Title: The Childhood Obesity Epidemic As a Result of Non-Genetic Evolution: the Maternal Resources Hypothesis

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Abbreviations:

BMI: Body Mass Index

CVD: Cardiovascular Disease

ME: Maternal effects

MRH: Maternal resources hypothesis

PA: Physical activity

PE: Phenotypic evolution

SEE: Socio-environmental evolution

T2DM; Type II Diabetes Mellitus

Abstract

Over the past century, socio-environmental evolution (e.g., reduced pathogenic load, decreased physical activity [PA], improved nutrition) led to cumulative increments in maternal energy resources (i.e., body mass, adiposity) and decrements in energy expenditure and metabolic control. These decrements reduced the competition between maternal and fetal energy demands and increased the availability of energy substrates to the intrauterine milieu. This perturbation of mother-conceptus energy partitioning stimulated fetal pancreatic beta-cell and adipocyte hyperplasia, thereby inducing an enduring competitive advantage of adipocytes over other tissues in the acquisition and sequestering of nutrient-energy via intensified insulin secretion and hyperplastic adiposity. At menarche, the competitive dominance of adipocytes was further amplified via hormone-induced adipocyte hyperplasia and weight-induced decrements in PA. These metabolic and behavioral effects were propagated progressively when obese, inactive, metabolically compromised women produced progressively larger, more inactive and metabolically compromised children. Consequently, the evolution of human energy metabolism was significantly altered. This phenotypic evolution was exacerbated by increments in the use of Caesarian sections that allowed both the larger fetuses and the metabolically compromised mothers who produced them to survive and reproduce. Thus, natural selection was iatrogenically rendered artificial selection, and the frequency of obese, inactive, metabolically compromised phenotypes increased in the global population. By the late 20th century, a metabolic tipping point was reached in which the post-prandial insulin response was so intense, the relative number of adipocytes so magnified, and inactivity so pervasive that the competitive dominance of adipocytes in the sequestering of nutrient-energy was inevitable, and obesity was unavoidable.

Preface

The purpose of this paper is to provide a reinterpretation and synthesis of existing empirical evidence in support of a novel theory of the etiology of the childhood obesity epidemic. The foundational theses are, 1) that obesity is the consequence of the competitive dominance of adipocytes over other cell types in the acquisition and sequestering of nutrient-energy, and 2) that the childhood obesity epidemic is the result of non-genetic evolutionary processes altering the interplay between maternal energy resources (e.g., body mass, adiposity), maternal patterns of physical activity, and the ensuing metabolic sequelae of pregnancy that impact subsequent fetal outcomes.

Introduction

The current gene-centric paradigm of inheritance and evolution has limited explanatory or predictive power with respect to the ubiquity, rapidity, and unidirectional nature of the dramatic increase in the prevalence of obesity and other significant phenotypic changes exhibited by infants and children over the past century (e.g., increased height and head circumference, body mass, precocious menarche[1-4]). While it may be true that "nothing in biology makes sense except in the light of evolution,"[5] for most of the 20th century, non-genetic vectors of inheritance and the evolutionary consequences of developmental dynamics leading to novel phenotypes were largely ignored.[6-8] This *a priori* constraint on heritability and evolution has no empirical or theoretic foundation, yet because theory affects research, clinical practice, and public health policy, the exclusion of non-genetic pathways for the intergenerational transmission of obesity and high-risk phenotypes has been unproductive.[9]

As noted by Harris (1904) more than 100 years ago, "Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest."[10] Given the heterogeneity of environments into which an organism may be born and the fact that phenotype-environment interactions are the substrate upon which natural selection acts, evolutionary fitness (i.e., enhanced survival and reproduction) necessitates mechanisms by which the salient environmental exposures that generated the (successful) phenotype of the mother are translated to offspring (i.e., the "arrival of the fittest"[10]). Because considerable environmental changes commonly occur from one generation to the next, adaptive phenotypes will not necessarily be generated via genetic inheritance. As such, I assert that the "missing heritability"[11] in the rapid phenotypic changes exhibited over the past century (i.e., inheritance not explained via gene-centric paradigms) will not be found in the genome and propose a novel conceptualization of inheritance in which non-genetic vectors of evolution (i.e., maternal effects, socio-environmental and phenotypic evolution) are the predominant causal elements in the recent rise in the prevalence of childhood obesity.

Conceptual Foundation

In this paper, I provide a reinterpretation and synthesis of existing evidence to support a novel theory of inheritance and the evolution of the childhood obesity epidemic: the Maternal Resources Hypothesis (MRH). Stated simply, the MRH posits that the childhood obesity epidemic is the result of non-genetic evolutionary processes over the past century leading to a *metabolic tipping point* in human energy metabolism in which adipocytes (i.e., fat cells) outcompete other cell types in the acquisition and sequestering of nutrient-energy. This competitive dominance was established and is maintained by the confluence of excess maternal

resources (e.g., body mass, adiposity) and inactivity-induced decrements in metabolic control during pregnancy. Given the continuum of fetal metabolic dysfunction induced via the confluence of maternal resources, inactivity, and sedentarism, I posit that the most inactive and obese familial lines have evolved beyond this *metabolic tipping point* (e.g., non-Hispanic blacks, Pima Amerindians).[12-15] For the majority of individuals in these groups, increasing obesity and metabolic dysfunction are inevitable without significant preconception and prenatal intervention.

For this novel conceptualization of inheritance, evolution, and the etiology of obesity, there are a number of essential, interrelated, and empirically supported arguments. First, all living cells compete for nutrient-energy,[16] and the strategies used for the acquisition, storage, and use of nutrient-energy vary across cell types[17] and contexts.[18] Thus, if obesity is defined as an excessive storage of energy as lipid in adipocytes, then it can logically be viewed as the result of the competitive dominance of adipocytes over other cells, tissues, and organs in the acquisition and sequestering of nutrient-energy resources. Second, the recent competitive dominance of adipocytes in children (i.e., the childhood obesity epidemic) was established and is maintained and/or exacerbated by three parallel, reciprocal evolutionary processes: maternal effects (ME),[19] phenotypic evolution (PE),[20] and socio-environmental evolution (SEE).[21,22]

Operational Definitions

Table 1[23-32] provides operational definitions for the key terms used in this manuscript. The definitions are broad and encompass the multi-dimensional nature and interdisciplinary structure of my hypotheses, which link non-genetic evolutionary processes and observed epidemiologic trends in maternal phenotype to the physiological mechanisms driving the

childhood obesity epidemic. Throughout this paper, the term "evolution" is used broadly and refers to progressive, unidirectional changes over time in the variable under examination. This definition subsumes changes in inherited characteristics over successive generations (i.e., descent with modification[33]) and more restricted uses (e.g., changes in allele frequencies). This use is inclusive of the inheritance of both biological and non-biological (i.e., abiotic) characteristics (e.g., an impoverished postnatal environment).

Background for Key Concepts

Maternal Effects

ME are non-genetic vectors of inheritance (i.e., intergenerational transmission) in which maternal phenotype (e.g., age, body mass, metabolism, behavior) and extended phenotype (e.g., environmental modifications)[23] induce rapid, phenotypic alterations in offspring, independent of genotype.[24-28] As such ME represent a mechanism by which the environmental exposures that generated the phenotype of the mother are translated directly (via developmental plasticity[34]) into the phenotype of the offspring.[24] ME may be induced via direct physiological effects on the fetus in utero[35,36] and/or the transmission of behavior[25,28] from mothers to infants and children via social learning, imitation, and operant and/or classical conditioning.[37-40] ME are ubiquitous in nature[25,26] and contribute significantly to the variation of phenotypes derived from any given genotype.[24-28,41,42] ME are causal elements in ontogeny and phenotypic plasticity in response to environmental heterogeneity[24] and are of evolutionary significance[19,42] because they are an essential component in generating the substrate upon which natural selection operates (i.e., the phenotype).[19,24,25,32,42] Within a permissive environment, ME may be cumulative[43,44] and can produce a progressive acceleration or regression of both phenotypic and genotypic evolution, as

well as effects that may be in direct contrast to traits favored by natural selection (i.e., non-adaptive).[7,25,27,45] ME occur in two developmental contexts, the prenatal (i.e., intrauterine) and postnatal environments, and are a major driver of the other evolutionary processes: phenotypic evolution (PE) and socio-environmental evolution (SEE).

Phenotypic Evolution

PE is a unidirectional, progressive alteration in ontogeny that is propagated over multiple, successive generations and may be quantified as the change over time in the population mean for the trait under examination (e.g., height, obesity). As will be presented in detail in a later section, PE is neither mere phenotypic plasticity nor acute adaptations to environmental heterogeneity but the progressive intergenerational transmission of acquired characteristics over multiple successive generations. PE may occur in anatomic and/or physiologic traits (e.g., height, weight, size at birth, age at menarche, hyperplastic adiposity, organ mass and function) or behavioral traits (e.g., inactivity, sedentarism). Because natural selection operates directly on the level of phenotype, PE has direct evolutionary consequences and may be induced via genetic, epigenetic, or non-genetic pathways of inheritance.[32]

Socio-environmental Evolution

SEE is a progression of social and/or cultural practices that significantly alters behavior and/or the physical environments in which humans exist.[21,22] It has been posited that SEE can be measured by a population's "ability to utilize energy for human advancement or needs."[46] SEE

occurs in multiple contexts such as social practices (e.g., healthcare) or changes in the physical environment (e.g., sanitation, food supply, labor and time-saving technologies, heating and air conditioning). SEE may be considered both process and product of numerous factors including both technological innovation[21] and social learning and imitation (e.g., memes).[47] Because SEE may affect the development of phenotype and significantly alter the environmental context and consequent phenotype-environment interactions, it has direct evolutionary consequences. In social species, conspecifics and the environmental context may have a greater impact on an individual's survival than his or her genetic inheritance. SEE, PE, and ME can have reciprocal relationships as phenotype-environment interactions drive developmental dynamics that in turn drive the evolution of the social and environmental milieus.

Figure 1 is a conceptual depiction of the MRH.

The Maternal Resources Hypothesis (MRH)

The Recent Evolution of Human Energy Metabolism

Human metabolic, cardiovascular, and musculoskeletal systems evolved in environments in which survival necessitated prodigious amounts of physical exertion and high levels of energy expenditure.[48] Evading predators, the hunting and gathering of food, and the literal "chopping wood and carrying water" of daily existence provided a wholesome dose of physical activity that obviated the need for deliberate exercise.[49] Nevertheless, over the past few centuries, humans have become extremely adept at altering the environments in which they exist, and the evolution of their physical, social, and cultural milieus (i.e., SEE) has proceeded much more rapidly than genetic evolution.[22] SEE has altered the evolution of human energy metabolism by inducing

substantial decrements in the energy expenditure (EE) imposed by daily life,[50] while improving both the quality and quantity of nutrient-energy availability.[51] For example, as thermo-neutral environments became ubiquitous,[52] the energy cost of thermoregulation declined, and improved sanitation (e.g., clean water, safer food)[53] and vaccinations[54] decreased the energy cost of supporting parasites (e.g., fleas)[55] and resisting pathogens (e.g., communicable diseases, diarrheal infections).[56] Together, these changes not only decreased EE, but dramatically curtailed periods of low energy consumption via reductions in both illness-induced and hyperthermic hypophagia.[57]

By gradually reducing the energy costs of survival and increasing nutrient-energy availability,[53] SEE increased the energy available for development, growth, and reproduction. The positive energy balance facilitated by SEE led to the evolution of many human characteristics (i.e., PE). For example, improvements in health and nutrition over the last century have led to progressive and cumulative increases in height,[1] body stature and mass,[58] birth weight,[59-61] organ mass,[2,62] head circumference,[3,63] and fat mass/adiposity.[64] In concert with these increments has been a progressive global decline in the age at which adolescents attain sexual maturity, with breast development (i.e., thelarche) and menses (i.e., menarche) in girls and testicular development in boys beginning a year earlier in many populations.[4] This PE has been ubiquitous and significant. A recent examination of the validity of the 1975 "Reference Man"[65] for determining the safety of medication doses and occupational radiation exposure found that men and women in 2010 were heavier, taller, and had more fat and skeletal muscle mass and larger organ masses.[65]

Given that reproductive capacity is an essential facet of evolution, and in humans reproduction cannot occur without sufficient maternal resources (i.e., body mass, adiposity),

these alterations in phenotype have non-genetic evolutionary consequences (i.e., they alter survival and reproductive success independent of changes in gene or allele frequency). Logically, these results are representative of PE because each of the aforementioned characteristics developed with a progressive, unidirectional linearity that was transmitted over successive generations. For example, from 1900 to 2000, the median height for Japanese boys and girls increased 20 cm and 19 cm at ages 13 and 11, respectively.[1] These changes were neither mere developmental plasticity nor acute adaptations to improved nutrition and/or decreased energy expenditure via reductions in pathogen load. These changes in phenotype were indicative of a gradual, progressive, and *enduring* intergenerational transmission of greater stature over many generations that was robust to acute variations in environmental influences (e.g., food shortages).

The Late 20th Century and Increments in Maternal Resources

Until the middle of the 20th century, SEE and PE were adaptive, given that in most species, mothers with greater energy resources (i.e., physiologic or environmental) beget more robust offspring,[41] and it is well-established that human mothers with adequate or ample physiologic and environmental resources produce healthier, more robust infants and children than women with fewer resources.[51] Nevertheless, I posit that as the century drew to a close, sustained SEE and PE began driving maternal effects (ME) that led to the childhood obesity epidemic.

By the late 20th century, humans in industrialized nations were immersed in environments explicitly engineered to reduce manual labor,[66-68] increase physical comfort (e.g., the ubiquity of chairs and thermo-neutral environments[52]), and afford passive entertainment.[69] As a result,

physical inactivity and sedentary pastimes (e.g., web-surfing, TV viewing) became both ubiquitous features of the post-industrial world[51] and leading global risk factors for mortality and morbidity.[70] Importantly, the confluence of passive transportation, spectator-based entertainment and decrements in occupational and household PA[66,68,71] led to significant declines in PA energy expenditure (PAEE) and increments in sedentary behaviors in children, women, and mothers.[66-68] From the 1960s to 2010, estimated maternal household PAEE decreased ~1,200–1,500 kcals/week, as the time spent in sedentary leisure (e.g., watching television) doubled to more than 2.5 hr/day.[68] A majority of pregnant women currently spend >50% of their waking hours in sedentary behavior, and >15% of pregnant women spend more than 5 hr/day in leisure-time screen-based media use.[72] Recent work suggests that by the 1990s, women and mothers allocated more time to screen-based media use (e.g., watching television) than to all forms of PA combined.[68] In concert with the progressive increments in sedentarism, inactivity, and PAEE, were progressive decrements in population-level metabolic control[73-75] and substantial increases in maternal pregravid obesity,[76] gestational weight gain,[77] and gestational diabetes (GDM).[78]

The Necessity of Physical Activity for Metabolic Health

Skeletal muscle (SM) activation via PA is an absolute requirement for metabolic health.[79] Therefore, as mothers spent more time in sedentary behavior and the intensity, frequency, and volume of maternal PA decreased,[67,68] there were marked reductions in SM activation and energy flux. Because SM is the principal tissue for both insulin-mediated glucose disposal[17] and fatty acid oxidation[18] and an essential element of energy metabolism,[80] the progressive reductions in maternal PA and PAEE over the past century would result in progressive decrements in

metabolic,[17,29,31,81-83] glycemic,[83-85] and lipidemic control.[86-88] This loss of metabolic control led to both transient hyperglycemia (i.e., glycemic excursions) and hyperlipidemia,[89-91] the former driven by reductions in insulin signaling resulting from replete myocyte glycogen stores,[92,93] and the latter from reduced SM energy demands and consequent decrements in total fatty acid oxidation,[86-88,94] increments in hepatic and adipocyte de novo lipogenesis,[95-97] and lipid accumulation in adipose tissue.[98,99]

The Maternal Effects of Inactivity and Insulin Resistance

While inactivity has dire effects on human energy metabolism[29,30,100,101] and health,[70] given the recent SEE and PE, it is substantially more pathologic to pregnant women and their fetuses. Human pregnancy is characterized by numerous metabolic changes that promote the accretion of adipose tissue in concert with impaired insulin sensitivity and insulin resistance.[102] As explained previously, SM is the principal tissue for glucose disposal, and normal pregnancies will exhibit a hormone-induced 40–60% reduction in insulin-mediated glucose disposal.[103] This decrement in insulin sensitivity drives a 200–300% increase in insulin secretion to maintain maternal glycemic control.[103] I posit that the progressive reductions in maternal PA and PAEE and consequent reductions in SM activation over the past half century act synergistically with the naturally occurring metabolic sequelae of pregnancy (i.e., hormone-induced insulin resistance, increased adiposity) to exacerbate the negative metabolic consequences of inactivity[29,30,100,101] and drive fetal pathologies. The reductions in insulin sensitivity and increments in transient hyperglycemia and hyperlipidemia[91] substantially increase the availability of energy substrates to the intrauterine environment. Because the human placenta evolved in a context of intense

competition between maternal resources and fetal demands (i.e., low to moderate maternal body mass and adiposity in concert with moderate to high levels of maternal EE, PA, and PAEE[104-106]), the current context of high maternal resources in combination with low PA represents an evolutionary mismatch. Given that the partitioning of nutrient-energy between the mother and conceptus is a major determinant of fetal outcomes,[107] the perturbation of the intrauterine milieu via the mismatch of increased maternal metabolic resources (e.g., body mass, adiposity) and inactivity driven decrements in PAEE has significant metabolic consequences for offspring.[108]

Excess intrauterine energy substrates stimulate the hypertrophy and hyperplasia of both pancreatic beta-cells[35,109-113] and adipocytes,[114-118] upregulate fetal fatty acid and glucose transporters,[117] increase the direct free fatty acid uptake and storage as triglyceride in fetal adipocytes,[119,120] alter myogenesis and increase collagen accumulation and crosslinking in fetal SM,[121,122] and increase expression of enzymes mediating de novo lipogenesis.[117] These points are critical. First, fetal adipose de novo fatty acid synthesis is a primary mechanism for the accumulation of lipid in fetal adipocytes.[123] Second, maternal glucose is the major substrate for fetal lipogenesis, is highly correlated with newborn body fat,[124] and is a predictor of the fat mass of pre-pubertal offspring.[114] In the third trimester, maternal PA will be at its lowest point,[125,126] and, therefore, maternal glycemic control will be at its nadir. Consequently, fetal lipogenesis and adipocyte hyperplasia will be maximized when compared to metabolically healthy (e.g., lean, active) mothers due to a number of processes. First, maternal hyperglycemic excursions will drive fetal hyperglycemia, which in turn results in fetal hyperinsulinemia (via enhanced beta cell mass and function) and drives growth factors that result in excessive fetal growth and adiposity.[127-130] Second, maternal inactivity decreases maternal SM fatty acid oxidation and

consequently promotes lipid transfer to the fetus by increasing the maternal–fetal fatty acid gradient.[115]

Given the strong inverse relationship between the oxidation of dietary fat in SM and obesity (i.e., obese individuals partition more fatty acids to storage as lipid, while lean individuals oxidize a greater relative amount[131]), the cumulative effect of alterations in fetal myogenesis and impaired SM morphology in concert with a greater number of adipocytes and increased pancreatic beta cell function (i.e., enhanced insulin secretion) produce metabolically compromised infants predisposed to life-long inactivity, metabolic dysfunction, and obesity due to the competitive dominance of adipocytes in the acquisition and sequestering of nutrient-energy.

Additionally, while SEE led to large and significant decrements in maternal activity and glycemic control, it also led to substantial declines in maternal smoking.[132] Unfortunately, despite the maternal and fetal health benefits associated with reductions in tobacco use, the mild fetal hypoxia induced via smoking[133] may have played a role in delaying the negative effects of inactivity on maternal glycemic control and consequent mother-conceptus energy partitioning by altering fetal glucose transporter regulation[134] and growth.[135]

Figures 2 and 3 depict the hypothesized consequences of the perturbation of maternal-conceptus energy partitioning and fetal outcomes.

Counterfactual Support for the Maternal Resource Hypothesis

The aforementioned results are in direct contrast to women in non-industrialized nations who have not experienced similar SEE and PE over the past century. These women have

relatively high levels of PA in concert with low energy resources (i.e., low body mass, adiposity, and nutrient-energy intake).[136] Given that the evolutionary forces that induced increments in maternal energy resources and decrements in PA are not present, the net result is a decrease in the energy available to the intrauterine milieu. In the absence of maternal resources to buffer fetal demands,[136] the competition between fetal energy requirements and maternal energy needs results in intrauterine growth restriction[107] and associated pathologies.[137] In congruence with the thrifty phenotype (i.e., Barker) hypothesis,[138,139] the MRH posits that in the context of high levels of PA and low nutrient-energy intake, maternal myocytes and other metabolically active tissues (e.g., organs) outcompete both maternal adipocytes and fetal tissues for nutrient-energy. This results in the loss of maternal body mass and permanently alters fetal development and consequent energy metabolism while predisposing offspring to chronic non-communicable diseases (e.g., type II diabetes mellitus [T2DM], and cardiovascular disease [CVD]) when the post-natal environment permits low levels of PA in combination with adequate nutrition. Figure 4 depicts fetal outcomes as maternal resources and PA vary.

The MRH and the extant evidence suggest a continuum of metabolic control and mother-conceptus energy partitioning with both restricted[136] and excess maternal resources[140] pathologically altering the metabolic health of offspring.[141] As such, the ideas presented herein subsume and extend both the Barker[139] and Pedersen hypotheses,[140] and offer a non-genetic mechanism for the intergenerational transmission of obese and other high-risk phenotypes. Stated simply, the MRH posits that the risk for obesity, T2DM, and CVD are propagated progressively via the interplay between maternal energy resources, maternal patterns of physical activity, and the ensuing metabolic sequelae of pregnancy.

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Postnatal Maternal Effects

The intergenerational transmission of behavior is well accepted in social animals such as humans.[142] Because the primary ecological niche of an infant is the social environment that caregivers create, the processes of postnatal ME provide non-genetic mechanisms by which the environmental exposures generated by the behavioral phenotype of the mother (or caregiver) directly alters the behavioral phenotype of infants and children. Numerous potential mechanisms have been posited including social learning, modeling (i.e., observational, operant, and/or classical conditioning.[37-40,143-145] It is well established that a mother's television (TV) viewing behaviors influence her progeny's TV behaviors;[37] therefore, as with the intergenerational transmission of smoking behavior,[144] children who grow up with an inactive, sedentary caregiver may be more likely to be sedentary, inactive, and obese as adults.[143,146] For example, if a woman develops the habit of breastfeeding while watching TV, her infant may associate the sights and sounds of the TV with feeding behavior. Given that maternal attention and feeding are powerful reinforcers,[147] the process of classical conditioning may (metaphorically speaking) turn the TV into Pavlov's dinner bell.[145] The conjoined behaviors of feeding and TV viewing will be continuously reinforced when TV and food are used to control infant behavior (i.e., used as a babysitter).[14,69]

This conceptualization of the intergenerational transmission of inactivity and sedentary behavior is supported by research demonstrating strong relationships between mother-daughter BMI and obesogenic behaviors (e.g., eating in front of the TV).[148] Maternal TV viewing and obesity are associated with greater infant TV exposure,[146] with infants as young as three months

old exposed to an average of > 2.5 hours of TV and/or videos daily, and nearly 40% of infants exposed to >3 hours of daily TV before 12 months of age.[146] Having a TV in the bedroom is one of the most powerful predictors of childhood obesity,[149] and large-scale epidemiologic studies have demonstrated that one of the strongest determinants of obesity and cardio-metabolic risk factors in later life was TV viewing in early life.[150] In addition to the metabolic effects of *postnatal ME*, there are also cognitive effects. TV viewing before the age of three is associated with cognitive delays, decrements in language development, attentional issues, and sleep disorders.[151]

Screen-based Media as Caregiver (i.e., TV as Babysitter)

I posit that current obese phenotypes are predisposed at birth via prenatal ME, and that these predispositions are permanently entrenched by the infant's and child's early social environments. Over the past 50 years, the use of screen-based media has increased significantly,[152] and by the late 1990s, mothers and children were spending the vast majority of their leisure time watching TV.[69,148] Screen-based media (e.g., TV) is often used as a surrogate caregiver (i.e., "babysitter")[69] for precisely the same reason that it is detrimental to infants and children: it captures their attention and keeps them relatively immobile. In a non-media-enhanced world, the child will stimulate his or her nervous system via movement and "exploration" facilitated by the activation of SM. Because osteocytes, myocytes, and adipocytes share a common pool of progenitor cells, reduced PA leads to a reduction in the physiological resources (e.g., muscle development, strength, coordination) necessary for lifelong PA, and every kilocalorie of energy that is not used to build muscle and bone may be used to further

increase adipocyte size and/or number.[121,153] As such, the predisposition to obesity would be instantiated via accelerated hyperplastic adiposity, inactivity, decrements in the physiological resources necessary for movement (e.g., strength, coordination), and the initiation of a positive feedback loop that negatively alters health trajectories over successive generations via mother-daughter transmission.

Iatrogenic Artificial Selection

The excessive fetal growth induced via evolutionary processes has resulted in larger and fatter infants over the last few generations (e.g., increased neonate organ mass, head circumference, fat mass and birth weight[2,3,60,63]). Because the evolution of infant head circumference[154] has progressed more quickly than the evolution of the birth canal,[155] the prevalence of dystocia-related caesarian sections (i.e., surgically assisted births) has increased substantially.[15,154,156] This SEE (i.e., progression of medical technology and practice) allowed both larger fetuses and the mothers who produced them to survive and reproduce, thereby increasing the frequency of metabolically compromised, obese phenotypes in the global population. As such, "natural selection" was iatrogenically and unintentionally rendered "artificial selection." Support for the artificial selection of metabolically compromised infants is clearly evidenced by numerous facts: familial line is a major predictor of both dystocia[157] and caesarian birth,[158] childhood obesity has a strong relationship with cesarean birth,[159] and, most importantly, the frequency of caesarian births is greatest in the population that is most inactive, sedentary, and obese (i.e., non-Hispanic black)[13-15] and has had the largest increments in TV viewing over the past 50 years.[160]

Metabolic Tipping Point

The greatest declines in maternal activity (via our data[67,68]) occulted from the 1960s to the 1970s, although prior research suggests that the declines began earlier.[161] This suggests that the female children of the increasingly inactive mothers of the 1950s through the 1970s would themselves be having metabolically compromised children and grandchildren 20 to 50 years later (i.e., from the early 1970s to late 2000s). As these metabolically compromised female children matured and transitioned through puberty, adipocyte number and mass were further exacerbated via the hormonal milieu[162] and obesogenic environment (e.g., inactive caregivers producing inactive children and adolescents). When these women reproduced, the anatomic, physiologic, metabolic, and behavioral trajectories induced by the previous generation's phenotype (i.e., the ME) were propagated progressively as the ontogeny of their offspring was initiated at a point further along the continuum of phenotypic plasticity (i.e., advanced baseline). This evolutionary process of accumulative maternal effects[19] was facilitated by medicalized childbirth and led to *anatomic, physiologic, metabolic, and behavioral tipping points* that ensured an escalating competitive dominance of adipocytes in the acquisition and sequestering of nutrient-energy in many human sub-populations (e.g., African Americans). Within a few generations, the intensified post-prandial insulin response was so large (via enhanced beta-cell mass and function and inactivity-induced insulin resistance), the relative number of adipocytes so excessive, and inactivity so pervasive that the sequestering of nutrient-energy in adipocytes was inevitable and obesity was unavoidable.

Consequences of the MRH for Obesity Research

The majority of obesity research is based on the conceptual framework of energy balance derived from the first law of thermodynamics (FLT).[163] The fundamental *a priori* assumption is that relative imbalances between nutrient-energy consumption and energy expenditure *cause* the excessive storage and sequestering of energy as lipid in adipocytes. This paradigm assumes a temporality that has no empirical foundation and merely provides a valid description of the increase in the storage and sequestering of energy (i.e., an analytic truth). As such, these paradigms offer no insight into the causal mechanisms or the temporal nature of the increase. I argue that because all tissues compete for energy, obesity is the result of adipocytes outcompeting other cells, tissues, and organs in post-prandial periods. The initial trajectory that engenders this competitive dominance of adipocytes (and consequent obesity) is initiated *in utero* due to maternal effects induced via reduced metabolic control leading to the confluence of an intensified insulin response (via enhanced beta-cell mass and function), decreased fatty acid oxidation via decrements in myogenesis and myocyte morphology, and the law of mass action (i.e., a larger relative number of fat cells disposing of a larger percentage of energy intake).

This conceptualization is strongly supported by extant research, given that increments in fat mass are a function of adiposity,[164] adipocyte number is a primary determinant of obesity,[165,166] and early development is a major determinant of adipocyte number.[165] As such, the infant born to an inactive mother would be metabolically compromised via the confluence of the *prenatal ME* (e.g., adipocyte hyperplasia, reduced myogenesis) and the *postnatal ME* (e.g., learned inactivity). This hypothesis is strongly supported by the facts that the adipose tissue of young obese children differ both qualitatively and quantitatively from lean children[167] and that adipocyte number increases throughout early development.[168] Additionally, monozygotic twins concordant for birth weight exhibit similar adipocyte numbers, while in those discordant for birth

weight, the smaller twin displays both lower body weight and adipocyte number.[169] I posit that these results suggest an in utero "training effect" in which the chronic partitioning of energy to storage in adipose tissue induces numerous metabolic sequelae that lead to obesity via adipogenic nutrient partitioning and an exacerbated recruitment and differentiation of mesenchymal cells to mature adipocytes.[170]

Importantly, the increase in the storage and sequestering of nutrient-energy in adipocytes reduce the substrates and metabolic stimuli that inhibit hunger and appetitive processes (e.g., ATP/ADP ratio, hepatic energy flux, glucose and fatty acid oxidation).[171,172] As such, this sequestration engenders a perception of fatigue[173] (and consequent inactivity and inactivity-induced decrements in metabolic control), depression,[174] decreased energy,[173] and an accelerated development of hunger and consequent shorter inter-meal interval and/or increased energy density per meal. These phenomena result in a positive feedback loop that leads to excessive food and beverage consumption that exacerbates the vicious cycle of adipogenic nutrient-energy partitioning, increasing adiposity, decreased metabolic control, and obesity.

Logically, people do not develop excessive adiposity simply by being in positive energy balance; if this were true, the increases in muscle mass and parallel decreases in relative body fat as demonstrated by bodybuilders would be impossible. As such, the genesis of obesity is predicated on a greater allocation, storage, and sequestering of lipid in adipocytes as a function of adipocyte number, pancreatic beta-cell function (i.e., insulin secretion), and SM energy metabolism (i.e., glucose and fatty acid oxidation, glycogen synthesis).

Obesity as an Inherited, Chronic Condition

The MRH suggests that the energy metabolism of affected individuals is permanently altered in utero, and strategies such as reductions in energy intake (i.e., “dieting”) and other energy manipulations (e.g., exercise) will be offset, not by a regulatory mechanism per se, but by the fact that the nature of the nutrient-energy partitioning will not be altered via the loss of lipid content in the adipocytes or an increase in fatty acid oxidation by other tissues. Because it can be assumed that human energy metabolism evolved under intense selective pressures, it will be robust to acute perturbations. In other words, as long as the predisposing metabolic impairments exist, the individual will continue to store a greater relative amount of energy as lipid in adipocytes when compared to an individual with normal SM metabolism, pancreatic beta cell function, and adipocyte number. Hence, for the majority of individuals, obesity is a chronic condition of adipocyte dominance in the acquisition and sequestering of nutrient-energy that cannot be “cured” via “moving more and eating less.”

Practical Implications of the Maternal Resources Hypothesis

Given the breadth, scope, and strength of the evidence that supports the MRH, there are a number of practical implications. First, the acknowledgment that obesity is the result of non-genetic evolutionary forces and not gluttony and sloth[175] may help to alter the moralizing and demoralizing social and scientific discourse that pervades both public and clinical settings. Second, the conceptual framework of tissues competing for nutrient-energy substrates has consequences for both the research community and clinicians. Future research may be most productive if funding is directed away from naïve examinations of energy balance per se and redirected to investigations of interventions that alter the competitive strategies of various

tissues. From the standpoint of the clinician, accurate patient phenotyping (inclusive of family obstetric history and metabolic profiling) may allow the targeting of women most likely to be a part of populations that have evolved beyond the metabolic tipping point and therefore require significant preconception intervention.

Summary of the Maternal Resources Hypothesis

The MRH posits that the childhood obesity epidemic is the result of the evolutionary processes of ME, PE, and SEE leading to a *metabolic tipping point* in human energy metabolism in which adipocytes outcompete other cell types in the acquisition and sequestering of nutrient-energy. The recent competitive dominance of adipocytes was achieved via the confluence of multiple evolutionary processes. Over the last century, SEE and PE facilitated increments in maternal resources (e.g., body mass, adiposity), inactivity, and sedentarism that induced decrements in maternal metabolic control (e.g., insulin sensitivity). This PE pathologically increased the energy substrates available to fetuses, causing mothers to produce progressively larger, fatter, more inactive, and consequently more metabolically compromised and less physically fit[176] offspring predisposed to chronic non-communicable diseases.[177] Increments in the use of caesarian sections allowed the frequency of metabolically compromised female offspring in the population to increase. When these females reproduced, the ME of hyperplastic adiposity, intensified pancreatic beta cell function, altered SM myogenesis, and inactivity were progressively propagated to successive generations, thereby making obesity inevitable in many human familial lines. The consequences of the MRH suggest that recent evolutionary trends have

not been adaptive,[178] and that the evolutionary fitness (i.e., survival[178] and reproduction[179]) of some human familial lines are in decline.

Conclusion

The MRH posits that obesity is the result of the competitive dominance of adipocytes over other tissues in the acquisition and sequestering of nutrient energy, and that the current population-wide dominance of adipocytes (i.e., the childhood obesity epidemic) is the result of non-genetic evolutionary processes altering the interplay between maternal energy resources, maternal patterns of physical activity, and the ensuing metabolic sequelae of pregnancy over multiple generations. Given that maternal metabolic control is a strong determinant of fetal metabolic outcomes and health (e.g., risk for obesity, T2DM, CVD), the health and wellbeing of future generations depend on policies and preconception interventions that can ameliorate the effects of more than a century of non-genetic evolutionary processes and overcome the current competitive dominance of adipocytes.

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Table Legend

Table 1: Operational Definitions

Figure Legend

Figure 1: Conceptual depiction of the MRH

Figure 2: Hypothesized Consequences of Excess Maternal Glucose on Fetal Pancreatic beta-cell Function; T2DM = type II diabetes mellitus, CVD = cardiovascular disease.

Figure 3: Hypothesized Consequences of Excess Intrauterine Energy on Fetal Adipocyte Development

Figure 4: Hypothesized Consequences of Maternal Energy Balance on Fetal Development; SEE = Socio-Environmental Evolution, PE = Phenotypic Evolution, LGA = Large for Gestational Age, SMA = Small for Gestational Age.

Table 1: Operational Definitions

Environment	**External:** the totality of the biotic and abiotic factors that are independent of an organism but influence development. **Internal:** the totality of the anatomical, physiological, and metabolic constituents that form an organism.
Evolution	Progressive, unidirectional changes over time in the variable under examination; inclusive of changes in inherited characteristics over successive generations and the inheritance of biological and non-biological (i.e., abiotic) characteristics (e.g., environmental resources).
Inheritance/Heritability	The intergenerational transmission of social and biological traits, attributes, characteristics, and/or features. Inheritance may occur via non-genetic (e.g., physiologic, cultural), epigenetic, and genetic vectors.
Maternal Effects (ME)	ME are non-genetic vectors of inheritance (i.e., intergenerational transmission) in which maternal phenotype (e.g., age, body mass, metabolism, behavior) and extended phenotype[23] directly induce rapid, phenotypic alterations in offspring, independent of genotype.[24-28]
Nutrient-Energy	Energy derived from the consumption of food and beverages that is available for metabolic processes.
Nutrient Partitioning	The metabolic fate of consumed nutrient-energy (e.g., anabolism, storage, oxidation). Body composition, physical activity and hormonal status (e.g., puberty, menopause) are the primary determinants.[29-31]
Phenotype	An organism's observable characteristics or traits, including but not limited to its morphology, development, physiology, metabolism, behavior, and products of behavior.[23]
Phenotypic evolution (PE)	Unidirectional, progressive alterations in ontogeny that are propagated over multiple, successive generations and may be

	quantified as the change over time in the population mean for the trait under examination (e.g., height, obesity). PE is driven by developmental plasticity and adaptations to environmental heterogeneity. Because natural selection operates directly on the level of phenotype, PE has direct evolutionary consequences and may be induced via genetic, epigenetic, or non-genetic pathways of inheritance.[32]
Socio-environmental Evolution (SEE)	SEE is a progression of social and/or cultural practices that significantly alters behavior and/or the environments in which humans exist.[21,22] SEE has direct evolutionary consequences because phenotype-environment interactions are the substrate upon which natural selection acts. In social species, conspecifics and the environmental context may have a greater impact on an individual's survival and reproduction (i.e., evolutionary fitness) than his or her genome.

Figure 1:

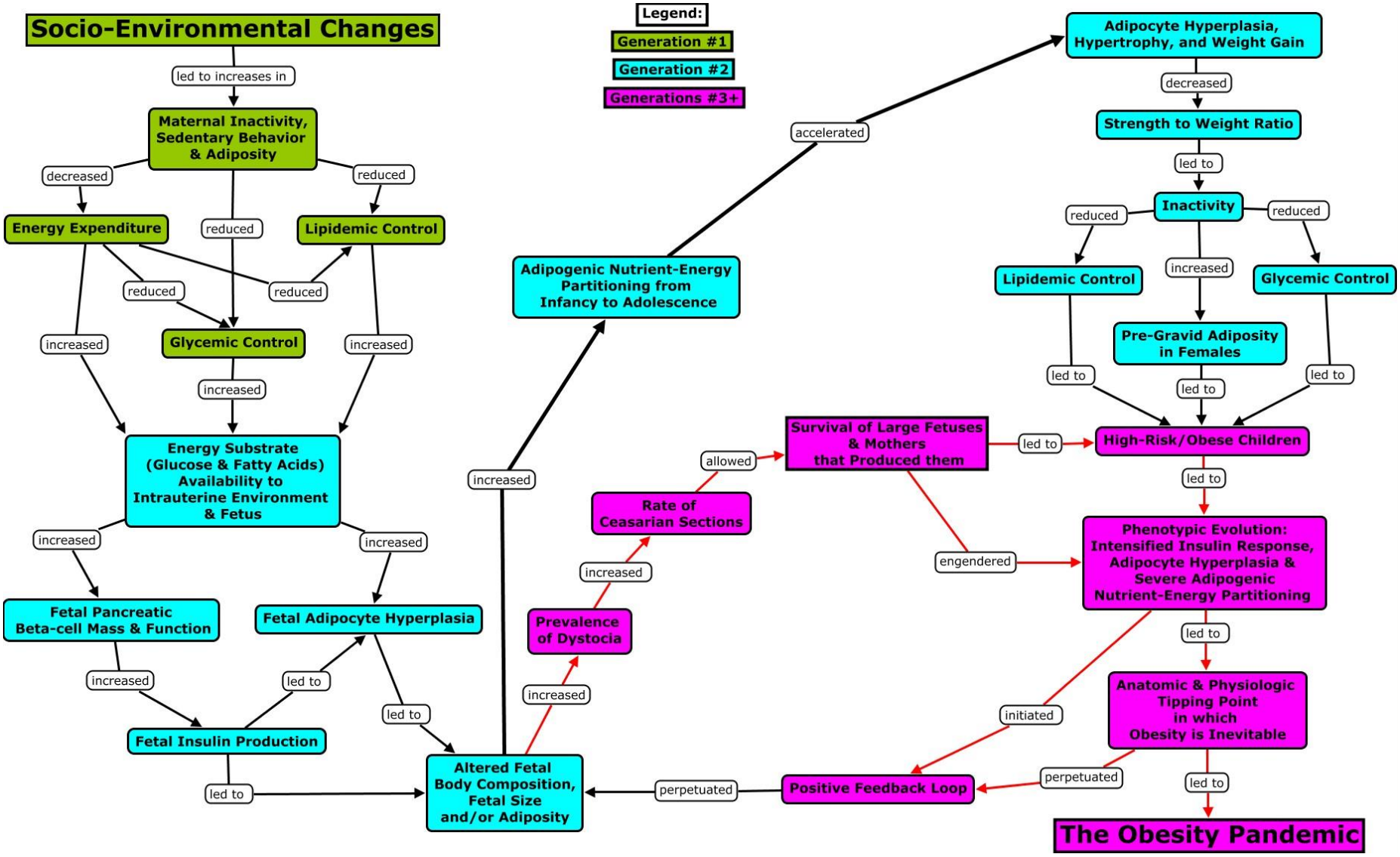
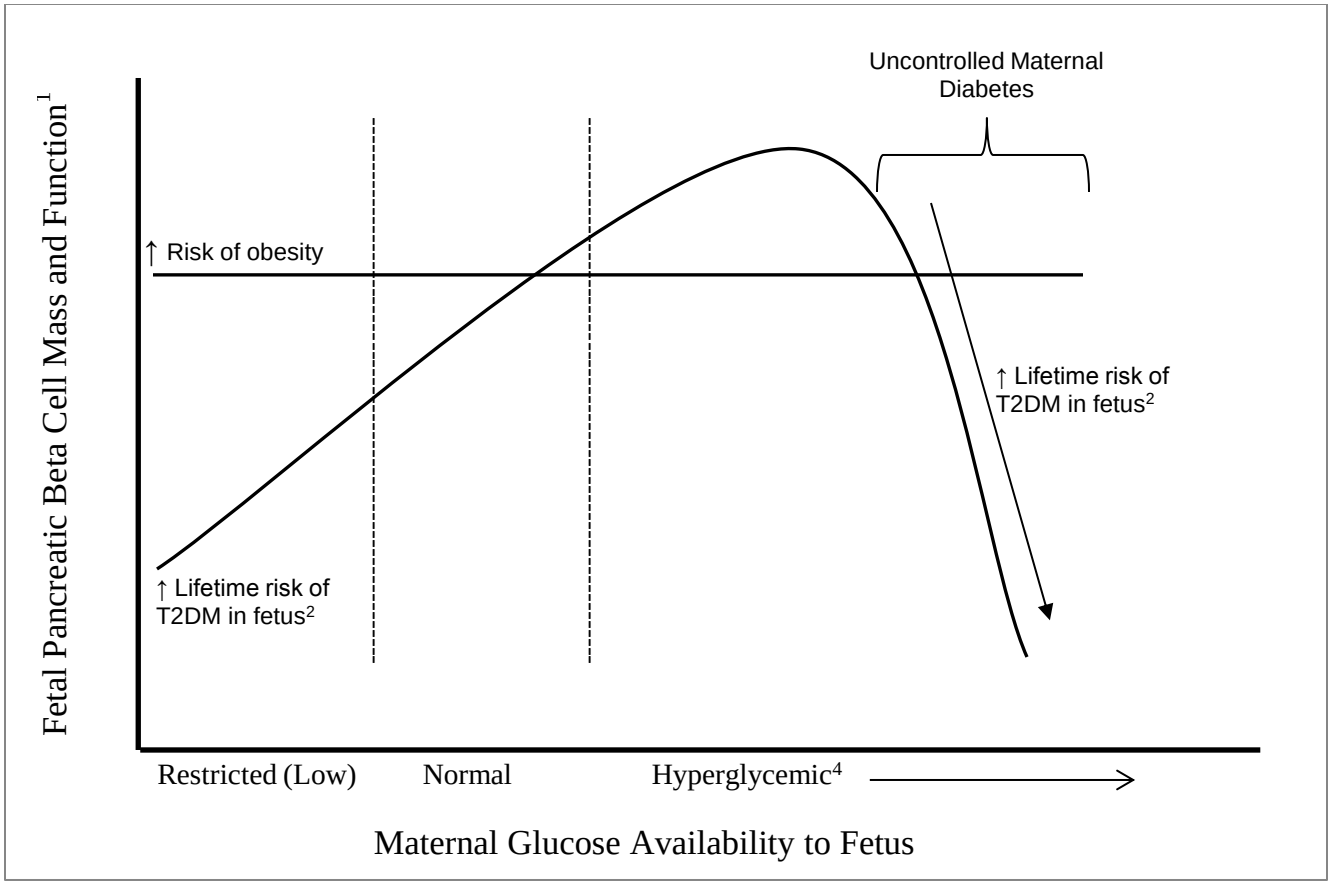

Legend:
Generation #1
Generation #2
Generations #3+
Socio-Environmental Changes
led to increases in
Maternal Inactivity, Sedentary Behavior & Adiposity
decreased
reduced
Energy Expenditure
reduced
Lipidemic Control
reduced
reduced
increased
Glycemic Control
increased
increased
Energy Substrate (Glucose & Fatty Acids) Availability to Intrauterine Environment & Fetus
increased
increased
Fetal Pancreatic Beta-cell Mass & Function
Fetal Adipocyte Hyperplasia
increased
led to
led to
Fetal Insulin Production
led to
Altered Fetal Body Composition, Fetal Size and/or Adiposity
perpetuated
Positive Feedback Loop
increased
Prevalence of Dystocia
increased
Rate of Ceasarian Sections
allowed
Survival of Large Fetuses & Mothers that Produced them
increased
Adipogenic Nutrient-Energy Partitioning from Infancy to Adolescence
accelerated
Adipocyte Hyperplasia, Hypertrophy, and Weight Gain
decreased
Strength to Weight Ratio
led to
Inactivity
reduced
reduced
Lipidemic Control
increased
Pre-Gravid Adiposity in Females
Glycemic Control
led to
led to
led to
led to
High-Risk/Obese Children
led to
Phenotypic Evolution: Intensified Insulin Response, Adipocyte Hyperplasia & Severe Adipogenic Nutrient-Energy Partitioning
engendered
led to
Anatomic & Physiologic Tipping Point in which Obesity is Inevitable
initiated
perpetuated
led to
The Obesity Pandemic

Figure 2: Hypothesized Pancreatic β-cell Function and Maternal Glucose Availability to Fetus



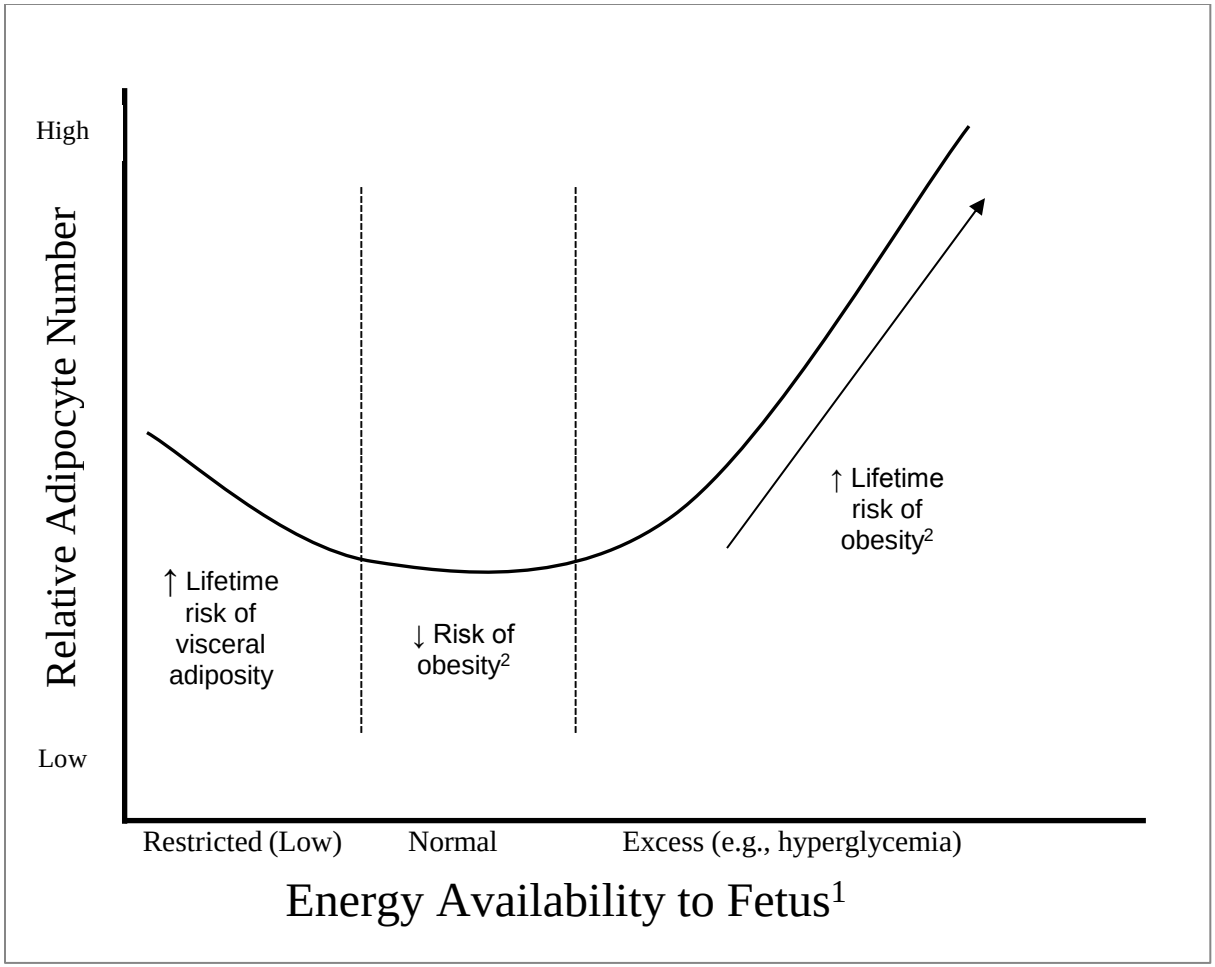
[1] Hypertrophy and hyperplasia of fetal pancreatic beta cells.[105-108]

[2] An inactive lifestyle as a child and adolescent is a necessary condition for risk to be actualized.

[3] Increased hyperglycemic-induced apoptosis increases risk of immune response generalization and subsequent destruction of pancreatic β-cells.

[4] Hyperglycemia may be transient (e.g., acute excursions induced via mild insulin resistance) or chronic (frank diabetes).

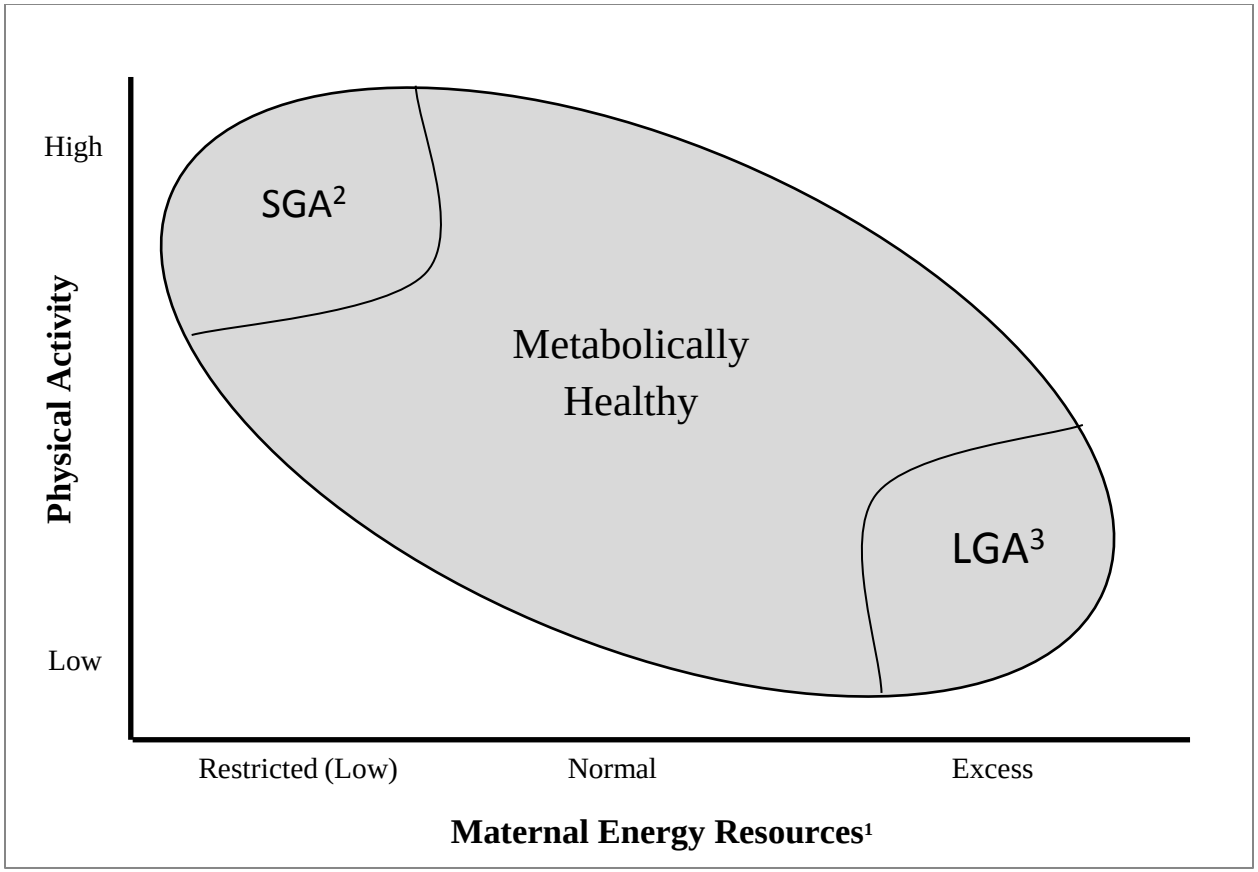
Figure 3: Hypothesized Obesity Risk: Adipocyte Hyperplasia and Maternal Energy Available to Fetus



[1] Determined by maternal adiposity, energy intake, physical activity, and total daily energy expenditure.

[2] Obesity as categorized by body mass index (BMI) >30kg/m^2.

Figure 4: Hypothesized Fetal Birth Outcomes: Physical Activity and Maternal Energy Resources



[1] Maternal resources determined by SEE, PE of familial line, prenatal body mass, adiposity, and energy intake.

[2] Small for Gestational Age (SGA): predisposed to visceral adiposity type II diabetes mellitus (T2DM), and cardiovascular disease (CVD).

[3] Large for Gestational Age (LGA): predisposed to obesity, T2DM, and CVD.