Behavioral, Environmental, Metabolic and Intergenerational Components of Early Life Undernutrition Leading to Later Obesity in Developing Nations and in Minority Groups in the USA

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ABSTRACT

Nutritional transition, urbanization, and physical inactivity are primary factors responsible for the worldwide epidemic of overweight/obesity (OW/OB). However, these factors fail to explain the epidemic of OW/OB in developing countries and in recent-migrants to developed countries. Among these, OW/OB is associated with short/stunted stature and coexists with undernutrition at much higher rates than is statistically expected. Changes in metabolic pathways toward reduced fat oxidation and increased metabolism of carbohydrate may explain, in part, this phenomenon. Also, intergenerational consequences of malnutrition and poor health of the mothers may lead to impaired phenotypes in their offspring. We propose a novel methodology to assess the history of early life undernutrition by assessing the sitting height ratio of the mothers. The degree of short leggedness reflects undernutrition when the mother was an infant/child. Collectively, behavioral, environmental, metabolic and intergenerational components of early life undernutrition may provide a more satisfactory explanation for later life obesity.

Key words: undernutrition, overweight, obesity, metabolism, intergenerational effects

Introduction

We present an extensive review of the literature concerning the epidemic of overweight and obesity (OW/OB), both in developed and in developing countries, and suggest a novel methodology to access the effects of early life undernutrition on the growth and health status of children. The epidemic of OW/OB is a worldwide phenomenon and it has been broadly documented in recent years1–13. All the research agrees that the nutritional transition (excessive intake of dietary fat and the general increase in consumption of nutritionally dense foods), the increase in the levels of urbanization, and the reduction in physical activity are primary factors responsible for this worldwide epidemic14–25.

This constellation of factors (nutritional transition, urbanization, and sedentarism) explains this phenomenon in developed countries, where OW/OB is associated with normal-to-tall stature-for-age and where the prevalence of undernutrition (stunting, or chronic malnutrition; and wasting, or acute malnutrition) is very low26–31.
However, it fails to fully explain the epidemic of OW/OB in developing countries and in groups of recent migrants from developing to developed countries. In these cases, OW/OB is associated with short or stunted stature and coexists with undernutrition at much higher rates than is statistically expected.\(^7,11,26,30–38\).

For example, Florêncio et al.\(^{39}\) studied a very poor Brazilian community composed of 315 families and found the coexistence of undernutrition and obesity not only within the same community, but also within the same family. More specifically, 30 percent of the families had, at least, one malnourished member and one OW/OB member. Furthermore, 30 percent of the stunted individuals were also OW/OB. The coexistence of stunting and OW/OB in the same individual is the worse possible combination of nutritional characteristics because it adds to all the health problems that arise from being OW/OB.\(^{40}\) and all of the negative outcomes of being short or stunted in stature, as a consequence of environmental insults.\(^{41,42}\)

The association of undernutrition and OW/OB was rarely found in populations of the developing world prior to 1990, but is now commonly reported.\(^{11,30–39,43,44}\)

Migrants from the developing nations to the richer nations tend to show less prevalence of undernutrition but are at an even higher risk for OW/OB than their non-migrating counterparts and the host population.\(^{1,5,7,8,33,34,45}\) Smith et al.\(^{7}\) for example, analyzed a sample of 296 Maya-American (ages 6–12 years) living in Los Angeles and in Florida and found that 11.5 percent of these children were stunted, 48.6 percent were overweight (BMI > 85\(^{th}\) percentile) and 42.2 percent were obese (BMI > 90\(^{th}\) percentile). The risk for OW/OB applies to the migrants themselves, including child migrants, and the children of the migrants born in the host country.\(^{7,5,45}\) These children are usually short in stature even when they do not show stunting, as defined by a height-for-age ≤ −2 z-scores of the mean reference data. The children of Maya immigrants from Guatemala, for example, average at the 25\(^{th}\) percentile of height-for-age of the National Center for Health Statistics (NCHS) references, but the mean weight-for-height and BMI-for-age approximate the 85\(^{th}\) percentile of the references.\(^{45}\)

A childhood phenotype of short stature and OW/OB is a risk factor for coronary heart disease, diabetes and other metabolic diseases later in life.\(^{46,47}\) The existing research offers some explanations for these patterns of poor height growth with OW/OB in the populations.

One of the most comprehensive explanations for this phenomenon was proposed by Frisancho\(^{27}\), who points out the cumulative effects of the following factors: 1) Metabolic pathways for reduced fat oxidation and increased metabolism of carbohydrate, 2) Rural-to-urban migration or urbanization of rural communities, 3) Nutrition transition from traditional to globalization foods; and 4) Changes in patterns of physical activity with a steep decrease of energy expenditure.

In this paper, we add a fifth factor that we call the intergenerational consequences of malnutrition and poor health of the mothers leading to impaired phenotypes in their offspring. This intergenerational effects hypothesis includes: «fetal programming,» «perinatal adaptive responses,» and related concepts in the literature.\(^{46–49}\)

We suggest a novel methodology to assess the history of early life malnutrition in the mothers of children at risk for short stature and OW/OB. Our method is based on the sitting height ratio of the mother (SHR = sitting height/total stature\(^{*100}\)). The degree of «short leggedness» reflects undernutrition of the mother when she was an infant and/or a child.\(^{45–50,51}\) Maternal «short leggedness» has been associated with birth weight of their offspring\(^{52}\) and adult adiposity even after the models are controlled for age, age at menarche, parity, schooling, and parental obesity.\(^{53}\) We hypothesize that these five factors, working in synergy, produce a total impact on the risk for OW/OB that is more than the effect of each factor separately.

**Metabolic Pathways for Reduced Fat-Oxidation and Increased Metabolism of Carbohydrates**

Research has shown that individuals who suffered gestational or infantile nutritional deprivation will shift toward a preferential metabolic use of carbohydrates instead of fats.\(^{54–57}\) This shift leads to an increased deposition of body fat because the use of stored carbohydrates requires fewer biochemical steps than the use of stored fats.\(^{59}\) According to Frisancho,\(^{60}\) «...the same way that dietary carbohydrates are faster to absorb than fats, carbohydrate substrates stored in the blood are also more rapidly metabolized than stored fatty acids. The net effect of the preferential metabolism of carbohydrates is that fats are stored, increasing the risk of obesity under condition of undernutrition (p. 360).» In a sense, undernutrition in earlier ages will beget obesity in adulthood.

Several studies support this hypothesis. Malcolm,\(^{55}\) for example, conducted a study on children (with a mean age of 9.0 years) from Papua New Guinea. These children were classified as nutritionally deprived either during prenatal life or during the first two years of postnatal life and were given nutritional supplements for a period of 13-weeks. These supplements, however, did not have a major effect on growth in length or mid-upper arm circumference but had a significant effect in the skinfold thickness. These children showed a greater tendency to accumulate fat and did not use the extra energy to grow in length.

Similar results were found in the Jamaican Growth Study where nutritional supplementation was given to 18.5 month-old, growth-retarded children for one year. This supplementation did not have any significant effects in children’s growth in length, but did have a significant effect on the skinfold thickness.\(^{57}\) Spurr and Reina\(^{46}\) and Barac-Nieto et al.\(^{54}\) demonstrated that, after severe undernutrition, the caloric value of food supplementation increased body fat. The additional protein of the supplement increased muscle mass. There was no supplement-related increase in stature.
This tendency to accumulate body fat rather than use the energy for linear growth explains, in part, why stunting coexists with OW/OB in previously undernourished children, and it suggests that the etiology of obesity in these cases is not due only to an excessive caloric consumption but is also related to the activation of energy sparing-mechanisms. These energy sparing-mechanisms are activated when life-threatening undernutrition is present. Signals from the depleted fat stores to the brain lead to the suppression of thermogenesis, which results in the reduction of the basal metabolic rate (BMR) and, concomitantly, signals the body to accumulate fat. These processes of conserving energy lead to what Keys et al.\textsuperscript{61} called »poststarvation obesity« based on the results of the Minnesota semi-starvation experimental studies.

Laboratory support for this hypothesis comes from measurements using indirect calorimetry. The ratio between the volume of carbon dioxide produced and the volume of oxygen consumed is called the respiratory quotient (RQ) and it indirectly assesses the relative proportion of carbohydrate or fat that is being metabolized. A RQ greater than 0.9 indicates that carbohydrate is being used to meet energy needs, allowing the majority of fat intake to be stored\textsuperscript{22}. A RQ close to 0.70 indicates that fat is mainly used to meet energy needs.\textsuperscript{27} Several studies\textsuperscript{33,34,53–65} show that the preferential oxidation of carbohydrates rather than fat is an important contributor to the development of obesity. Previously malnourished populations tend to have higher RQ than normally-nourished populations. This means that previously malnourished subjects tend to oxidize more carbohydrates and store more fat than normally-nourished subjects.

However, Smith et al.\textsuperscript{66} found that fat oxidation could be accelerated if the individuals performed a level of physical activity, at least, 1.8 times higher than the resting metabolic rate (RMR). In contrast, under sedentary conditions (1.4 times the RMR) there were no significant changes in the rate of fat oxidation. Thus, sedentary lifestyles will enhance the tendency to store fat.

### Nutritional Transition from Traditional to Globalized Foods

There have been extensive changes in the dietary patterns of populations from developing countries, towards a more westernized diet. This »western diet« is characterized by a high consumption of fat, refined carbohydrates and processed foods and a decrease in the consumption of dietary fibers and complex carbohydrates\textsuperscript{60–71}. This nutrition transition was first noticed in the urban areas, but not homogeneously\textsuperscript{70} »...in the same population where undernutrition and food insecurity are found, other subpopulations, often even in the same household, suffer dietary excesses and obesity. It is this complex intertwining of economic and social conditions that creates this rapid transition among some urban subpopulation groups...« (p. 1905).

More recently, Leatherman and Goodman\textsuperscript{72} reported an increase in the »food commoditization« and a »cocolonization« (consumption of sweetened carbonated beverages) of coastal and inland villages in the Yucatan peninsula, Mexico, showing that this transition is spreading towards rural areas in developing countries. There seems to be two main reasons for this change. The first is linked with the growth of the road networks, that facilitated the spreading and consumption of foods and beverages from industrialized countries\textsuperscript{73–74}. The second reason is the development of the tourism business in the area that has employed many rural people in hotels and other service facilities. Both of these factors lead people to reduce their use of the traditional foods and to increase the consumption of »new« fast-foods, soft drinks and salted snacks loaded with fat and calories.\textsuperscript{72}

### Changes in Patterns of Physical Activity with a Steep Decrease of Energy Expenditure

There is a well-documented general trend in both the developed and developing nations for the decline of physical activity, covering all age-groups and, with some variation, all ethnic groups\textsuperscript{75,8,21}. In the past, more jobs were physically strenuous; people were essentially paid to engage in physical activity. However, technology has lead to a shift towards more sedentary jobs and has also reduced the amount of physical exertion needed to accomplish basic household chores. Lakdawalla and Philipson\textsuperscript{75} estimate that in the United States 60 percent of the gain in body weight of the population is due to declining physical activity on the job and at home, while 40 percent is due to improved agricultural technology making food cheaper to buy and consume. Similar dynamics may be at work in the developing countries.
The World Health Organization\textsuperscript{26} states that a sedentary lifestyle is one of the main causes of disease and impairment, emphasizing that more than two million deaths per year in the United States are attributed to physical inactivity. In the United States, physical inactivity, in combination with unhealthy food habits, constitutes the second leading cause of death, only exceeded by tobacco\textsuperscript{76}.

These findings on low physical activity and OW/OB seem to be true in the developing world as well. In a study conducted in the city of Merida, Mexico, Sauri Basán\textsuperscript{77} reported high frequencies of overweight (26.4 percent) and obesity (14.4 percent) associated with long periods of television viewing in 14–16 year old adolescents. Even in regions as remote as the Cook Islands the trend toward western and modernized lifestyles is having an effect on health. Uljaszek\textsuperscript{78} reports that 100 percent of the male population between 18 and 35 years of age in the villages he studied is OW/OB. Feasting (binge\textsuperscript{ing}), which used to take place a few times a year, now takes place every Sunday. Physical activity levels are very low, with motorbikes replacing walking. Uljaszek finds that the greater availability of food, the lack of physical activity, and the surge in OW/OB are consequences of modernization due to changes in the welfare politics that mostly affect people from a low socioeconomic status (SES) in the Cook Islands. The net effect of these changes is an extremely negative impact on the health of the population. Regarding this phenomenon, Frisancho\textsuperscript{27} writes, «Since one of the consequences of urbanization in developing nations has been a decrease in physical activity, the reduction of fat oxidation is probably also related to the low level of physical activity that characterizes populations in transition from rural to urban environments».

In developing countries and in communities of recent immigrants to developed countries the high levels of sedentarism are even more negative than for the long-term residents of developed countries. This is so because children, who suffered from gestational or infantile nutritional deprivation, even when given nutritional supplements, maintain lower levels of daily physical activities than controls\textsuperscript{79}. Prenatal and early postnatal undernutrition, then, may lead to lower energy expenditure in physical activity and further exacerbate the potential for OW/OB later in life.

**Intergenerational Influences Hypothesis**

The intergenerational influences hypothesis (IIH) was proposed by Emanuel\textsuperscript{80} and defined as, «...those factors, conditions, exposures and environments experienced by one generation that relate to the health, growth and development of the next generation». The original IIH was proposed to account for the persistence of low birth weight across generations. There is ample evidence in favor of the IIH as a non-genomic explanation for low birth weight and cardiovascular disease\textsuperscript{81}. In the context of this paper, the IIH relates to the existence of a non-genomic mechanism in which malnutrition of the mother during her fetal and early infancy development will have metabolic consequences both for the mother and her offspring\textsuperscript{82,83}.

Ravelli et al.\textsuperscript{82} conducted studies on the victims of the Dutch famine and their offspring during the Second World War. They found that the timing of the nutritional insult seems to be important in the determining the risk for OW/OB in adulthood. Exposure to famine during the first trimester of pregnancy showed significantly higher rates of obesity by age 19. In contrast, exposure to famine during the last trimester of pregnancy or during the first months of postnatal life led to significantly lower rates of obesity by age 19. The authors suggest as a possible explanation for the differences in risk the fact that nutritional deprivation in the first trimester of pregnancy will affect the differentiation of hypothalamic centers that regulate food intake and growth. Late in utero exposure to undernutrition may reduce the extensive adipocyte replication that occurs in the last trimester of pregnancy whereas late in utero exposure to overnutrition may cause adipocyte hyperplasia. Therefore, early undernutrition may impair the regulation of food intake, and predispose to later obesity\textsuperscript{83}.

In these cases obesity, together with heart disease, and late-onset diabetes, can trace its origins back to adverse conditions in the womb, or during infancy. It is not an individual's genes that predispose to obesity later in life; rather it is the intrauterine environment and the physiological condition of the mother during pregnancy\textsuperscript{47,48}.

Other findings from the following epidemiological studies support the IIH. For example, first-born offspring show higher incidence of low-birth weight (LBW) and increased obesity in childhood and adolescence than their subsequent siblings\textsuperscript{84}. Studies of the effects of famines show that long-term effects on offspring may depend on the duration and timing of undernutrition and can be independent of birth size\textsuperscript{85}. Fetal development can be affected by nutritional variation, even within the normal range of western diets when unbalanced dieting by mothers in early pregnancy is common. More specifically, high carbohydrate intake in early pregnancy suppresses placental growth, especially if combined with a low dairy protein intake in late pregnancy. These effects can have long-term consequences for the health of the offspring\textsuperscript{86}. Birth size is reduced in the offspring of women who themselves were fetuses during transient famine\textsuperscript{47}.

We propose that variation in the quality of the intrauterine and early postnatal environment will result in fetus/infant metabolic adjustments, both beneficial and harmful. These metabolic variations will influence the growth, development, and health of individuals for the rest of their life. In the case of women, whose reproductive systems are largely developed during their own fetal period, these variations will also influence their offspring.

The existing research suggests that adjustments toward an energy saving metabolism, with low fat oxidation and preferential fat storage, of the mothers will also
be found in their children. This is so even if the children develop under better nutritional and health circumstances. It may take three or more generations of development under good health conditions to completely over-ride the past history of poor health. If valid, the intergenerational influence hypothesis would help to explain the higher prevalence of OW/OB of minority groups and the children of immigrants in developed countries. Despite better conditions for development in the current generation of children than in the past, these children carry the legacy of undernutrition, heavy workloads, and poor health of their mothers and grandmothers.

Summary of the Review

We present in Figure 1 a summary of the complex associations between behavioral, environmental, metabolic and intergenerational factors that can cause impaired phenotypes, including stunting and a higher prevalence of OW/OB among populations in developed countries, recent immigrants in developed countries, and populations in developing countries. Long-term residents of developed countries tend to be tall and fat, recent immigrants in developed countries tend to be short and fat, and low SES residents of developing countries tend to be stunted and fat. We show what seem to be common factors leading to their specific growth status (i.e. excessive intake of dietary fat, excessive caloric consumption and lack of physical activity) and also the specific metabolic pathways, factors of urbanization and intergenerational effects that contribute to the specific outcomes in terms of growth and health.

Methodologies Proposed for Future Research

Most of the methodologies we propose to assess the components we describe in this paper are standard procedures. Indirect calorimetry should be used to examine the metabolic pathways for reduced fat oxidation and increased metabolism of carbohydrates. Indirect calorimetry measures the respiratory quotient (RQ) and the
substrate utilization (i.e. percentage of proteins, carbohydrates and fats that are being oxidized). Resting energy expenditure (REE), oxygen consumption (VO2), and carbon dioxide consumption (VCO2), are also collected as part of the procedure to estimate RQ. Anthropometric measurements may be used to assess the nutritional status of the subjects. Several types of questionnaires may be used to estimate body mass index (BMI) and/or the sum of skinfolds of the parents. The changes in patterns of physical activity can be assessed by accelerometers. Accelerometers are devices, placed around the waist of the subjects that measure body movements in terms of acceleration that can be used to estimate the intensity of physical activity over time. These devices provide a reliable indication of the energy expended in free-range daily activities.

The novel procedure that we propose here concerns to the assessment of the nutritional status of the mothers when they were infants/children. Most of the research that deals with the relationship between childhood OW/OB and parental physical characteristics focus on the relationship between growth status of the children and body mass index (BMI) and/or the sum of skinfolds of the parents. This relationship maybe an important component on the development of OW/OB, but is definitely not the only one.

We focus, instead, on the nutritional status of the mothers measured by relative leg length as assessed by the SHR. We will consider that the mother was malnourished during her growing years if her SHR is equal or below the percentile 5th of the NCHS reference data. The reasons for choosing relative leg length of the mothers in adulthood to assess their nutritional status as children concern directly the allometric characteristics of the pattern of human growth. Human growth is characterized by a cephalocaudal (head-to-foot) gradient in the sense that during prenatal life and at birth the growth of the head is more advanced than the trunk and the trunk is more advanced than the lower limbs. This is easily seen in children as a disproportionately large head and trunk compared with shorter legs. At birth, the head accounts for 2/8 of the total stature, the trunk for 3/8 of the total stature and the lower limbs account for 3/8 of the total stature. This means that the upper body accounts for more than 50% of the total stature. Though, by adulthood the head only accounts for 1/8 of the total stature, the trunk accounts for 2/8 and the lower limbs for 5/8, if no growth insults were suffered during the growing years. Therefore, if no insults are suffered between birth and puberty, the growth rate of the legs will usually have a faster rate of growth than that of the upper structures. However, if poor nutrition and disease during prenatal life and these factors and/or a heavy workload occur during the first six years of life then the individual undergoing these insults will result in an adult with reduced body length, mostly due to reduced leg length. Martin et al. showed that leg length of the mother was associated with offspring birth weight, independently of mother’s birth weight or mother’s final height. This study shows that leg length is a sensitive marker of adverse nutritional and social exposures during childhood and suggests that the mother’s early environmental exposures determine child’s future health. Additional research in animal models shows that exposure to undernutrition in fetal life determines limb length, fat distribution, locomotor activity and food intake.

Future Research Plans

We are planning to test our methods and hypotheses regarding the behavioral, environmental, metabolic, and environmental components of early life undernutrition leading to later obesity. We hope to carry out research at three sites: 1) Yucatan peninsula, Mexico, 2) a rural community in central Florida, United States, and 3) Detroit, Michigan, United States. The Yucatan and Florida site have large communities of Maya families. The Maya are the indigenous people of Central America. The Maya of the Yucatan are mostly very poor, even by the economic standards of rural southern Mexico. The Maya families of the Florida site represent recent immigrants from a poor, developing country (mostly Guatemala). In the United States these Maya are still of low income, but they can take advantage of a higher standard of living in terms of clean drinking water, programs for maternal, infant, and child nutrition, medical care, education, and employment. The Detroit site has a community of Mexican-American families, most with three or more generations living in the United States. These families are, generally, of middle-to-low income.

These three sites represent the continuum of human populations from developing countries, to immigrants in developed countries, to developed nations as outlined at the top of Figure 1. The behavioral, environmental, metabolic, and environmental components of early life undernutrition that we plan to measure will allow us to assess how these variables lead to later life obesity. With this new information we may also be able to design and implement intervention programs to help stem the ever rising tide of child and adult overweight/obesity that now plagues humanity.

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PONAŠAJNE, OKOLIŠNE, METABOLIČKE I MEĐUGENERACIJSKE KOMPONENTE
POTHRANJENOSTI U RANOJ ŽIVOTNOJ DOBI KAO ČIMBENICI PRETILOSTI U KASNIJOJ
DOBI U ZEMLJAMA U RAZVOJU I MANJINSKIH SKUPINA U SAD-U

S A Ž E T A K

Tranzicija u prehrani, urbanizacija i fizička neaktivnost primarni su faktori odgovorni za epidemiju prekomjerne tjelesne težine/pretilosti (OW/OB) u svjetskim razmjerima. Međutim, ovi faktori ne objašnjavaju tu epidemiju kod stanovništva zemalja u razvoju i nedavnih migranata u razvijene zemlje. Kod navedenih je epidemija OW/OB-a povezana s niskim/zakržljalim rastom i koegzistira sa pothranjenosti u mnogo većem udjelu nego što se to statistički očekuje. Promjene u metaboličkim putovima prema reduciranoj oksidaciji masti i povećanom metabolizmu ugljikohidrata djelomično objašnjavaju taj fenomen. Također, međugeneracijske posljedice pothranjenosti i slabog zdravlja majki mogu dovesti do oslabljenih fenotipova kod potomstva. Predlažemo novu metodologiju za procjenu pothranjenosti u ranom djetinjstvu određivanjem omjera sjedeće visine i ukupne visine majki. Stupanj »kratkonogosti« odraz je pothranjenosti majki u djetinjstvu. Ukupno gledano, ponašajne, okolišne, metaboličke i međugeneracijske komponente pothranjenosti u ranoj životnoj dobi omogućuju preciznije objašnjenje za pretilost u kasnijoj dobi.