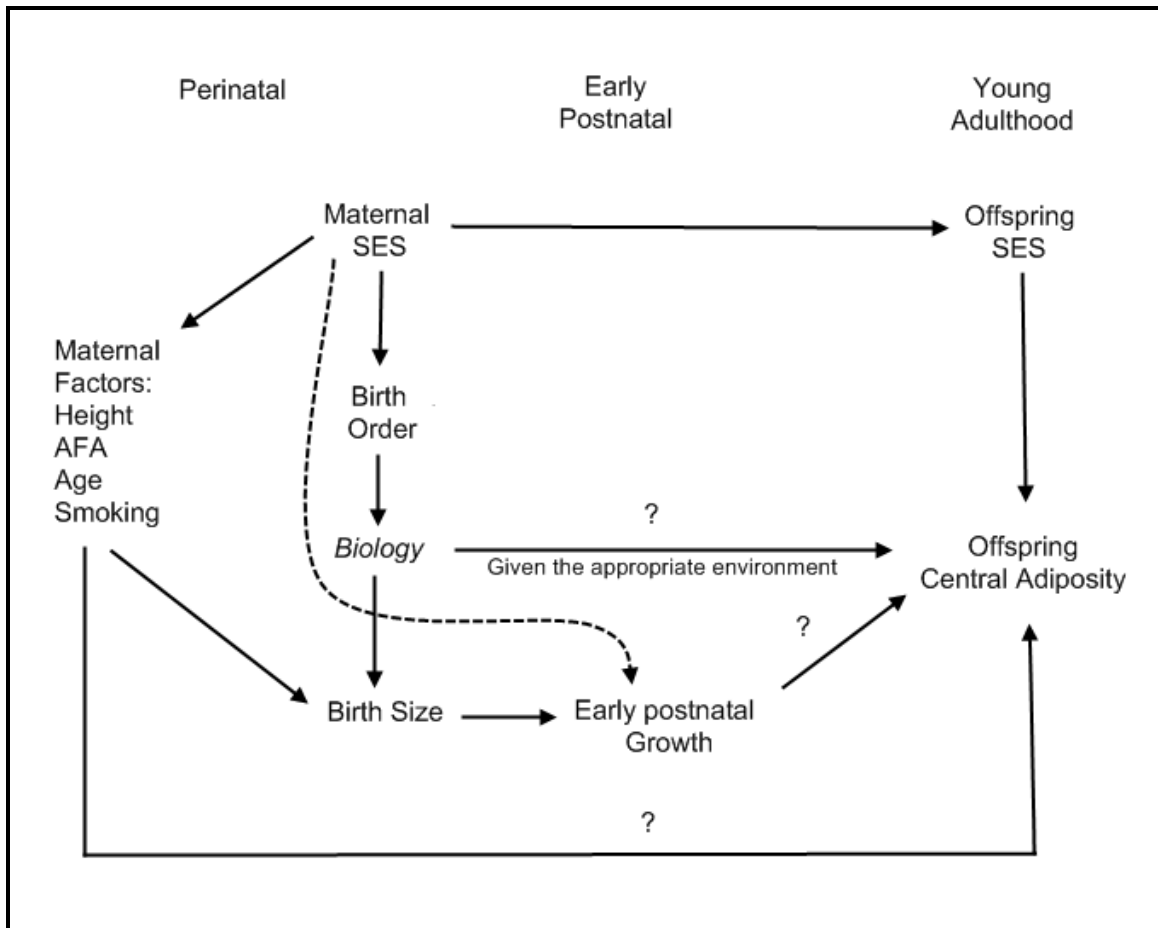
Table 5.4. . Multivariable linear models testing whether associations between socioeconomic status and waist circumference, or log odds of high waist circumference, are modified by birth order or firstborn status.

	Dependent Variable			
	WC (cm)		OR High WC	
Birth order models				
Birth order	-0.56	(-0.80 to -0.32)	0.77	(0.63 to 0.95)
SES (2005)	1.10	(0.83 to 1.37)	1.37	(1.19 to 1.57)
Maternal age <20 yrs	-1.14	(-2.50 to 0.22)	1.23	(0.53 to 2.86)
Maternal age 20-35 yrs	REF	-	REF	-
Maternal age >35 yrs	1.52	(-0.17 to 3.20)	1.65	(0.54 to 5.08)
Maternal height (cm)	0.23	(0.14 to 0.32)	1.11	(1.04 to 1.18)
Maternal AFA (cm ²)	0.20	(0.12 to 0.28)	1.08	(1.03 to 1.13)
Maternal smoking	0.73	(-0.63 to 2.09)	1.42	(0.51 to 3.96)
Birth order X SES interaction	-0.15	(-0.23 to -0.08)	0.95	(0.90 to 1.00)
Firstborn models				
Firstborn	1.38	(0.19 to 2.57)	0.97	(0.40 to 2.36)
SES (2005)	0.55	(0.37 to 0.74)	1.14	(1.03 to 1.26)
Maternal age <20 yrs	-0.90	(-2.35 to 0.56)	1.76	(0.71 to 4.38)
Maternal age 20-35 yrs	REF	-	REF	-
Maternal age >35 yrs	-0.07	(-1.53 to 1.40)	0.86	(0.31 to 2.38)
Maternal height (cm)	0.23	(0.14 to 0.32)	1.10	(1.04 to 1.17)
Maternal AFA (cm ²)	0.19	(0.11 to 0.28)	1.07	(1.03 to 1.12)
Maternal smoking	0.41	(-0.95 to 1.78)	1.16	(0.41 to 3.14)
Firstborn X SES interaction	0.44	(0.10 to 0.79)	1.24	(1.04 to 1.48)

AFA arm fat area; OR odds ratio; REF reference category; SES socioeconomic status; WC waist circumference

Point estimates and 95% confidence intervals reported as (Lower Limit to Upper Limit)

Figure 5.1. Theoretical model



AFA arm fat area; SES socioeconomic status

Figure 5.2. Cubic relationship between birth order and model predicted birth weight (adjusted for maternal age, height, arm fat area, smoking and socioeconomic status).

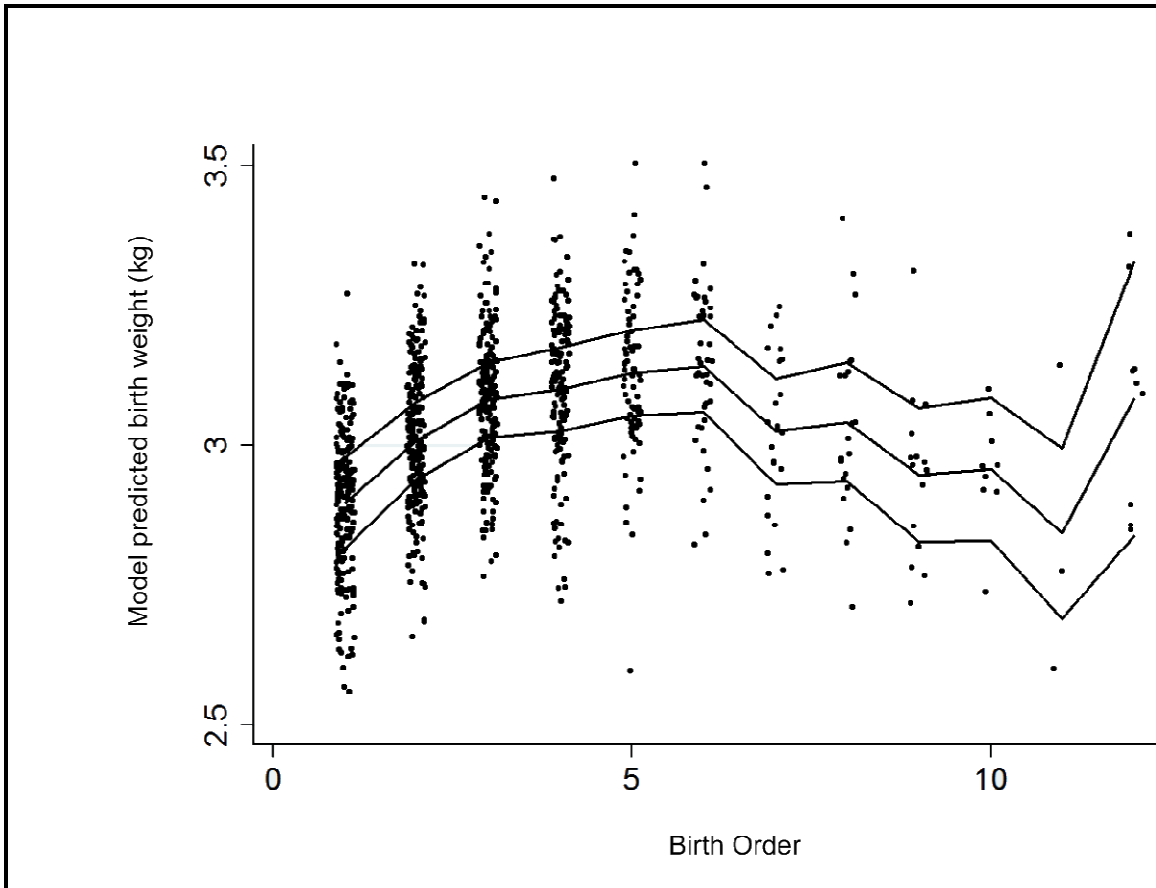
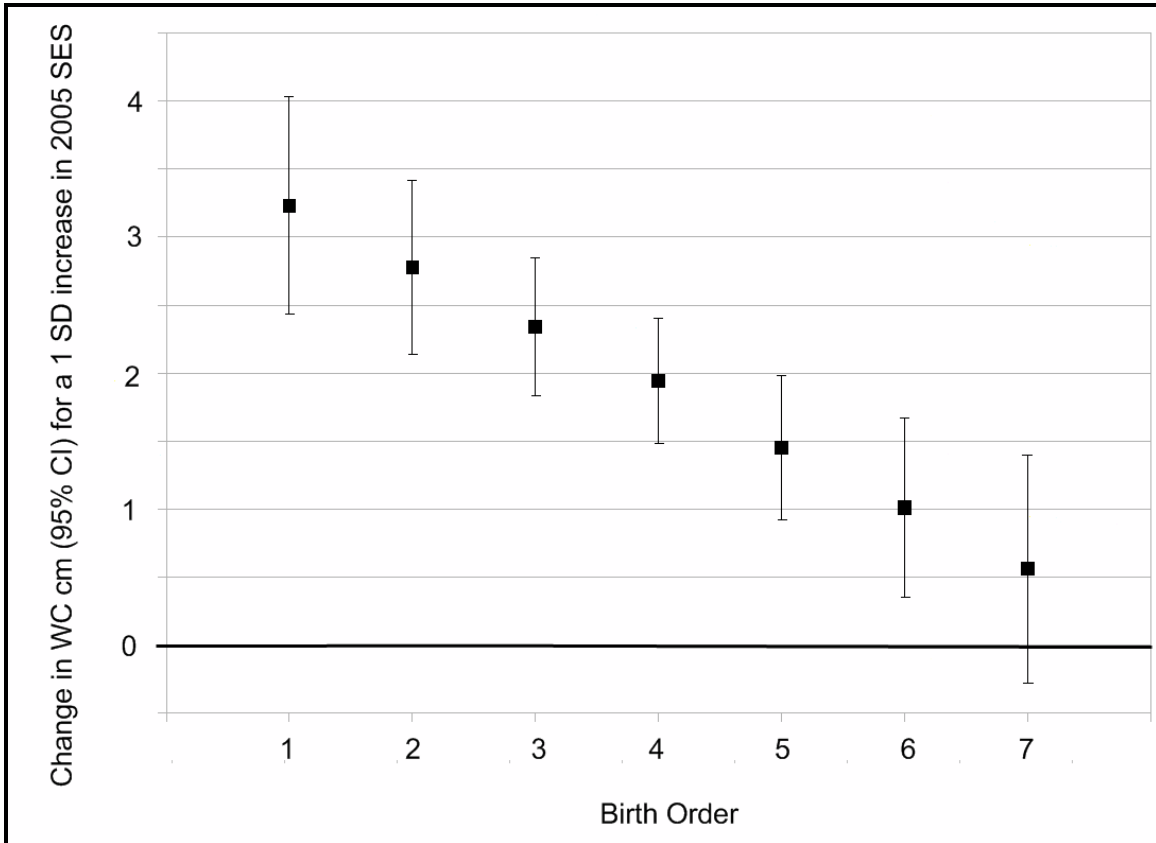
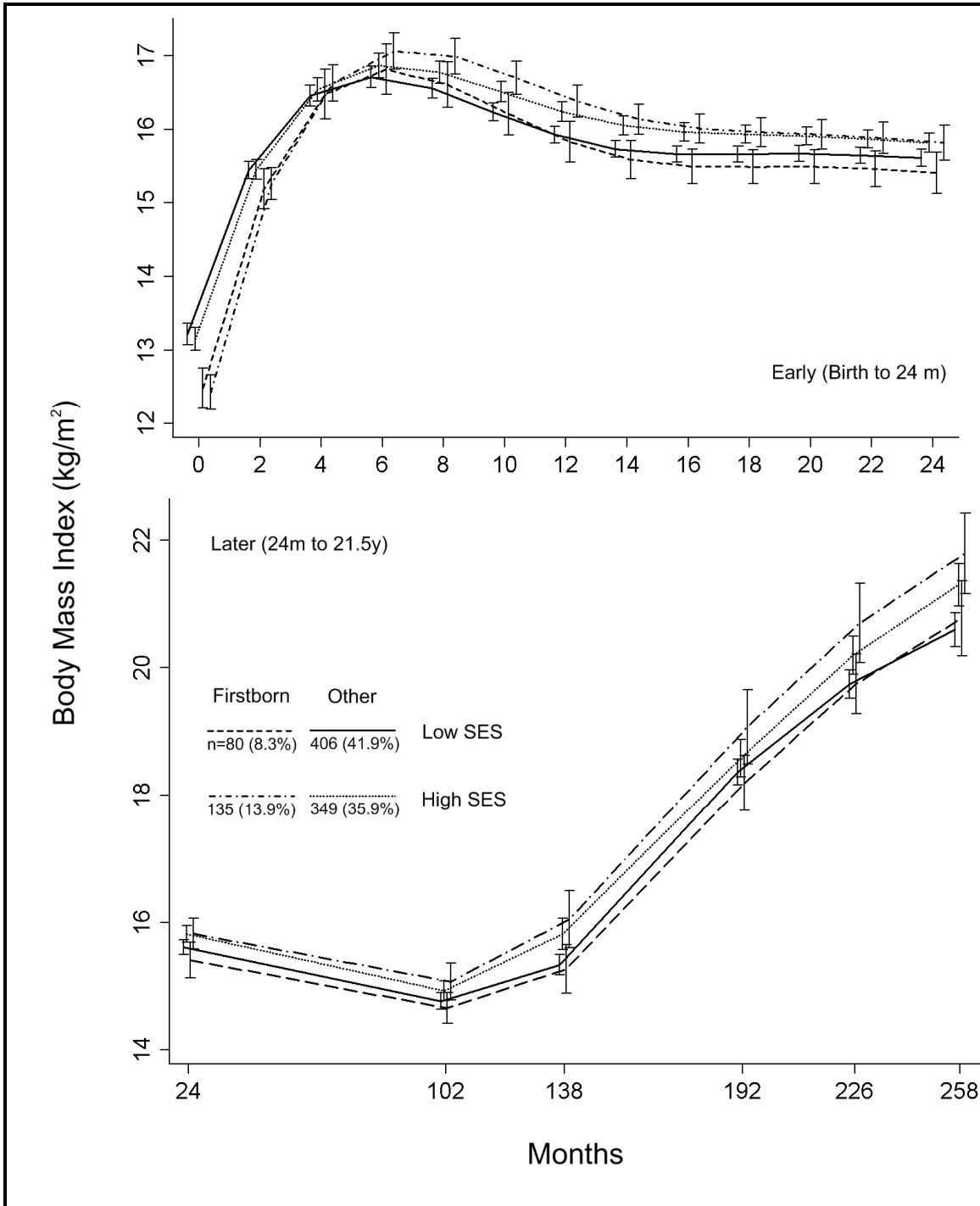


Figure 5.3. The impact of young adult socioeconomic status on waist circumference is amplified for lower birth orders.



CI confidence interval; SD standard deviation (=2.9; observed range -3.4 to 16.0)

Figure 5.4. Mean body mass index growth curves (with 95% confidence intervals) for groups of males defined by firstborn status and socioeconomic status at birth.



Chapter 6. Synthesis

A. Overview of results

Using data from a birth cohort of young adults enrolled in the Cebu Longitudinal Health and Nutrition Survey (CLHNS), we aimed to test the hypothesis that the obesogenic effects of modern environments were amplified in individuals whose fetal growth was maternally constrained. The crux of testing this hypothesis was finding a way to characterize exposure to obesogenic environments. Given our immediate goal, we were not as interested in explaining exactly why environments in Cebu are obesogenic. However we have tried to frame our research in a manner that contributes to a growing body of knowledge on how environments influence obesity risk in a lower-income, rapidly developing context.

Using two different but complementary analytical methods common to health geography, we explored the impact of barangay-level urbanicity and individual-level socio-economic status (SES) on body size in young adulthood. First we used the spatial scan statistic to locate spatial clusters of overweight, obesity, and central adiposity in our study participants when they were young adults in 2005. We compared the location of detected clusters to the spatial distribution of barangay-level urbanicity in Cebu, and evaluated the degree to

which the clusters were explained by spatial variation in individual-level SES. We then used cross-sectional generalized estimating equations to estimate the impact of urbanicity and multiple measures of SES on overweight and central adiposity. Based on these analyses, SES measured by household assets was found to be a crude but useful way to characterize exposure to an obesogenic environment in male study participants. In our final analysis we tested the hypothesis that the positive relationship between SES and central adiposity in the CLHNS males would be amplified by low birth order, a known constraint on fetal growth. We also tested for associations between birth order and size at birth, and explored body mass index (BMI) growth curves from birth to young adulthood in four sub-samples based on firstborn status and level of SES.

Spatial clustering of overweight, obesity, and central adiposity.

Using data from a sample of young adult Filipino males and females enrolled in the CLHNS, we classified participants as cases or non-cases based on their levels of adiposity. Using cutpoints appropriate for an Asian population, overweight was defined as body mass index (BMI) ≥ 23 ; obesity was alternately defined as BMI ≥ 25 , or body fat percentage (BF%) $\geq 25\%$ for males or $\geq 38\%$ for females; and central adiposity was defined as a waist circumference (WC) > 85 cm for males or > 80 cm for females. These data were aggregated based on the study participants' barangay of residence. The spatial scan statistic was then used to detect clusters of barangays where there was an unusually high or low

prevalence of each outcome, given the null hypothesis that cases are randomly distributed across Cebu.

We found varying evidence for spatial clustering of these outcomes in both males and females. Strong evidence of spatial clustering was defined by rejection of the null hypothesis of complete spatial randomness at $p \leq 0.05$. There was strong evidence for high prevalence clusters of overweight and obesity (BMI) in the males. These clusters were characterized by a prevalence ratio (PR) comparing the prevalence of a given outcome among individuals residing within the cluster to those outside the cluster. These PRs were 2.21 (95% CI 1.56 to 3.47) for overweight, and 2.33 (95% CI 1.68 to 2.93) for obesity. There was weaker evidence for high prevalence clusters of obesity defined by BF% and central adiposity (p -values of 0.108 and 0.104 respectively) though these clusters were associated with similar increases in outcome prevalence. There was also strong evidence for low prevalence clusters for overweight, and obesity defined by both BMI or BF%.

For females, there was strong evidence for high prevalence clusters of overweight, and central adiposity. Their respective prevalence ratios were 2.10 (95% CI 1.48 to 2.97) and 3.91 (95% CI 2.04 to 7.49). There was weaker evidence for high prevalence clusters of obesity defined by BMI ($p=0.062$) and BF% ($p=0.125$). There were no detected low prevalence clusters for the females.

We then compared the locations of these clusters to the spatial distribution of urbanicity in Cebu. Urbanicity was measured using a continuous scale measure developed for this research. The urbanicity of Cebu and the locations of

clusters were displayed graphically using ArcGIS. We found that high prevalence clusters for the various adiposity measures consistently included some of the most urban areas of Cebu. However, we did not find highly localized clusters that only included the most urban areas. We instead found more dispersed clusters that often extended into peri-urban and even some rural areas. We also found that low prevalence clusters for overweight, and obesity defined by BMI in the males were isolated to the more rural, southwestern region of Cebu. Though the low prevalence cluster for obesity defined by BF% in the males was also located in the southwestern region of Cebu, it extended into some urban areas.

We then repeated our analysis after adjusting for individual-level SES, measured using the score from a principle components analysis of household assets. Our goal was to determine whether the spatial clusters could be explained by the spatial distribution of SES among study participants. With the exception of overweight, evidence of spatial clustering was greatly reduced in the males. However, the adjustment for SES had no impact on the evidence of spatial clustering in the females.

Our results suggest that the development of obesity in these young adults has spatial determinants. These could include environmental factors that people share or other individual level factors that are themselves spatially determined. Barangay level urbanicity was a far from perfect predictor of obesity clusters. Spatial clustering in males seemed to be largely determined by the spatial distribution of SES. This was not true for the females.

Generalized estimating equations of the impact of barangay-level urbanicity and multiple individual-level indicators of SES on body size.

Using an alternate analytical method, we then investigated the impact of barangay-level urbanicity and individual-level SES on multiple measures of 2005 body size in the same sample of young adult Filipinos enrolled in CLHNS (less one male and one female with missing SES data). Body size measures were overweight ($BMI \geq 23$) and central adiposity ($WC > 85$ in males and $WC > 80$ in females). The CLHNS randomized cluster study design facilitated the use of random intercept logistic regression models to test for random barangay effects on body size. We used these models to estimate the proportion of variance in the outcome that was described at the community level. In the males, the estimated ICCs for overweight and central adiposity were 0.18 (95% CI 0.06 to 0.45) and 0.10 (95% CI 0.01 to 0.46) respectively. For females the respective estimated ICCs were 0.05 (95% CI 0.01 to 0.30) and 0.18 (95% CI 0.05 to 0.46). To account this statistical dependence we used generalized estimating equations to estimate the impact of neighborhood-level urbanicity and multiple 2005 SES indicators (household income, household assets, education, and marital status) on outcomes.

Results varied by gender, but were similar when comparing outcome measures within gender. In males each of the SES indicators, as well as urbanicity, was positively related to overweight in the unadjusted models. In the multivariable model, only assets, marital status, and college education remained

strong predictors of overweight. In females, marital status was the only crude predictor of overweight. Though there was no discernable relationship between education and overweight in females (OR 0.82, 95% CI 0.27 to 2.50), it was notably the only SES indicator with a point estimate that suggested an inverse relationship. There was an inhibitive interaction between urbanicity and assets for females. We interpreted this interaction as a reduction in the positive impact of assets on overweight as urbanicity increases. The difference in the estimated impact of assets on the odds of overweight at the ends of the observed urbanicity distribution was considerable.

We also explored the nature of this interaction by looking at the prevalence of overweight in groups crudely defined by tertiles of assets and urbanicity. Within the lower two tertiles of urbanicity, there was no clear relationship between assets and the prevalence of overweight. However, among women living in the most urban areas, there is an emerging trend for which the prevalence of overweight declines with increasing assets. The lowest prevalence of overweight in the entire sample is found for highly urban women with high assets scores (<1%).

Comparing results from these analyses

Not surprisingly there were some similarities in our results from the first two analyses. In the males, we found the stronger evidence of spatial clustering for overweight and obesity than we did in the females. Conversely, evidence of spatial clustering of central adiposity was strongest in the females. There were

similar findings from our analysis using random intercept logistic regression models. The estimated barangay effects on overweight and obesity were much stronger in the males, while the estimated barangay effect on central adiposity was much stronger in the females. Furthermore, the evidence of spatial clustering of overweight and obesity in males was minimally attenuated once the spatial distribution of SES (measured by assets) was accounted for. However, this same adjustment led to substantial attenuation in the evidence of spatial clustering of central adiposity in the males. Another similarity was that the adjustment for SES in did not affect the evidence of spatial clustering or the estimated random barangay effect on central adiposity in the females. Though it is challenging to interpret these results given the lack of previous research using these methods in a lower-income, developing country contexts, our results strongly suggest that there are important gender differences in how our study participants experienced their environments and that these differences may be specific to particular forms of obesity (i.e. central adiposity versus total adiposity).

Lower birth order attenuates the positive impact of SES on central adiposity in young adult males enrolled in the CLHNS.

Using data on the same sample of Filipino males (minus 17 individuals with missing data relevant to this analysis), we tested the hypothesis that lower birth order amplified the previously observed positive association between SES and central adiposity. We also examined the influence of birth order on birth size (independently of maternal age, height, arm fat area, and smoking), and explored

BMI growth curves (from birth to young adulthood) in groups defined by firstborn status and SES.

Firstborns were on average 190 g lighter (95%CI 259 to 121) and 0.35 cm shorter (9%CI 0.69 to 0.02) at birth. Body mass, but not length, continued to increase up to the sixth born, and then declined. Maternal age, height and AFA were important determinants of birth length but not ponderal index; and maternal smoking, like birth order, was an important predictor of ponderal index but not length.

Firstborn status and lower birth order were associated with higher young adult WC and log odds of high WC. After adjustment for potential confounders (maternal age, height, arm fat area [AFA], smoking; and 2005 offspring SES) each increase in birth order was associated with -0.56 cm of WC (95%CI -0.80 to -0.32) and a 23% reduction in odds of having a high WC (OR 0.77; 95%CI 0.63 to 0.94). Maternal height and AFA were consistent, positive predictors of central obesity. Maternal smoking and age were not meaningful predictors. We also detected a meaningful interaction between 2005 household assets and birth order that was consistent with the mismatch hypothesis. For example, a one SD increase in SES was associated with a 248% increase in odds of high WC (OR 2.48; 95% CI 1.65 to 3.76). However, the same increase SES coupled with an increase in birth order was associated with just a 214% increase in odds of high WC (OR 2.14; 95% CI 1.58 to 2.89). We found no evidence for a similar interaction between SES and the other prenatal variables (maternal age, height, AFA, smoking).

The high SES, firstborn group was characterized by low BMI at birth and rapid early postnatal gains in BMI. They had the largest BMIs by six months, though at two years they were not distinguishable from the other high SES group. However, they had the largest increase in BMI across childhood and adolescence, resulting in the highest BMIs in young adulthood. While BMI growth curves among high SES individuals were differentiated by firstborn status, there was no apparent impact of firstborn among lower SES individuals. These results suggest that the interaction between birth order and later environment may be driven by early post-natal growth, although more research is needed to explicitly test this hypothesis.

B. Research Strengths and Limitations

A key strength of the research was our use of CLHNS data, which we particularly well suited to our research objectives. All anthropometric data were collected by trained staff. The cluster randomized study design for which study participants were linked to a barangay of residence allowed us to place participants into the spatial context of Cebu. This of course broadly facilitated our ability to explore the environmental determinants of obesity in this sample. Detailed barangay level data allowed for the construction of a continuous scale measure of urbanicity, and will benefit our research efforts in the future as we try to explain why urban environments are obesogenic. Another strength was that Cebu is an environmentally diverse study area contained in a single contiguous space that facilitated an intra-regional approach. Furthermore, while Cebu is

environmentally heterogeneous, the ethnic and cultural make up of the area is fairly homogenous which simplified our analyses in many regards.

The data were also particularly well suited to testing the mismatch hypothesis. A key limitation of traditional DOHaD research was that it was initially limited to retrospective cohort studies that relied on recalled perinatal exposure data, which was usually limited to birth weight. However, over the past 5-10 years, more DOHaD research has emerged using data from prospective cohort studies like the CLHNS which were able to collect detailed maternal and household-level data during pregnancy. It is the existence of these data along with the environmental data we just described that allowed us to explicitly test the mismatch hypothesis in a human population for the first time.

Our research also benefited from the application of advanced statistical methods that have only rarely been used in studies of obesity or in a rapidly developing, lower income population. One of these methods was the spatial scan statistic we used to detect adiposity clusters. There are many ways to test for clusters, but the spatial scan statistic is ideal in that it both locates clusters and provides a statistical test of how unusual the clusters are given the null hypothesis of complete spatial randomness. Furthermore, the method accounts for multiple testing; it does not require *a priori* decisions regarding the scale of the analysis; and the clusters are robust to the spatial distribution of cases and controls within them. To our knowledge, results generated from using this technique have only been reported for one previous study of obesity. We also used advanced random intercept linear regression models to both account for

dependence among observations due to the CLHNS study design, and to test contextual hypotheses. Though the application of multi-level models has become increasingly popular, there were very few previous studies that reported the degree to which variability in obesity outcome was described at the neighborhood level, particularly in a rapidly developing, lower-income context. Another strength is our application of a previously developed scale measure of urbanicity to describe our study area.

The key limitation of the study, in so far that this is a study of obesity, is that there are very few obese people in this sample. The sample is very young and childhood obesity is not yet a serious public health problem in Cebu. This led us, in part, to use fairly low cutpoints to define overweight, obesity, and central adiposity. In a rapidly developing context such as Cebu, it is possible that some of the relationships we have seen are at least partly driven by overall changes in body size associated with improvements to overall nutrition in this study area. Furthermore, because the prevalence of obesity was so low in this sample at age 21, it constrained us to looking at cross sectional associations. However, as this sample continues to age we will be able to expand our analyses to capture environmental and socio-economic influences on this sample across their adult life course.

C. Future Research

One of our immediate goals was to find a way to characterize exposure to obesogenic environments that would facilitate our test of the mismatch

hypothesis. To this end we were not as interested in understanding why environments were obesogenic. However, our long term goal is to identify mutable, environmental features in Cebu that increase risk of obesity. To facilitate this objective, there are several ways to build upon the research we have reported here.

The first is to use spatial data on residential household location in future spatial analyses. These data were not available for this research, but will be for future efforts. Having the household location data will allow us to use spatial methods that combine the best features of the analytical methods we used in the current research. The spatial scan statistic allowed us to account for the spatial relationships of the barangays in Metro Cebu. This contrasts with the multi-level modeling approach, which is aspatial at the barangay level. The importance of this distinction is reflected by the stronger evidence of an environmental effect of obesity illustrated by the spatial clusters. This difference is largely explained by the fact that barangay of residence is not an accurate description of an individual's activity space, and that some of the characteristics of barangays that affect obesity are not confined to the borders of the barangays. However, the spatial scan statistic was limited in its ability to control for individual level characteristics that may account for the spatial distribution of obesity, whereas the multi-level approach clearly facilitates the inclusion of multiple individual and barangay-level characteristics into the analysis. The use of higher resolution spatial data will open up our research to techniques such as geographically weighted regression which will allow us to consider both individual-level and

shared characteristics while explicitly accounting for their spatial relationships. These data will also allow for a more accurate description of cluster locations.

The next way to improve on our investigation of the socio-environmental determinants of obesity is to move away from broad characterizations of environment such as urbanicity, and start testing hypotheses regarding specific environmental features that could affect obesity. Given our immediate goal of characterizing exposure to obesogenic environments, urbanicity was a useful construct. It also helps to generate hypotheses about why some environments are obesogenic. However, broadly defined urbanicity is not mutable and captures multiple environmental exposures that could each be related to obesity risk in very specific and different ways. Thus we will return to our spatial cluster results and using the detailed barangay level data work to identify specific, mutable features of those areas that affect obesity risk.

We have noted the methodological weakness of our multivariable linear modeling approach to investigating the impact of SES indicators of body size. While our research was an improvement over previous studies which have focused on a single SES indicator, we found a level of complexity among the multiple SES that is likely not well captured by linear models. Estimates from the linear models are based on a counterfactual that describes the effect of changing one variable while holding all others constant. This counterfactual may not be realistic because changes in any of the SES variables likely result in changes to other variables. While we wanted to move away from a unitary approach to SES and consider the individual, independent impact of the SES indicators on body

size, the reality is that these variables do in fact tend to co-occur in nature, and thus distinguishing the effects of one indicator from another can be problematic. We are currently exploring the application of latent profile or class models that evaluate patterns among the SES and body size variables that are observed in our sample. While these models can be more challenging to estimate and interpret, we think they have great potential to help us better understand how SES impacts body size, which should in turn help us better understand how to prevent obesity in Cebu.

Lastly, there are some very clear ways in which we can improve up our test of the mismatch hypothesis. We used linear models to test for an interaction between birth order and 2005 SES, which was our crude proxy for exposure to obesogenic environments in males. However, this analysis must be extended to the females enrolled in the CLHNS once we better understand how to similarly characterize them. We also plan to extend our simple linear modeling approach to more complex models that allow us to account for life course exposures that will help us ascertain if there are post-natal critical periods when environmental variables are most important. We found that rapid postnatal growth was associated with an overall growth trajectory that resulted in increased young adult BMI in high SES firstborn males. However, we were not able to determine whether this rapid post-natal growth is a mediator of prenatal exposures on later obesity, or whether the interaction between birth order and later environment operates independently of growth during the early post-natal period. Understanding these dynamics are particularly important because birth order is

not a target for public health intervention, and thus we must better understand its pre and postnatal mediators.

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