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## Fetal Origins of Adult Disease

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### Abstract

Dr. David Barker first popularized the concept of fetal origins of adult disease (FOAD). Since its inception, FOAD has received considerable attention. The FOAD hypothesis holds that events during early development have a profound impact on one's risk for development of future adult disease. Low birth weight, a surrogate marker of poor fetal growth and nutrition, is linked to coronary artery disease, hypertension, obesity, and insulin resistance. Clues originally arose from large 20<sup>th</sup> century, European birth registries. Today, large, diverse human cohorts and various animal models have extensively replicated these original observations. This review will focus on the pathogenesis related to FOAD and examines Dr. David Barker's landmark studies, along with additional human and animal model data. Implications of the FOAD extend beyond the low birth weight population and include babies exposed to stress, both nutritional and non-nutritional, during different critical periods of development, which ultimately result in a disease state. By understanding FOAD, health care professionals and policy makers will make this issue a high healthcare priority and implement preventative measures and treatment for those at higher risk for chronic diseases.

### Introduction

David Barker's keen observations have been popularized as the "Barker hypothesis," or "Fetal Origins of Adult Disease" (FOAD). It was his group that noted that low birth weight (LBW) serves as proxy not just for fetal, but also adult health. Today, LBW is associated with a host of chronic diseases ranging from coronary artery disease (CAD), Type II diabetes mellitus (T2DM), cancer, and osteoporosis to various psychiatric illnesses (See Table I).<sup>1–7</sup> FOAD is based on the premise of "developmental plasticity"—a single genotype, influenced by specific intrauterine events, has the capability to produce different phenotypes. This theory relies on the fact that there exist specific developmental periods whereby an organism is "plastic" or "sensitive" to its environment. Diversity is maximized to provide the best fit between phenotype and environment. For example, when faced with the adversity of malnutrition, a fetus will undergo remodeling thereby altering structure and function of various organs to preserve neurodevelopment and promote survival. These

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adaptations prepare the fetus for extrauterine life where additional stressors may be encountered. It must be recognized, however, that over time, this evolutionary advantage of “plasticity” is lost, and one’s response to environmental or pathological challenges becomes constrained. This phenomenon, known as “programming,” refers to the fact that stimuli, when applied during early development, generates permanent changes that persist throughout one’s lifespan. Programming is not just limited to the in-utero environment, but extends into childhood, where different organs and systems continue to adapt to various cues.

The FOAD theory was originally supported by large birth registries and human cohorts where gestating women and their offspring faced severe malnutrition in the form of famines.<sup>1,4,8,9</sup> These large registries recorded the birth history of men and women, and these subjects were then identified later in life. This allowed investigators to correlate birth weight and childhood growth with adult onset diseases. These findings were found to be independent of confounders such as tobacco use, diet, exercise, socioeconomic status, and family history. Although numerous epidemiological studies across various cultures and ethnicities support the link between LBW and future adult disease, LBW is not necessarily a prerequisite.<sup>10–13</sup> Those with “normal” birth weights, or appropriate for gestational age (AGA), may still be at risk depending on the type, timing, and duration of the original insult. Moreover, insults are not limited to malnutrition. Famines or severe calorie restriction merely provide a model for other afflictions. Alterations in diet composition, inflammation, infection, glucocorticoids, hypoxia, stress, and toxins also play a vital role in shaping the adult phenotype.<sup>14–20</sup> Although the literature tends to focus on the LBW, or small for gestational age (SGA) baby, special consideration must be given to the stressed AGA, large for gestational age (LGA), and premature neonate. And lastly, the transgenerational and socioeconomic implications of FOAD have far-reaching repercussions that cannot be underestimated; further research is still needed to unravel its complexities.<sup>21–23</sup>

The aim of this review is to provide the general clinician with a foundation to better understand how nutritional and non-nutritional perturbations result in chronic disease. Since Barker’s original observations, numerous epidemiological and human studies, further reinforced by animal models, have provided a plethora of support.<sup>12,19, 24–31</sup> Mice, rats, sheep, and monkeys have been subjected to adverse conditions during gestation to mimic the human condition. Models include global calorie or specific macronutrient or micronutrient restriction, hypoxic-ischemia induced by uterine artery ligation, and glucocorticoid exposure. The data, as a whole, force the clinician and researcher to question and discover how developmental stressors permanently alter structure, metabolism, and genetic expression resulting in cognitive, behavioral, and body composition changes ultimately leading to future disease. The literature points to opportunities for public health prevention, future pharmaceutical therapies, and innovative alternative nutritional/environmental strategies that could maximize population based well-being.

## Background

The Helsinki and Hertfordshire cohorts from the 1930s and 1940s, which comprised over 20,000 subjects collectively, linked poor fetal growth with CAD, hypertension, and insulin

resistance in adult men and women.<sup>1,2,9</sup> Differential mortality rates have been associated with variation in birth weights (Fig 1). Specifically, a LBW in either gender or a documented lower weight for males at 1 year of age was associated with an increased death rate from CAD. A similar trend was noted in both sexes for insulin resistance.<sup>2</sup> Moreover, these effects have been noted to extend beyond the first generation of offspring (F1 generation), with both short- and long-term health implications in future generations.<sup>21–23</sup>

During the relatively short Dutch famine of 1944–1945, the daily nutritional intake of pregnant women was reduced to approximately 400–1000 calories. The timing during pregnancy of this famine (early, mid, or late gestation) was linked to differential birth weights and subsequent development of adult disease. Infants who were subjected to mid or late gestation calorie restriction were lighter, while those who endured the famine in early gestation had normal birth weights. In addition, adults whose mothers were exposed to the famine during mid or late gestation demonstrated reduced glucose tolerance, while those whose mothers were exposed to the famine during early gestation revealed a more atherogenic lipid profile and higher body mass index (BMI).<sup>4,9</sup> Thus, although birth weight in some cases serves as a surrogate marker for the development of adult disease, it is the in utero environment that sets the trajectory for the subsequent acquisition of childhood or adult diseases.

Conversely, the Leningrad famine spanned more than 800 days and provided yet another opportunity to study how severe malnutrition during pregnancy and early infancy, both periods of critical development, affect adult disease. During this siege, fetuses subjected to severe calorie restriction also experienced malnutrition during infancy. However, these subjects, unlike their Dutch counterparts, did not demonstrate increased rates of insulin resistance, dyslipidemia, hypertension, or CAD.<sup>8</sup> These two famines, although similar at first glance, differed in the duration and severity of the malnutrition the population endured. These two infamous natural disasters, with effects documented in large European databases, provided David Barker and others with clues to what subsequently was described by the term FOAD, or known as the “Barker hypothesis.” Even today, despite a plethora of human and animal data, scientists continue to debate the mechanistic link(s) between abnormal growth and adult disease. In addition, in humans, the genetic make-up and environment cannot be dismissed, and it has been a challenge to separate these influences from each other.

### “The Mismatch Concept”

The contrast between two natural disasters, namely the Dutch famine and Leningrad siege, highlights the “mismatch concept.” Fetal survivors of the Leningrad siege developed a “thrifty phenotype” that served them well in their extrauterine life.<sup>32</sup> In other words, the superimposed stress of malnutrition in their intrauterine environment was well-matched to the malnutrition experienced outside the womb, and may have offered a form of “protection” from future adult disease. The Dutch, by contrast, exhibited “catch-up” or compensatory growth during infancy. Their intrauterine environment which supported short-term survival was ill matched with their subsequent extrauterine environment. Thus, the Dutch fetuses paid the price for their intrauterine adaptation—“there is no short term gain

without long term pain.” In other words, when there is a “match” between the predicted and the actual environment, survival is maximized. Conversely, when the two environments are “mismatched” a predisposition to disease may result; an individual’s full potential may not be realized because of maladaptation to the new disparate extrauterine environment predisposing to disease states (Fig 2).

This concept of “mismatch,” and its subsequent consequences, also applies to contemporary times. The World Health Organization estimates that over 30 million infants are born LBW, defined as a weight less than 2.5 kg.<sup>33</sup> In addition, many poorly resourced countries are being industrialized or swept over by the “Mc Donald’s” fast food phenomenon. This “mismatch” is not confined to poor resourced nations; it also plagues well resourced societies with access to modern health care and high standards of living. High-calorie and high-fat diets coupled with limited active play and excessive media viewing have become the norm in Western nations. In the USA, obesity has more than doubled among children and adolescents. In comparing the two periods 1976–1980 and 2003–2006, the percentage of obese adolescents increased from 5% to 17.6%.<sup>34</sup> Insulin resistance is intimately linked to T2DM, CAD, hypertension, and dyslipidemia. T2DM is now a global epidemic affecting over 170 million people; by 2030 this number is expected to double.<sup>35</sup>

Considering these statistics, one may ask—what developmental “hits” are considered detrimental? And during which time periods? When is too much truly too much? And practically speaking, how should the pediatrician, obstetrician, and neonatal-perinatal subspecialist promote growth during pregnancy and the various postnatal periods (neonatal, infancy, and childhood)? How should clinicians monitor the fetus, and later the infant, child, and adult when an adverse environment is experienced early in gestation? Can these negative outcomes be prevented or reversed?

## Catch-up Growth

Today, numerous human and animal studies have revealed that LBW followed by exponential childhood growth increases the risk for the metabolic syndrome, which is characterized by obesity, insulin resistance, dyslipidemia, and hypertension.<sup>2,32,36,37</sup> This tendency to “catch-up” in growth reflects the body’s natural response to nutrient deprivation. Moreover, both the parents and clinician may not understand the dangers of rapid weight gain and may actually promote it. Catch-up growth, however, is associated with increased visceral adiposity.<sup>38,39</sup> Recent findings in a group of racially diverse American children mimicked those of the 1930–1940s’ English cohort revealing an association between the tendency to store fat intra-abdominally and LBW. In this study specific markers of central adiposity, as measured by central-to-peripheral and subscapular-to-tricep skinfolds, were increased in LBW children as early as 5–11 years of age.<sup>38</sup> Similarly in a cohort of Hispanic and non-Hispanic Caucasians, LBW was associated with elevated fasting insulin levels and truncal obesity. For each tertile decrease in birth weight, the risk for “insulin resistance syndrome” increased 1.72.<sup>10</sup>

Studies of children with T2DM have revealed that many of them were characterized as being small at birth, but during childhood and adolescence they began to cross growth

percentiles. The odds ratio for developing T2DM was 1.38 for each 1 kg decrease in birth weight, and 1.39 for each increase in weight standard deviation between 7 and 15 years of age.<sup>37</sup> Therefore, the thin toddler who begins to rapidly gain weight, or finally “catches-up” to his peers, is at the same risk, if not greater, for developing T2DM compared to his overweight age-matched peer.

Anthropometric data for over 1,400 men and women from Delhi, India, was collected during the first 3 decades of their life from 1970 to 2000. This Indian study conducted during modern times is reminiscent of the Dutch famine. The authors describe this period in India as a “transition” to a more Western lifestyle—a lifestyle marked by increased food availability and reduced physical activity. Results of this study revealed that those individuals with increased insulin resistance were more likely to be small at birth, grow slowly during the first couple of years in life, and then develop “an adiposity rebound”.<sup>12</sup> These children however were not described as overweight or obese with this “rebound” growth. Instead, they were described as rapidly gaining body mass. This “catch-up fat” during childhood and early adulthood occurs at a disproportionately faster rate in comparison with lean body mass, and is one of the main promoters of early insulin resistance.

This “nutritional transition” is not solely limited to India but has occurred on all continents. The quantity and quality of the world’s food supply varies from country to country, and even neighborhood to neighborhood; while some individuals face starvation, others consume high-calorie, high-fat meals that lack significant nutritional value, which in itself is a different form of starvation.

The tendency for the LBW infant to store fat, particularly in the abdominal compartment, has received considerable attention.<sup>10,38,40,41</sup> LBW infants are known to have adipocytes that demonstrate increased numbers of insulin receptors, glucose uptake, and basal and insulin-stimulated insulin-receptor substrate 1 (IRS-1)-associated phosphatidylinositol 3-kinase (PI3K).<sup>42,43</sup> Moreover, these adipocytes are resistant to insulin and demonstrate serine phosphorylation of IRS-1, resulting in a state of anti-lipolysis.<sup>43</sup> In addition, increased central adiposity is associated with increased free fatty acids, which stimulate the production of cholesterol and glucose, which in turn decrease insulin sensitivity.<sup>24</sup> As fat deposition progresses in the liver, permanent structural hepatic changes occur.<sup>44</sup>

This molecular “switch” in insulin signaling “protects” the LBW fetus and neonate by promoting storage of fat, a calorically dense nutrient. However, over time this altered metabolism sets the stage for the development of disease. Considering its impact on childhood growth, a clinician may then question whether replacing this quick “rebound” with slow steady measured growth could result in increased lean body mass rather than fat accumulation. Moreover, could any of these cellular aberrations resulting in chronic disease be avoided?

## Biological Basis

Growth is largely determined by a mother’s ability to nourish her fetus. The provision of this nourishment depends on the maternal diet, the placenta’s ability to supply nutrients (amino

acids, glucose, fat, oxygen, and growth-stimulating hormones), and the mother's own in utero experience.<sup>21–23</sup> In other words, the effect of FOAD extends beyond the first (F1) generation. Considering the medical and socio-economic implications of programming, it is critical that all health professionals promote healthy pregnancies to maximize each child's potential and growth trajectory.

So why would growth or other insults in early life alter one's disease potential? First, cell number and growth are exquisitely sensitive to their metabolic and hormonal milieu. Undernourished animals and babies have reduced renal volumes and nephrons, which can result in hypertension. Autopsies of hypertensive humans who died in motor vehicle accidents have demonstrated reduced numbers of, but hypertrophic, glomeruli.<sup>45–47</sup> Similar to humans, growth-restricted animals have decreased numbers of glomeruli and develop chronic renal disease later on in life. Moreover, measurements of mammalian target of rapamycin, a nutrient sensing biomarker, are reduced in growth-restricted kidneys.<sup>48</sup> Second, any stress can alter hormonal concentrations, hormone receptors, and hormonal responses. Receptors can be down- or up-regulated and mutations may result in structural transformations. Hormonal responses can be blunted, or exaggerated.

Consistent with this paradigm is the SGA child who later develops T2DM. These individuals have a reduced number and function of pancreatic  $\beta$ -cells resulting in decreased insulin production and consequently a high glucose/insulin ratio. This outcome leads to abnormal skeletal muscle, liver, and adipocyte insulin signaling and/or glucose production with each of these perturbations resulting in insulin resistance. The same is true with leptin, a critical hormone secreted by adipocytes. Leptin acts on the central nervous system to decrease food intake and increase energy expenditure. The SGA neonate has decreased leptin concentrations at birth, but with increased adiposity becomes hyperleptinemic during the period of "catch-up" exponential growth. This hyperleptinemic state is associated with decreased and/or resistant hypothalamic leptin receptors, which result in hyperphagia and decreased energy expenditure. Dysregulated insulin and leptin serve as two examples of how hormonal perturbations predispose the SGA infant to T2DM and other co-morbidities.

### Small for Gestational Age Infant

It is important to acknowledge the spectrum of LBW, which includes SGA, intrauterine growth restriction (IUGR), and very low birth weight (VLBW) infants, some who are not only born prematurely but at times also with superimposed IUGR. While SGA is defined as a birth weight or birth length less than the 10<sup>th</sup> percentile with respect to gestational age, IUGR refers to an infant who does not reach his or her predetermined genetic potential because of some pathologic insult. This insult can be categorized as maternal, placental, or fetal, with the most common etiology thought to be placental insufficiency. Although IUGR infants may be SGA, all SGA infants are not necessarily IUGR.

Not surprisingly, prenatal and postnatal periods are exquisitely sensitive to any factor that can affect growth as these are periods of exponential cell replication, division, and growth. Infants born SGA are at increased risk for developing obesity, T2DM, CAD, hypertension, kidney disease, premature pubarche, and Polycystic Syndrome (PCOS), dyslipidemia, short

stature, and osteoporosis.<sup>1-4,13,32,37,45,46,49-50</sup> Many of these phenotypic changes are known to be secondary to or associated with insulin resistance.

## Height

Although fetal growth is usually discussed in terms of birth weight, it is important not to dismiss the aspect of birth length. Infants with low birth length, LBW, or premature birth are more likely to be short adults.<sup>49-52</sup> Most neonates who fall 2 standard deviations below the growth curve for length, however, are likely to “catch-up” to their peers during childhood. At 1 year and 18 years of age, respectively, only 13.4% and 7.9% of short babies remain stunted.<sup>53</sup> Those that remain short often are referred after the age of 2 to the pediatric endocrinologist for growth hormone therapy or at an older age for evaluation of the metabolic syndrome because of their increased risk of obesity.

It is difficult to separate out the individual contributions of low birth length, LBW, prematurity, and other important factors such as parental height on the individual’s ultimate height and the associated complications, such as obesity and T2DM. Each characteristic may have an additive, synergistic, or independent effect. When only females were examined, being short for gestational age was associated with a fivefold increase in short adult stature, while being SGA was associated with only a twofold increase. Interestingly, females who are short at birth, not SGA, are at higher risk for obesity.<sup>49</sup> At the other extreme, larger and longer babies are even more likely to become heavier adults in comparison with light and short babies.<sup>54</sup> As is seen in infants born to mothers with gestational diabetes (GDM) secondary to maternal hyperglycemia, the GDM fetus becomes hyperinsulinemic, resulting in accelerated in utero growth. For every 1 kg increase in birth weight, full-term babies have a 50% increase in adolescent obesity.<sup>55</sup> Short and large babies, both at risk for insulin resistance, are two distinct, separate populations, and are most likely the result of two different programming mechanisms.

Bone growth affects not only one’s ultimate height and risk for obesity, but also bone disease. Osteoporosis is linked to fractures, which are linked to a high risk for morbidity and mortality later in life. In a study of a Finnish cohort of patients admitted to the hospital for fractures, low birth length and slow growth were correlated with increased fracture risk during adult life.<sup>56</sup> SGA status and slow growth during the first year of life predict decreased adult bone mass even after adjustment for other predictors of osteoporosis and osteopenia.<sup>6</sup> Studies of twins have proven to be very useful in supporting the FOAD hypothesis. Twin studies are valuable as they help correct for well-known genetic and environmental confounders. The dizygotic or monozygotic co-twin with LBW is more likely to have a lower bone mineral density at specific sites.<sup>57</sup> This data, along with results from other twin studies, suggest that even in genetically identical monozygotic twins, the co-twin with the lower birth weight is predisposed to lower adult bone mass and to developing the metabolic syndrome.<sup>58</sup>

Growth hormone, other insulin-like growth factors, and vitamin D are among many factors that influence a child’s growth and bone mass. The growth hormone/insulin-like growth factor-1 axis and receptors are most likely altered in individuals who fail to realize their growth potential. Adults with decreased bone mineral density are more likely to have

decreased growth hormone and to have been smaller children.<sup>59</sup> Other investigators have explored this area even further and have discovered a strong interaction between SGA, poor adult bone mass, and certain single nucleotide polymorphisms (SNPs) in the growth hormone, vitamin D, and calcium-sensing receptor.<sup>60–64</sup> In a SNP analysis, the insulin-like growth factor-1 receptor was altered in 2 short children with low birth weights and postnatal growth restriction.<sup>64</sup> Reduced insulin-like growth factor receptors impact not only a child's ultimate height, but also the child's ability to maintain glucose homeostasis and sustain good brain growth. In summary, like weight, length at birth and height serve as predictors for future disease.

### Insulin Resistance/Diabetes

While LBW is undoubtedly associated with insulin resistance, the search for a mechanistic link continues. Many investigators suggest that the pancreas is “programmed” resulting in decreased  $\beta$ -cell mass and function and over time skeletal muscle becomes insulin resistant. Some authors, by contrast, have failed to replicate or generate data to support this theory and believe that insulin resistance, not production, is the primary culprit.<sup>65, 66</sup> In their opinion, once insulin resistance sets in, the pancreas increasingly is stressed to produce more insulin and over time responds to its overwhelming exhaustion with progressive failure of its  $\beta$ -cells.

**Pancreas**—In support of the former theory, many studies have demonstrated decreased insulin secretion and normal insulin sensitivity in young SGA adults. In one study of adults born with LBW, insulin secretion was reduced by 30%, while insulin sensitivity was determined to be normal.<sup>27</sup> In examining this phenomenon more closely, the IUGR population was noted to have pancreatic dysfunction even before birth; this was evidenced by decreased insulin, glucose, insulin/glucose ratios, and  $\beta$ -cell number and function.<sup>67–69</sup> Interestingly, in some studies, this reduction in  $\beta$ -cell function was initially accompanied by increased insulin sensitivity.<sup>70</sup> These changes persisted after birth and were accompanied by further alterations. When rats are subjected to calorie restriction in-utero,  $\beta$ -cell mass is initially reduced by approximately 35%. When caloric restriction extends into the neonatal period, impaired  $\beta$ -cell development persists with a 40–66% reduction. Later as adults, these animals are described as glucose intolerant.<sup>68,71</sup> Moreover, pancreatic duodenal homeobox-1 (Pdx-1), a well-known transcription factor controlling pancreatic development, is reduced. At 28 days of life, insulin secretion and Pdx-1 protein expression is reduced when compared with controls.<sup>30</sup>

In another commonly used IUGR model, the uterine artery of pregnant rats is ligated, resulting in a severe, abrupt reduction of uteroplacental blood flow. These IUGR rats are growth-restricted at birth but later demonstrate accelerated weight gain, surpassing their age-matched controls. As they age, the rats become insulin resistant and glucose intolerant. Studies have demonstrated that early on, their  $\beta$ -cell mass is equivalent to that of controls. However by 26 weeks, the rats pancreatic mass is notably decreased to approximately 50% of their control counterparts. Using this same model, deterioration in the rats'  $\beta$ -cell function is accompanied by mitochondrial dysfunction, as evidenced by decreased adenosine triphosphate (ATP) production, increased reactive oxygen species, and mitochondrial point



mutations. In addition, all of these markers demonstrated a steady increase over the first 15 weeks of life.<sup>19</sup> When faced with undernutrition, cell division is slowed (as evidenced by decreased Pdx-1 and  $\beta$ -cell-mass) and cell function is altered (as evidenced by decreased hormonal supply and cellular damage).

An alternative hypothesis to FOAD is the “fetal insulin hypothesis.” T2DM is known to have a strong genetic component. According to this theory, because insulin is key for fetal growth, any genetic variant that impairs insulin secretion may reduce birth weight and simultaneously result in T2DM. In other words, the genotype, not LBW, predisposes one to T2DM. Supporting this theory, Freathy et al, using SNPs, demonstrated that alleles for increased T2DM risk that reside at two separate loci, *CDKAL1* and *HHEX-IDE*, also were associated with LBW.<sup>72</sup>

Although one cannot ignore the genetic component to T2DM, SGA humans and growth restricted animal studies clearly have served as models for FOAD and insulin resistance. Evidence is now accumulating about specific nutritional and non-nutritional alterations that may or may not alter growth and result in a similar pancreatic phenotype. This is the case with essential amino acids, glucose, and micronutrient deficiencies.<sup>14,73,74</sup> Thus, clinicians must be aware that perturbations, small or large, in the fetal and postnatal environment can have long-term consequences.

**Skeletal muscle, liver, and fat**—Although the debate still continues whether the pancreas or skeletal muscle is the key instigator behind the T2DM FOAD theory, evidence from both camps is convincing. Taken together, human and animal studies highlight the importance of crosstalk between pancreas, skeletal muscle, liver, adipose tissue, and brain. Skeletal muscle, one of the principal sites of action for glucose and insulin, is prone to dysregulation in T2DM. LBW infants have decreased lean body mass and increased visceral adiposity.<sup>75–77</sup> This “sarcopenic obesity” is considered one of the major culprits in the development of T2DM.<sup>39,75–77</sup> Fat tends to accumulate viscerally and in ectopic sites, such as the liver. When children with nonalcoholic fatty liver disease were examined, close to 40% of the population was born SGA and this subset also was more likely to progress to non-alcoholic steatohepatitis.<sup>44</sup> In addition to an increased risk for hepatic disease, it is hypothesized that LBW infants and later adults have increased hepatic glucose production. In fact, in the uterine artery ligation model, IUGR rats exhibited increased hepatic glucose production as evidenced by impaired oxidation of pyruvate and increased phosphoenolpyruvate carboxykinase before the onset of T2DM.<sup>78</sup>

Like many of the features in FOAD, there is subtle evidence of future pathology before clinical presentation. With respect to skeletal muscle, programming affects multiple areas—skeletal muscle development and/or fiber composition, glucose uptake, downstream insulin signaling molecules, glycolysis, and glycogen synthesis. Non-diabetic SGA young adults, when compared with age matched controls, demonstrate hyperinsulinemia at baseline and during oral glucose tolerance tests.<sup>24</sup> When challenged with a hyperinsulinemic-euglycemic clamp, those born small have decreased peripheral glucose uptake and reduced activation of PI3K/Akt proteins.<sup>24,79,80</sup> Looking more closely at muscle histology, LBW was associated with increased fast-twitch, glycolytic type IIx fibers, and larger type IIa and type I slow-

twitch, oxidative fibers.<sup>81</sup> Larger fiber size and a shift toward more type II fibers are associated with skeletal muscle insulin resistance. When examining the insulin signaling pathway, we and others have noted decreased protein expression of several key proteins, protein kinase C (PKC)  $\zeta$ , p85, and insulin responsive glucose transporter (GLUT4), in both LBW adults and growth restricted rats.<sup>28,30,79,80</sup> No difference was noted in insulin receptor expression, suggesting the defect lies downstream.<sup>80</sup> To examine muscle glycolysis in LBW adult females, investigators analyzed ATP production with <sup>31</sup>P-magnetic resonance spectroscopy and found that ATP production was reduced in LBW adults subjected to exercise.<sup>82</sup>

With regards to adipose tissue, adipocytes are smaller in the SGA/IUGR fetus and neonate and with aging increase in size and number.<sup>83</sup> Moreover, as the SGA child accumulates more adipose tissue in extraneous sites, alterations in lipid metabolism occur and derangements in total cholesterol, low-density lipoprotein, and high-density lipoprotein become apparent.<sup>13,25,84–86</sup> When the SGA population is examined as a whole, those who become obese adults are more likely to have abnormally high total cholesterol and low-density lipoprotein serum concentrations.<sup>86</sup>

How birth weight alters adipokines, adiponectin and leptin, and the implications of these changes remains an area of active research. Adiponectin, an insulin-sensitizing and anti-inflammatory protein, is inversely correlated with fat mass and is decreased in diabetic states. Although adiponectin's role in adult disease is well-defined, its role in children and specifically in LBW infants is less clear. SGA fetuses have increased circulating adiponectin, and over time concentrations decrease. As expected, in the SGA population adiponectin is negatively correlated with weight, height, and BMI.<sup>87–89</sup> In a series of studies, however, no difference in adiponectin in SGA and AGA children was noted.<sup>87–89</sup> When a sub-group analysis was conducted, however, adiponectin was statistically higher in SGA subjects who did not exhibit "catch-up" growth or who were severely growth restricted at birth.<sup>87</sup>

In contrast to adiponectin, leptin concentrations correlate closely with fat mass and insulin resistance. Leptin, a satiety factor, acts on the hypothalamus and is responsible for regulating food intake and energy expenditure via a negative feedback loop. At birth IUGR neonates have decreased leptin, and by 1 year of age, leptin is increased compared with AGA controls.<sup>90–92</sup> All neonates, undergo a "leptin surge," and this surge occurs prematurely in growth-restricted rodents and sheep.<sup>26,93</sup> In normal two-week-old sheep, leptin concentrations are inversely related to feeding activity. In other words, as leptin decreases, feeding activity increases. However, in growth-restricted sheep, this relationship is reversed, and plasma leptin correlates with increased suckling.<sup>26</sup> As adults, LBW infants have abnormally high leptin concentrations even when BMI is taken into account.<sup>94</sup> This hyperleptinemia, at various stages of the life cycle, may represent a form of "leptin resistance," which acts to increase energy intake and decrease energy expenditure. When faced with the stress of a high fat diet, growth-restricted rats become obese and have higher leptin concentrations and decreased energy expenditure when compared to growth-restricted rats consuming standard chow or non-growth restricted rats on a high fat diet.<sup>26</sup>

Perinatal stress has been shown to alter neuronal circuitry. Studies have shown that intrauterine nutritional imbalances affect the rat/mouse hypothalamic orexigenic peptide, neuropeptide Y and anorexic peptide, cocaine- and amphetamine-regulated transcript.<sup>95</sup> In addition, emerging evidence supports perturbations of circadian oscillator genes, or “clock genes.” Recently, a hyperphagic, hypoactive, preobese mouse was found to have altered clock genes in the brain and liver.<sup>29</sup> Thus, undernourished fetuses are programmed for abnormal eating behaviors and energy metabolism and bear a predisposition towards obesity.

As emphasized above the FOAD hypothesis centers around reshaping the individual’s metabolism and body composition. To promote survival during periods of starvation, food intake increases, basal metabolic rate decreases, and energy is preferentially stored as fat. To increase glucose availability, pancreatic insulin production decreases, skeletal muscle and adipose tissue become insulin resistant, and hepatic glucose production is increased. This results in a state of hyperglycemia and increased de novo lipogenesis, which is further complicated by impaired action of growth and steroid hormones and leptin resistance. Overall, these events create a vicious cycle of adipose deposition (Fig 3). These adaptations are aimed at conserving energy and diverting scarce nutrients to vital organs. However, if there is “mismatch” in environments, or a transition from a nutritionally poor to nutritionally rich state, organ dysfunction and later disease become apparent.

A LBW neonate, symbolic of a perturbed in utero state, is at increased risk for developing insulin resistance/T2DM. In addition, the individual’s growth during infancy, childhood, and adolescence, whether it is rapid, slow, or steady, at any stage, can further modify the eventual phenotype. The trajectory of one’s growth and future disease profile may be significantly impacted very early, even before conception. However, we have demonstrated that interventions with exercise and drug therapy suppress hepatic glucose production and increase skeletal muscle insulin responsiveness in the IUGR animal.<sup>96,97</sup> Understanding how and why insulin resistance occurs in this population is key to developing strategies to reduce the burden of the metabolic syndrome and other associated diseases.

## Puberty

Considering the implications of reduced fetal growth on the endocrine axis, it appears plausible that LBW children could have gonadal dysfunction and disturbed sexual maturation. In one study of SGA females, puberty and menarche occurred earlier than in the control population.<sup>98,99</sup> Other studies, however, have demonstrated that SGA children enter puberty at the appropriate age, but progress more rapidly through puberty.<sup>100</sup> In contrast to these observations, other studies have demonstrated that birth weight had no effect on the timing or progression through puberty.<sup>101,102</sup> When height was taken into account, it was noted that SGA children enter puberty at “the normal age,” but this was not “normal” when considering their short stature.<sup>103</sup> There has also been a recent trend, specifically in Western countries, for earlier menarche. As a result, it is difficult to dissect environmental influences, perhaps related to exposure to endocrine disruptors, from the programming effect. There are limited studies on how LBW affects fertility and menopause in females, and the onset of puberty in males.

Ibanez et al published a collection of articles describing the hormonal dysfunction of Northern Catalonian Spanish girls. In these studies, LBW status was linked with precocious pubarche and adrenarche.<sup>104,105</sup> Adrenarche is characterized by the maturation of adrenal glands, and the production of sex steroids, such as dehydroepiandrosterone, which are responsible for pubarche. The hallmark of pubarche is the appearance of pubic hair, which usually occurs after the age of 8. These reports describe a “sequence of events” beginning with reduced growth, which progresses to pronounced adrenarche and precocious puberty, followed by ovarian hyperandrogenism, and finally insulin resistance. In these studies SGA girls have higher concentrations of dehydroepiandrosterone compared with AGA girls. Girls diagnosed with precocious puberty are more likely to have LBW status, and those with precocious puberty are more likely to have hyperandrogenism and hyperinsulinemia/insulin resistance.<sup>104,105</sup>

It is unclear if the link between precocious puberty and polycystic ovarian syndrome with SGA is secondary to early alterations of endocrine set points and/or a consequence of rapid weight gain during childhood.<sup>50</sup> In an Australian cohort of children with precocious puberty, 65% were obese and 35% were SGA.<sup>98</sup> As described above, exponential childhood growth is associated with central adiposity and insulin resistance, which is known to increase androgen and IGF-1 production.<sup>10,38,39</sup>

Overall, the link between LBW and premature precocious puberty and associated abnormalities appears plausible, but studies are limited by small, non-heterogeneous populations. Moreover, two other studies by different investigators have failed to replicate some of these results.<sup>101,102</sup> Further work is needed before unequivocal conclusions can be reached.

## Premature Infant

Equally challenging for the clinician is the preterm infant. The VLBW infant, and specifically the extremely low birth weight infant, is at high risk for postnatal growth failure during their intensive care stay, which is intimately linked to poor cognitive outcomes. VLBW is defined as a birth weight less than 1.5 kg; extremely low birth weight infant is defined as a birth weight less than 1 kg. In one investigation of infants studied at 36 weeks corrected gestational age, 100% of neonates with a birth weight < 1000 g were characterized as having postnatal growth restriction, and the majority remained restricted at 36 months.<sup>106</sup> Despite aggressive, early parenteral nutrition and the introduction of enteral nutrition, the smallest infants remain small throughout childhood and neurodevelopmentally delayed.<sup>106–109</sup>

On the converse, preterm babies whose growth does not falter early demonstrate better cognitive outcomes. With the introduction of preterm formula, which is higher in calories and protein compared to term formula or breast milk, as an intervention in a preterm population, data revealed that males had higher verbal IQs and larger caudate volumes; however, both sexes demonstrated increased insulin resistance with higher split proinsulin levels and also higher diastolic blood pressures.<sup>110,111</sup> In another study of VLBW infants as young adults, they were found to have a 6.7% increase in their 2 hour glucose concentration,

a 16.7% increase in their fasting insulin concentration, a 40% increase in their 2-hour insulin concentration, and a 4.8 mm Hg increase in systolic blood pressure when compared to controls.<sup>112</sup> However in another study, individuals with better weight gain post-hospitalization or after reaching term were noted to have better intelligence scores, and a small, possibly clinically irrelevant increase in blood pressure.<sup>113</sup>

So the question remains, when and how should postnatal growth be fostered? Breast milk is considered the gold standard nutrition for the full-term, AGA infant. However, if term formula does not meet the needs of the growing premature infant, will breast milk? Does fortified breast milk carry any unforeseen risks? In a recent study LBW babies were assigned to exclusive breast milk feedings or fortified breast milk. Those that received exclusive breast milk demonstrated less weight gain, but had lower fasting glucose and insulin concentrations at 3 months of age.<sup>114</sup> Others have demonstrated that breast milk protects against rapid, exponential childhood growth.<sup>115</sup> However, how that applies to the VLBW and/or premature population remains unclear, and longitudinal follow-up studies are still needed.

Before the 1950s, few preterm infants survived. Today, with use of mechanical ventilation, surfactant replacement, antibiotics, and state-of-the-art neonatal intensive care nurseries, these children are reaching adulthood. Opportunities now are available for investigators to study the programming effects of prematurity in children, adolescents, and adults. These effects are far-reaching, and extend beyond cardiovascular, metabolic, and cognitive perturbations, and affect the family and society as a whole. Follow-up studies of VLBW infants have revealed that they are less likely to graduate from high school or obtain a university degree; however, rates of employment do not differ between those who were VLBW and non-VLBW infants.<sup>116–118</sup> Researchers have found that thoughts of depression and anxiety are more common in the follow-up of female VLBW infants, while males who were VLBW infants are more likely to exhibit attention deficit and hyperactivity disorder.<sup>116,119,120</sup> In studies of the Helsinki Cohort, depressive symptoms increased in a linear fashion with decreased gestational length, and growth restriction was associated with increased anxiety traits.<sup>121</sup> Additional evidence from a large Swedish cohort confirmed that infants born prematurely were more likely to suffer from psychiatric disorders and exhibit suicidal behavior.<sup>122,123</sup> Thus, while the provision of suboptimal nutrition has deleterious effects perhaps in a gender-specific manner on the preterm's cognitive development, prematurity also is associated with serious psychiatric implications. This is not necessarily surprising given that a good portion of CNS development occurs outside the womb in a foreign environment.

Other stressors, such as infections, hypoxia, and exogenous glucocorticoids, can permanently alter the neuroendocrine system.<sup>15,16,124</sup> When faced with chronic or repeated perinatal and postnatal stress, the hypothalamic pituitary axis (HPA) is activated, resulting in elevated adrenocorticotrophic hormone (ACTH) and adrenal hypertrophy.<sup>125,126</sup> An altered HPA carries significant long-term implications for atherosclerosis, dyslipidemia, T2DM, and immunosuppression. Prenatal glucocorticoids have been demonstrated to reduce hepatic production of insulin-like growth factor binding protein 1, which affects the child's height, can alter hepatic gluconeogenesis and increase blood pressure.<sup>127</sup> Providing yet another link

between birth weight and adult insulin resistance, studies have demonstrated that LBW infants have elevated plasma cortisol concentrations as adults.<sup>128</sup>

Considering that the HPA is intimately tied to behavior, it is not surprising that HPA programming can lead to aberrant behavior and thoughts. If subjected to a hostile environment, a pregnant mother produces a “stress response,” which is transmitted to the fetus. When gestating rats were exposed to light and noise stress, their offspring had increased corticosterone levels and demonstrated impaired hippocampal function. This effect is most likely secondary to a reduction in pyramidal neurons and decreased synaptogenesis.<sup>17</sup>

Postnatal manipulations, like prenatal manipulations, can result in imprinting. When fetal rats are exposed to high levels of glucocorticoids in utero, their birth weights are reduced. As adults their HPA is chronically activated, and they exhibit anxiety-like and depressive behaviors.<sup>15</sup> Increased in utero exposure to glucocorticoids, which can be seen with maternal protein restriction, is associated with increased blood pressure in offspring.<sup>129</sup> There now is a growing body of evidence linking viral CNS infections with the development of schizophrenia, and glucose deprivation with autistic-like behaviors.<sup>130,131</sup>

### Large for Gestational Age Infant

The other end of this spectrum finds the neonate born LGA, or with a birth weight greater than the 90<sup>th</sup> percentile secondary to gestational diabetes or idiopathic macrosomia. The obese or diabetic pregnant mother represents another form of programming. LGA, like SGA, is linked to future obesity and insulin resistance. LGA children are less likely to receive breast milk and exhibit rapid weight gain in the first 6 months of life.<sup>112,132</sup> Although exclusive breast milk feeding appears to provide some protection from obesity, not all epidemiological studies consistently support this finding. LGA infants have been tracked to be heavier children with increased mid upper arm circumference at the level of the triceps and subscapular sites, and they are more likely to develop hypertension and hypertriglyceridemia and become obese adults.<sup>55,132–136</sup>

Mothers with GDM are at increased risk for delivering an LGA or SGA neonate. GDM is a spectrum; severe GDM is characterized by vasculopathy and nephropathy, both of which are known to produce IUGR fetuses. In most cases, however, GDM produces an increased delivery of glucose and other macronutrients to the fetus, resulting in increased fetal production of insulin, the dominant fetal growth hormone. Infants born to mothers with GDM have increased adiposity and elevated insulin and leptin levels.<sup>137,138</sup> GDM also is hallmarked by maternal transmission; GDM mothers are more likely to have been born to mothers with T2DM, and GDM offspring are more likely to develop T2DM.<sup>31,139</sup>

It is important to remember that birth weight is merely a “symptom” of FOAD. In other words, it may or may not be a presenting feature or sign. It is imperative to recognize and acknowledge the AGA neonate born to a GDM mother. Although they appear “normal,” they too were subjected to in utero compromise and are at increased risk for future disease.<sup>31</sup> Their in utero environment results in an increased secretion of hormones that promote the

deposition of adipose tissue and increased insulin secretion early in life, thereby setting the fetus up for an abnormal body composition and future disease.

## Cancer

In addition to being at increased risk for developing metabolic derangements, being LGA at birth is associated with an increased risk of cancer. As a result, fetal determinants are receiving new attention. Birth weight has been speculated to be associated with the development of breast, ovarian, prostate, testicular, and colon cancers. While fetal growth factors, such as insulin, are regulated by maternal substrates, it is also known that maternal concentrations of estrogen and testosterone can alter the offspring's hypothalamic-pituitary-testicular/ovarian axis. By altering a specific tissue's exposure to nutrition and steroid hormones, the risk for tissue dysplasia and subsequent cancer can be altered. Unlike insulin resistance, which demonstrates a U-shaped curve with respect to birth weight, colon cancer exhibits a J-shaped curve, with the heaviest babies carrying the largest risk.<sup>140,141</sup> In a population-based cohort of over 10,000 men and women, macrosomia carried a hazard ratio of 2.57, while VLBW infants carried a modest, yet statistically significant, increase in incidence.<sup>141</sup> Studies have demonstrated that when rats fed excessive calories were then exposed to carcinogens, they exhibited an increased number of colorectal tumors in comparison with similar controls who received a calorically appropriate diet.<sup>142</sup>

The strongest evidence for cancer and FOAD exists for breast cancer.<sup>5,143–150</sup> A case-control study nested within the US Nurses' Study revealed that those individuals at birth who weighed less than 2.5 kg were half as likely as those who weighed greater than 4 kg to subsequently develop breast cancer.<sup>5</sup> Similarly, in a cohort of 2221 British women, a birth weight > 3.5 kg was associated with an increased risk for cancer, specifically premenopausal breast cancer, even after adjusting for confounders.<sup>145</sup> Trichopoulos first proposed that in utero exposure to high levels of estrogens, either endogenous or exogenous, increased the number of stem cells and/or mitogenic activity of undifferentiated breast tissue. Consistent with this theory, mothers with advanced age, dizygotic gestations, or macrosomic or preterm babies demonstrate higher concentrations of estrogen. As a consequence, their fetuses are at an increased risk for breast cancer development.<sup>148,149</sup> Conversely, mothers diagnosed with pregnancy-induced hypertension have decreased estrogen concentrations, and therefore, their offspring are relatively protected from breast cancer. In fact, in one study, pre-eclampsia/eclampsia was associated with a substantially lower breast cancer rate ratio of 0.24.<sup>150</sup> Moreover, women who are taller in childhood and have higher growth rates seem to carry an even higher risk. For every 5-cm increase in height, there is an 11% increase in breast cancer, thus implicating growth factors, such as the insulin-like growth factor, potentially yet another carcinogenic culprit.<sup>146</sup>

## Epigenetics

Cancer, like the metabolic syndrome, is a complex and multifactorial disease. Genetic mutations and environmental triggers are not sufficient to explain the pathogenesis and the rising incidence of cancer, obesity, and T2DM. Epigenetics, which means "on top of genes," describes how the environment interacts with the genome to produce heritable changes resulting in phenotypic variation without altering the DNA of the genome. Epigenetic

processes include DNA methylation and demethylation and post translational processes such as, acetylation phosphorylation and methylation of core histones, which result in an altered histone code. The DNA methylation of cytosine-guanine dinucleotides is commonly described in the literature. DNA methyltransferase enzyme isoforms (Dnmt 1, 3a, 3b) methylate DNA, causing the DNA to be tightly coiled or wound (i.e., heterochromatin). This state results in transcriptional repression and is maintained by heterochromatin protein, HP1. Methylation is maintained by the methyl donors, methionine, choline, and various cofactors, such as folic acid. By contrast, loosely wound DNA, known as euchromatin, allows active transcription (Fig 4).

Epigenetic changes, previously well-described in the field of cancer, are now implicated in the pathogenesis of obesity and insulin resistance. Epigenetic modifications have been implicated in the SGA neonate, affecting promoters of glucose transporter 4, Pdx-1, glucocorticoid receptor, and peroxisomal proliferator activated receptor- $\alpha$  genes.<sup>151,152</sup> Whether methyl donor supplementation before or during pregnancy can reverse the SGA phenotype remains to be elucidated. While epigenetic modifications have been described in various animal studies, replications in human samples have proven to be challenging. This is perhaps related to the fact that human samples have been limited to blood cells while most of the epigenetic changes have been observed to be tissue-specific.<sup>153</sup>

## Summary

To curb the epidemic of rising chronic diseases, some attention must be given to FOAD. David Barker's observations continue to stand the test of time across multicultural populations subjected to various constraints. The FOAD hypothesis has far-reaching implications as indicated by the following statement by the World Health Organization, "The global burden of death, disability and loss of human capital as a result of impaired fetal development is huge and affects both developed and developing countries."<sup>154</sup> The purpose of this review was to summarize some of the epidemiological, human, and animal data and provide pediatricians with a more complete understanding of the pathogenesis of chronic disease that are making their appearance earlier in childhood rather than waiting until adulthood.

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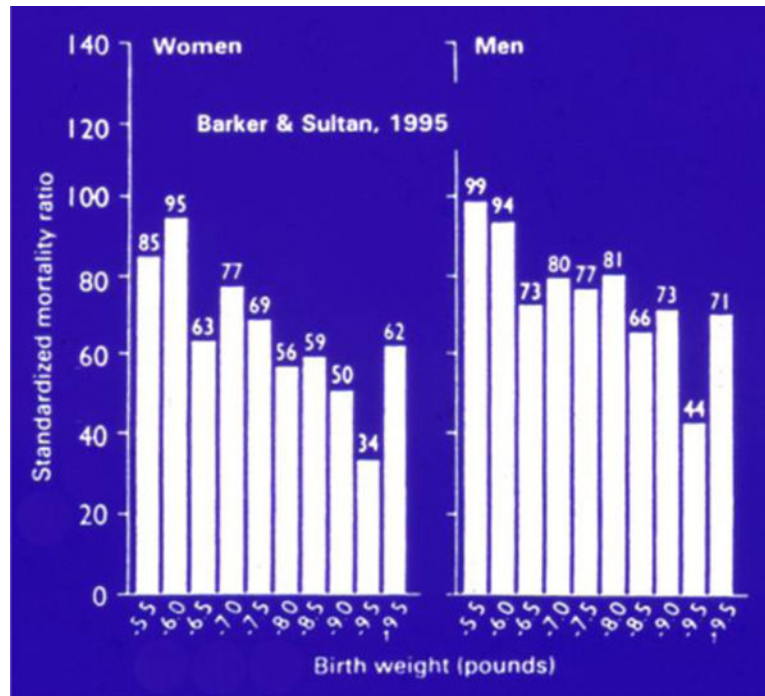
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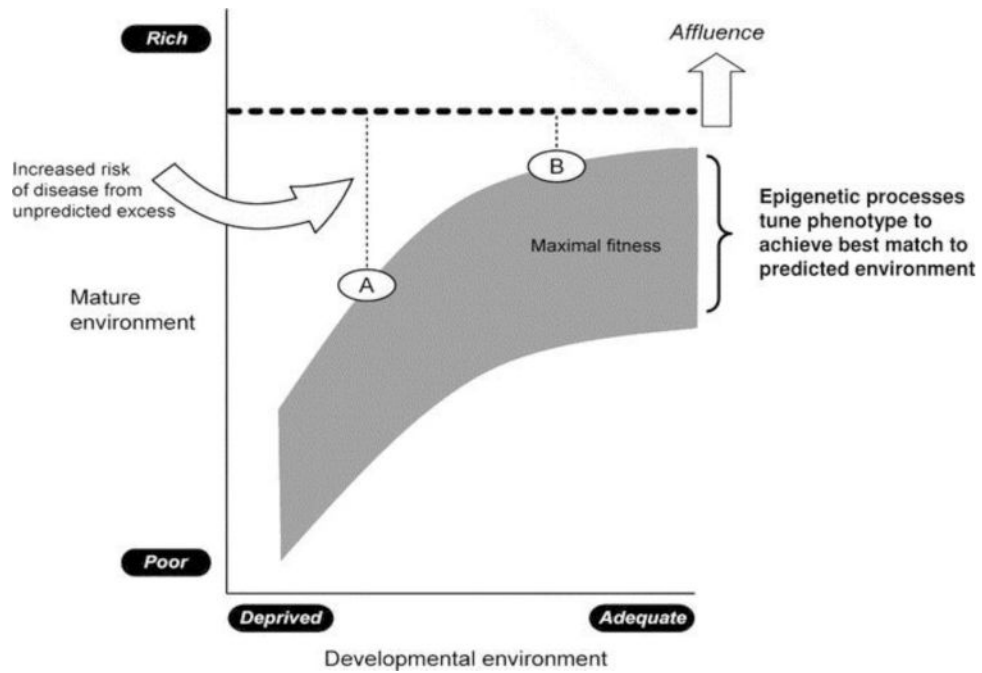
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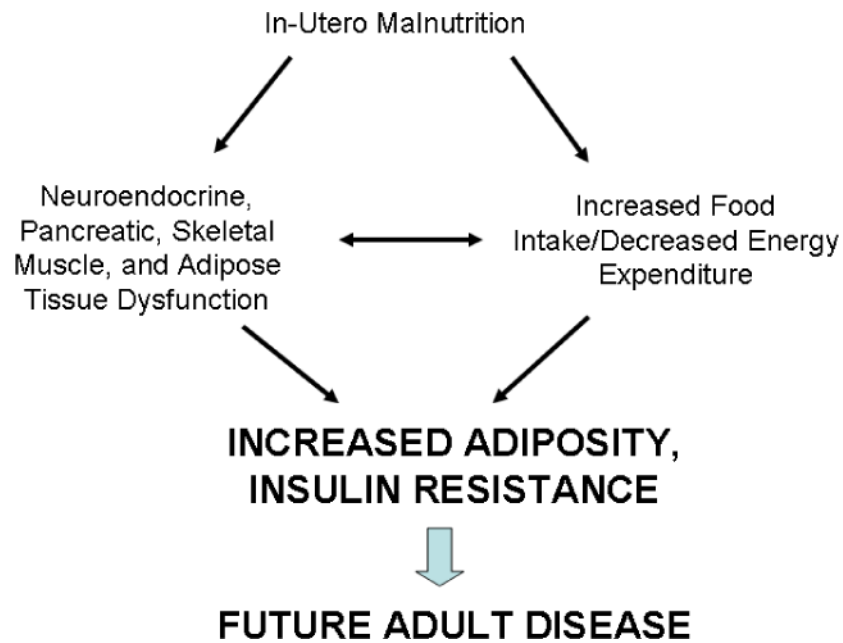


**Figure 1.** Standardized mortality ratio by gender based on birth weight in pounds. (Reprinted with permission from Barker DJ, Sultan HY. Fetal programming of human disease. In: Hanson M, et al, editors. Fetus and neonate physiology and clinical applications: growth. Vol. 3. Cambridge: Cambridge University Press; 1995.)

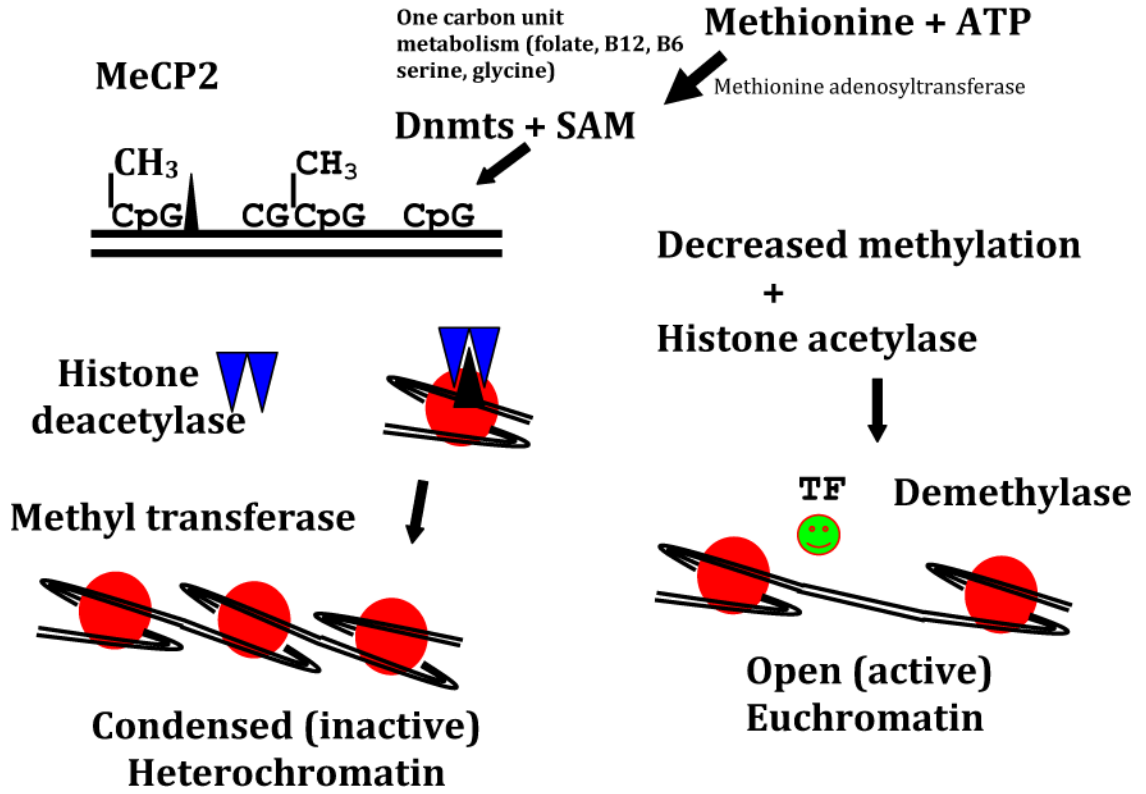


**Figure 2.**

The “thrifty hypothesis.” Schematic representation of risk of disease based on the “mismatch concept,” which focuses on the degree of disparity between the intra- and extrauterine environment. During the period of developmental plasticity, epigenetic processes are thought to alter gene expression in the fetus based on maternal environmental cues to produce phenotypes in the offspring best suited for the environment. Greater mismatch between pre- and post birth environments results in greater risk of disease (e.g., development in a poor environment followed by transition to an affluent Western lifestyle with unpredicted excessive richness of high calorically dense food with sedentary lifestyle as seen in A versus B). (Reprinted with permission from Godfrey KM, et al. Epigenetic mechanisms and the mismatch concept of the developmental origins of the health and disease, *Pediatr Res* 61:5R, 2007).



**Figure 3.** Schematic representing the pathogenesis of Fetal Origins of Adult Disease (FOAD.) In-utero malnutrition results in neuroendocrine, pancreatic, skeletal muscle, and adipose tissue dysfunction, and increased food intake and decreased energy expenditure. This leads to increased adiposity and insulin resistance, and ultimately future adult disease.



**Figure 4.** Simplistic scheme showing methylation (CH<sub>3</sub>) of CpG islands achieved by DNA methyltransferases (Dnmts) and S-adenosyl-L-methionine. Methylated DNA attracts methylated CpG binding protein (MeCP2), which recruits histone deacetylases and histone methylases, resulting in histone deacetylation and methylation. This process occurring in a gene promoter causes heterochromatin formation, resulting in failure of gene expression, which further is stabilized by the binding of the heterochromatin protein (HPI). In contrast, hypomethylation of DNA attracts histone acetylases and demethylases, which results in the opposite effect with increased euchromatin formation, transcription factor binding, and the activation of gene transcription adenosine triphosphate (ATP). (Reprinted with permission from Devaskar SU, Thamocharan M. Metabolic programming in the pathogenesis of insulin resistance. *Rev Endocr Metab Disord* 2007; 8:105).

**Table I**

Chronic diseases associated with the Fetal Origins of Adult Disease (FOAD) hypothesis

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Chronic diseases attributed to “Developmental Origins”

- Diabetes Mellitus
- Obesity
- Dyslipidemia
- Hypertension
- Coronary Artery Disease
- Stroke
- Kidney Failure - glomerulosclerosis
- Liver Failure – cholestasis, steatosis
- Lung Abnormalities – BPD, reactive airway disease
- Immune Dysfunction
- Reduced Bone Mass
- Alzheimer’s Disease
- Depression, Anxiety, Bipolar Disorder, Schizophrenia
- Cancer

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