Chapter 1
Epidemiology of Early Nutrition and Adult Health: Metabolic Adaptations and Body Composition

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Abstract The intrauterine period of growth is extremely important for lifelong health as growth and development of fetal tissues and organ systems occur at a very rapid pace. Any perturbation to this process, either through nutritional insufficiency or exposure to endocrine disruptors or toxins, not only interrupts or delays the growth process, but in some cases results in metabolic abnormalities that challenge adult health. In terms of early childhood nutrition and growth, a number of studies have reported that stunting is a risk factor for obesity and central adiposity. However, other studies have reported divergent findings. Regardless, it is well accepted that nutrition during early childhood through adolescence has a profound effect on healthy growth and deficits in energy or specific micronutrients have a negative impact of adult height and growth. More important, the growth pattern, such as slow or rapid growth, is now considered to be a primary factor in terms of body composition and health. This chapter will describe the relationship between poor growth in utero and early childhood as a risk factor for adult chronic diseases based on epidemiologic and clinical studies. As well, the influence of poor growth during childhood on metabolism and body composition will be explored as potential areas in which mechanisms may explain epidemiological studies.

Keywords Early nutrition · Metabolic adaptation · Body composition · Lifelong health · Adult disease · Obesity

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1.1 Introduction to the Developmental Origins of Adult Health and Disease

Human health is often defined as the absence of disease. However, the absence of disease is not a simplistic definition, but a complex set of characteristics determined by a number of factors related to diet, environment and economics, as well as country of residence and educational status. All of those factors, contributing to a real state of health, highlight the interplay of both biological and socio-economic factors that allow a normal developmental process to occur, key to an optimal health during the lifetime. Yet, there is debate as to how specific factors, such as pre-conception health of the mother and father, maternal exposure to sufficient or insufficient calories, protein, and micronutrients, fetal exposure to environmental toxins or drugs, as well as nutrition during early childhood interact to influence fetal and offspring growth and development.

It should really come as no surprise that nutrition from conception through childhood contributes to the long-term health of any organism, including humans. There is substantive evidence that nutritional deficiencies either in utero or during early life has permanent effects on growth, development and later health. As well, the impact of maternal and child malnutrition on growth is a well-known public health issue and is most apparent when discussing the long-term effects of micronutrient deficiencies on a child's health and development. For example, vitamin D deficiency leads to poor differentiation of enterocytes that also impairs the intestinal absorption of calcium and phosphorus, limiting or halting bone mineralization, resulting in rickets (Sahay and Sahay 2012). Perhaps one of the most significant examples of how vitamin deficiencies can cause long-term disease is the effect of folate deficiency on fetal growth. Folate is critically important for fetal DNA synthesis and cell proliferation which is why a mother's daily requirement is 5–10 times greater than a non-pregnant woman (Antony 2007). A deficiency in maternal folate intake causes abnormal neural development resulting in lifelong cerebral and neurologic impairments, neural tube defects and even death. The importance of folate for lifelong health is clear when one considers that periconceptional supplementation with folate reduced the risk of delivering a child with neural tube defects by 60% compared to women who consumed a placebo (Mulinare et al. 1988). In addition to nutrient deficiencies, the excess of some nutrients, such as alcohol, can result in impaired growth and "fetal alcohol syndrome" (Astley et al. 2016; Carter et al. 2013). Thus, deficiencies of specific nutrients that support development are known to have permanent effects on a newborn or infant and has been known for several decades. However, what was less accepted among the scientific community was that general deficiencies, such as energy restriction, or weight gain or exposure to an excess concentration of hormones (e.g. cortisol), may have lasting metabolic and endocrine responses that increase the risk of chronic diseases for offspring of mother who experienced such problems.

Since the mid-1980s, there has been a steady increase in the number of scientific publications on the influence of nutrition in utero and during critical periods of growth on adult health. This should not be a novel idea considering the evidence

of "programming" in other species as well as human. For example, it is well documented that the sex of turtles, alligators, and lizards develop differently depending on the temperature at which eggs are incubated (Gilbert 2000) Similarly, profound disruptions to brain and neurological development in humans occurs when exposed to the Zika virus (Rasmussen et al. 2016). This nascent areas of research quickly became an important field due to its impact in the scientific and public health arenas, giving rise to what is now called "developmental origins of health and disease" (DOHaD).

Barker and Osmond first documented that chronic diseases normally associated with higher income were prevalent in lower income regions of England and Wales. Specifically, there was a high correlation between infant mortality and ischemic heart disease as well as cerebro-vascular disease (Barker et al. 1993). This initial study was complemented by an analysis of mortality and birth weight in the same region and it was found that among men, the standardized mortality rate declined as birth weight increased (Barker et al. 1993). The standardized mortality rate between low and normal birth weight men was no different when analyzed using body weight at age 1 year. A similar relationship was found for women, but for birth weight only. At the same time, it was reported that breastfeeding until 1 year of age was associated with CVD in men, but not women. There is no clear explanation for this finding, but it was suggested that breastfeeding may down-regulate thyroid function and increase low density lipoprotein (LDL) concentration. At the same time, there may be differential development of the liver during gestational growth retardation as Barker also reported that infants born with a small abdominal circumference, reflecting a small liver, were more likely to have higher serum total cholesterol and LDL concentrations, independent of gestational length, social class, and alcohol and smoking status (Barker et al. 1993). Nonetheless, it is apparent that the intrauterine experience programs health and risk for disease differently for men and women, but subsequent analyses were not able to test the interactions with environmental, hormonal, or dietary factors that exist during growth and adulthood and may mitigate existing associations.

Since Barker's early publications, a great number of studies were developed with the Hertfordshire cohort where over 15,000 babies had birth weight and early feeding practices documented in the early part of the 20th century. As there is a rich dataset with several important anthropometric and dietary measures, including breastfeeding, approximately 265 studies have been conducted to assess the impact of those early nutritional parameters on risk for chronic diseases in adulthood. A number of these studies are discussed below and form a very small percent of the number of studies that have been published using data from the Hertfordshire cohort. Still, the striking and consistent results of many of the studies from the Hertfordshire cohort inspired others to either investigate similar existing cohorts or use the lessons learned from Barker and others to form new and even more detailed longitudinal cohort studies.

1.2 Famine and DOHaD

Famines are an unfortunate part of civilization and have occurred for thousands of year and continue to occur even in modern time. As with many human disasters, famines are often associated with "natural events", such as drought or disease, but in reality are intimately related to socio-political events that are intended to exert control over others or used as a means to gain political power. While unfortunate, the existence of famines has allowed for a number of novel scientific questions related to DOHaD to be asked using retrospective designs. Aside from the large number of such studies, the vast number of publications that have been generated is well beyond the scope of this chapter. However, a brief critical summary of some of the more salient famine studies will be presented with an emphasis on those studies related to chronic diseases.

1.2.1 Dutch Famine

Perhaps the most well known of famine studies is that of the "Dutch Winter Famine" that occurred between late 1944 and early 1945 in which a specific segment of Holland was under Nazi control and food rations allowed into the restricted zone contained an average of 800–1,200 calories per person, per day. Women who conceived or were already pregnant during famine gave birth to children who would then become part of the "Dutch Famine cohort". Roseboom et al were among the first to study the long-term impact of the exposure to the Dutch famine prenatally and in the first period of infancy on the survival of 2,254 people born in Amsterdam. They found that the no significant differences in mortality from 18 to 50 years of age, but a significant increase in mortality i in the first 18 years of life relative to birth weight, length and head size such that being born small increased the risk of early mortality (Roseboom et al. 2001). Similarly, Painter et al found no association between adult mortality and prenatal exposure to famine. The authors also report a positive relationship between birth weight and cancer mortality that is not mediated through famine (Painter et al. 2005). However, the authors argue that the trends indicate a positive association between famine exposure and mortality at later ages and propose that the lack of significance is due to follow-up time and overall cohort age. The argument by Painter et al was corroborated by a study published almost a decade later in which famine exposure in the first trimester increased the risk of mortality by 12% compared to those not exposed to the famine in utero (Ekamper et al. 2014). Additionally, an 8% increase in risk for mortality was reported in the cohort exposed to the famine during the first days of life after birth. The findings reported by Ekamper et al. were possible after enough follow-up had been reached for the necessary number of outcomes to reach statistical power, an improvement over previously conducted. These results are consistent with the concept that an early stimulus or insult, depending of the development stage, result in long-term consequences for function of the organism

(Hoffman et al. 2017). This programming effect is exemplified by the relationship between anthropometric measures reported by Roseboom, as well as the differences between first trimester and first days of life exposure to famine, where those exposed in the first trimester had a higher risk of mortality compared to those who were exposed at a later stage.

1.2.2 Chinese Famine

Previously termed the "Great Leap Forward Famine", the Chinese famine lasted longer than the Dutch famine and affected a mostly rural population. From data collected on the Chinese famine, it was found that the relationship between famine exposure and mortality was similar to those from the Dutch famine (Song 2009), but important methodological aspects of working with this type of cohorts are quite different. In the work of Song, mortality hazard related to famine exposure of those born right before and right after the famine are respectively, 1.2 and 1.09 ($p < 0.05$). However, this result was primarily confounded by a "period effect" caused by the unusually higher mortality risk of being born during a famine. Thus, Song concludes that the Chinese Famine had a limited effect on mortality, but that this effect did not continue after the famine was over.

In addition to mortality, another topic explored with the Chinese famine cohort was mental health and cognition at later ages. Huang and Zhou explored the influence of famine exposure in cognitive abilities among 2,685 of 45 years old and above exposed to the famine while in the uterus or in the first infancy (Huang and Zhou 2013). From this analysis, they reported an inverse association between famine exposure and cognitive abilities in later life and argue that this association is most likely to be due to socioeconomic disadvantages more than neuro-physiological pathways. However, the authors recognize that the sample size is small and that their results are not generalizable to all of China. Moreover, it was reported that women born during the famine had higher risks of developing mental disorders compared to those not exposed to the famine (Huang et al. 2013).

The physiological influences of famine exposure appear to not be limited to mental disorders or chronic diseases, but may influence even acute health disorders. In one such study, those exposed to the famine prenatally and in early life had higher prevalence of anemia in adulthood in comparison to those who were not exposed (Shi et al. 2013). As well, the authors reported a 37% increase risk of anemia in the prenatally exposed group, even after adjusting for socioeconomic indicators, hypertension, BMI and alcohol and tobacco consumption. Thus, a great deal of knowledge has been gained studies of the Chinese famine, especially important is the consideration that some of the studies have elegantly merged famine exposure relative to current diet, modeling the interaction between biological and environmental exposures.

China's Great Famine distinguishes itself from the others not only due the magnitude of its impact on the total number of deaths, but also the fact that most of the people affected were from rural areas. One leading hypothesis behind the effects of

in utero famine exposure on health in later life is that during the period of scarcity, potential epigenetic mechanisms act to prepare the offspring or newborn to the seemingly hostile environment (Bateson et al. 2004; Fleming et al. 2018). However, this mechanism has a threshold and if the environmental insult is too great the organism perishes. Nonetheless, such hypotheses explain the period effect that may have confounded the results of Shige Song. However, when looking to specific physiological differences, the influence of early mortality is reduced, corroborating the results reported by Cheng Huang et al. and Shi et al.

1.2.3 Finnish Famine

The Finnish Famine lasted from 1966 to 1968, during which 102,921 people were born and 36,022 survived to the age of 60. One study on the effect of famine exposure on mortality found no association between famine exposure and epigenetic profiles relative to mortality (Saxton et al. 2012). A similar conclusion was reported by Hayward et al in which the effects of the famine are most likely to influence mortality around the time of birth and not in later-life (Hayward et al. 2015). The discordance between the findings from the Finnish Famine cohorts and the other mentioned may be due the fact that after the Finnish Famine, the population returned to its previous levels of consumption and production. Some studies indicate that DOHaD is not only modulated by the severity of the insult during development, but also by the mismatch between the environment to which the organism adapted and the one that it was truly exposed (Jablonka and Raz 2009). The logic behind such explanations callback to the idea of "programming" in the sense that a program can only work properly in the settings in which it was built, otherwise problems, manifested as diseases, may begin to emerge.

1.3 Historical Birth Cohorts and DOHaD

As famines are unnatural occurrences, the ability of to collect data well during a famine is severely restricted due to ethical and practical constraints. Thus, research on DOHaD relies on historical cohorts that have often been initiated without the forethought that they would be used for research, but for which quality data on diet, size at birth, and infant health are available.

1.3.1 Poor Growth as a Risk Factor for Obesity

Nutritional deprivation, either as insufficient energy, micronutrient, or protein intake, during conception through early childhood, manifested in being born small for ges-

tational age (SGA) or growth retarded, is associated with adult obesity (Lucas et al. 1999). Based on existing studies, the link between poor growth and later risk for obesity appears to be related to the specific gestational exposure to famine. Among one of the first studies of in utero famine exposure and obesity found that men from the Dutch famine cohort who were exposed to famine during the first two trimesters of gestation had a higher risk of being classified as obese compared to those exposed during late gestation and early infancy (Ravelli et al. 1976). Similar to results from the Dutch famine studies, women who had been exposed to the Chinese famine in utero were more likely to be obese compared to those who were born after the famine (Meng et al. 2018). As well, a study from Sweden reported a U-shaped relationship for birth weight and BMI reporting that adults born weighing less than 2500 g or greater than 3500 g had a higher risk of obesity compared to those born weighing 3000 g (Eriksson et al. 2001). Furthermore, the pattern of disease risk varied according to gender and growth trajectory. Recently, it has been reported that exposure to famine as a fetus may have trans-generational effects on risk of poor health as offspring of women from the Dutch famine cohort were born with a higher ponderal index and were twice as likely to report "poor health" as adults (Eriksson et al. 2001). Additionally, offspring of fathers born during the Dutch famine had a higher BMI compared offspring from fathers who were not exposed to the famine (4.9 kg, CI 0.8–9.1), even after adjusting for sex and age (Veenendaal et al. 2013). Within these studies is an important caveat to consider as BMI was used as the index for adiposity and is an imperfect tool for assessing excess body fat mass. However, BMI is generally accepted as a screening tool for clinical studies and is useful for population studies. Still, there are a number of important limitations to BMI that lessen the impact of studies seeking to determine the relationship between early nutrition and later body composition or body fat distribution. Regardless, many recent studies have used advanced body composition techniques, such as stable isotope dilution and imaging, that support specific many results presented in this chapter.

The size of a newborn, be it birth weight, length, or ponderal index, is simply one dimension of growth and it has become increasingly recognized that growth during the post-natal period may play an equal, if not greater, role on adult health. Specifically, the rate of growth, using either change in BMI Z-score (BMIZ) or rate of weight gain, has been found to be predictive of adult BMI or body composition (Salgin et al. 2015). A very important cohort study that addresses growth patterns, along with social and biological factors that may influence growth and development is the Birth to 20 (Bt20) study in South Africa (Musa et al. 2016). In the Bt20 study, 3,200 newborns were recruited in Soweto, Johannesburg, South Africa in the early 1990s and underwent measures of body composition, growth, and socioeconomic indicators. The post-natal growth patterns were then used to determine how growth, relative to size at birth, acted as a risk factor for later health outcomes. It was reported that birth weight and weight gain were not associated with "unhealthy" lipid profiles, adjusted for linear growth from birth to 4 years (Musa et al. 2016). Yet, rapid gain of height and weight from birth were associated with being overweight in adolescence. Moreover, when rapid weight gain occurred early in life, children were found to have earlier menarche and increased adult adiposity, risk factors for

metabolic disorders and some forms of cancer (Charalampopoulos et al. 2014). On the other hand, a study of intrauterine growth retarded children in the U.S. found that they had a higher waist circumference and increased insulin resistance compared to children born with normal birth weight, even when controlling changes in BMIZ from birth to age 10 years (Crume et al. 2014). It was argued that the lack of statistical association between body composition may be related to the time of follow-up and is wholly consistent with a study from Brazil in which early rapid growth was positively associated with obesity in adulthood (Monteiro and Victora 2005). Yet one more study found that children who had greater weight gain, also had greater fat mass (FM), independent of birth weight, compared to children with a slower rate of weight gain (Leunissen et al. 2009). As well, results from the Project Viva study of U.S. children emphasized how interactions between birth weight and weight gain in early childhood was associated with greater adiposity, adjusted for birth size (Perng et al. 2016). In other words, children who experience a rapid change in BMIZ from six months to one year postnatal were more like to have insulin resistance, regardless of birth weight. Similarly, a rapid gain in BMIZ during the first six postnatal months was associated with higher systolic blood pressure in childhood (Crume et al. 2014). These results are consistent with the evidence that early nutritional programs and interventions that target weight gain may offer a great impact on obesity later in life (Ling et al. 2016).

It is important to note that excess body fat mass is not necessarily pathogenic, although it has been associated with an increased risk of metabolic disorders. Indeed, children born small who underwent more rapid growth than peers were more likely to be insulin resistant than children who experienced slower post-natal growth rate (Crowther et al. 2008). It has also been reported that birth size and post-natal growth have independent effects on skeletal development, depending on the timing of growth. In a study of South African children, Vidulich and colleagues found that born small and remaining small through the first year of life was associated with both smaller bones and bone with lower mineral content in the femoral neck (Vidulich et al. 2007). Finally, children from the Southampton Womens's Survey had a positive association between intrauterine growth, bone size and bone density, indicating that the effects of the DOHaD cannot disturb metabolic pathways only, but also have long term influences on skeletal development (Harvey et al. 2010).

In summary, clearly nutrition during gestation has profound and lasting effects on body size and body fat distribution, but also on other components of body composition that may promote osteoporosis and limit the development of metabolically active tissue, contributing to metabolic disorders. It is necessary to temper the impact of such studies as different methods to assess body composition were used, as well as different statistical analyses. Therefore, it is an important caveat that future studies attempt to normalize methods so that new results are more comparable with existing studies.

1.3.2 Poor Growth as a Risk Factor for Chronic Diseases

While obesity per se is not considered to be a chronic disease, it is associated with an increased risk for many metabolic disorders. Still, there are a number of studies from well documented famines that have shown that poor gestational and post-natal growth also increased the risk for certain metabolic diseases. One clinical study of the Dutch famine cohort found that lower glucose tolerance existed for adults who were exposed to the famine during gestation compared to those that were never exposed to the famine (Ravelli et al. 1998). In a separate study, the relationship between gestational famine exposure and hypertension found that adults who had been exposed to famine during any 10 week period of gestation were more likely to have hypertension compared to unexposed adults (Stein et al. 2006). In fact, a higher birth weight decreased the odds of hypertension by 33%, independent of gender. Yet, there is no clear association between specific periods of famine exposure and hypertension, most likely due to the smaller sample size when the complete cohort is split into sub-groups for more detailed analyses. Nonethelesss, one study of the Chinese famine found that adults who were exposed to the famine during middle childhood had a 50% increased risk for T2D compared to those not exposed to famine (Wang et al. 2016). More important, this relationship persisted even after adjustment for drinking and smoking status, and family history of diabetes. The risk, however, changed according to period of exposure, being higher in the middle childhood group, and according to sex, reporting a higher risk for women. A similar study of the Chinese famine also reported that adults exposed to the famine during the first years of childhood were almost three times more likely to have hypertension compared to those who had no being exposed to the famine (Chen et al. 2018). Consistent with these studies, adults who experienced gestational exposure to famine in Bangladesh and were underweight as adults were reported to be overweight as well as hyperglycemic compared to unexposed adults (Finer et al. 2016).

Finally, a study of Utah pioneers prenatally exposed to a severe food shortage during critical periods of in utero development within the winter months of 1855–1856 were more likely to die earlier compared to those who were not exposed. The effect of famine exposure on mortality was more significant for men compared to women, owing to a number of confounding factors such as activity, gender bias, or stress (Hanson and Smith 2013). It was concluded that in utero programming can have deleterious effects on future health, but the authors were cautious in their conclusions and added that catch-up growth of offspring during the first years of life could play a role in the outcome of interest. While there are certainly methodological differences between various studies of famine exposure and later health, the basic aspects of such studies are relatively consistent and allow for broad conclusions to be based on their findings.

1.3.3 Poor Growth as a Risk Factor for Mental Health Diseases

One less studied area of DOHaD focuses on the impact of poor nutrition in utero or early childhood on mental health. An accumulating number of studies, however, reported a link between poor nutrition early in life and cognitive development and later-life mental health. In the Dutch famine study prenatal exposure to the Dutch famine nearly tripled the risk for schizophrenia (Hoek et al. 1998). Strikingly similar results were published in which prenatal exposure to the Chinese famine from 1959 to 61 nearly doubled the risk of schizophrenia for adults in the famine exposed group compared to those born after the famine (St Clair et al. 2005). These studies provide significant evidence that nutrient deprivation appears to have a profound effect on later mental health due to acute exposure to famine. The relevance of finding similar results in the Dutch and Chinese cohorts is strengthened by the fact that they are two vastly different cultures, a factor well known as being a confounder in mental disorder studies, as well as having very different post-natal nutritional and social environments.

Aside from mental health, studies from different countries have reported that poor nutrition in childhood has a significant negative impact on cognition. In Peru, stunted children (defined as height-for-age Z-score or HAZ < -2.0) scored significantly lower on a series of cognitive tests compared to taller children (Crookston et al. 2010). Furthermore, children who experienced catch-up growth (indicating a positive change in HAZ) had cognitive scores similar to children who remained stunted. However, when a multi-country study was conducted on growth and cognitive performance with over 8,000 children from four developing countries, children who recovered height from age 1 to 8 years performed poorly compared to children who were never stunted but scored better than children who remained stunted (Crookston et al. 2013), suggesting that timing of nutritional interventions is vital to improving human capital. This point is made even more clear by a study of stunted children in Jamaica who received psychosocial stimulation and scored markedly higher on IQ, verbal, and reading tests compared to stunted children who did not receive such stimulation. Recently, as some of the children from this cohort are now parents, it was reported that offspring of stunted parents scored lower on a battery of cognition tests, independent of birth weight and height-for age but it is not clear if the effects are related to social or biological factors. Furthermore, stunted children in India who received nutritional supplementation for six months had cognitive test scores similar to children who remained stunted, as well as those who recovered height (Sokolovic et al. 2014). While the degree of stunting at age two years has shown consistent and long-term cognitive deficits, such deficits in a cohort from Cebu, Philippines, declined by age 11 years (Mendez and Adair 1999). Based on the studies reviewed, the timing of interventions is clearly critical to the overall impact of nutrition on brain development during gestation and childhood. This is an area of research that warrants much greater attention to improve human capital throughout the world, but especially in lower income countries.

In summary, a large number of studies provide evidence that supports the concept of DOHaD. As presented, most studies using data from famine and longitudinal cohorts have reported that poor nutrition or growth during the "first 1,000 days" are risk factors for a number of chronic diseases later in life. Exactly how and when different tissue and organ systems are influenced by nutrient deprivation remain major research questions, but new studies are providing intriguing insights into potential mechanisms behind DOHaD as discussed below. Still, it is important to consider how improving the understanding of nuances between conflicting studies can inform the research community in a way that shapes future research designs and agendas.

1.4 Growth Retadation and DOHaD

Regarding post-natal nutrition insults, while stunting is formally defined as children whose length or height is below the 10th percentile of healthy children of the same age, there is some discussion as to the appropriateness of using cutoffs outside of programmatic or epidemiologic research. Simply, using a categorical definition of poor growth restricts the population or sample under investigation to the "worst of the worst" in the sense that a child who is slightly above the cutoff is categorized as "healthy", but may actually be more anthropometrically or physiologically similar to an "unhealthy" child than a child well above the cutoff. Thus, research on growth needs to be clear as to the objective and determine a priori if poor growth should be defined using a categorical or a continuous measure.

1.4.1 Global Prevalence of Stunting

Globally, the percentage of stunted children decreased from 40 to 27% between 1990 and 2010, respectively, and is expected to reach 22% by 2020 (de Onis et al. 2011). Asia experienced an overall decrease in stunting from 1990 to 2010 (49–28%), however, in Africa, the prevalence of stunting has remained at 40% since 1990. It is predicted that this trend will continue and, in 2020, Africa and Asia will have the same number of stunted children (de Onis et al. 2011). There are a number of reasons some countries have seen an improvement in the nutritional status of their children while others have not. For example, civil strife disrupts a large number of sectors of civil society and is often accompanied by a deterioration in health care, food security, and sanitation, factors associated with a quality diet, health and optimal growth. For areas of the world that have been subject to civil unrest and economic challenges, the prevalence of stunting remains high, such as 50% in Eritrea and East Timor, 47% in Guatemala and Yemen, and 41% in Afghanistan and East Timor (United Nations 2018). Thus, while it is important to look at global and regional trends in the fight against undernutrition, it is necessary to focus on countries that are not doing as well

as others to best determine policies or practices that may be improved, even in the face of political or social challenges.

1.4.2 Stunting in Latin America

In Latin America, much progress has been made in the past 20–30 years to decrease the prevalence of poor growth, but such efforts have been eclipsed by the "nutrition transition" and the emergence of the double burden of disease. Nonetheless, at present, 9.6% of children are severely to moderately stunted and 1.3% are moderately to severely wasted in Latin America and the Caribbean (World Health Organization 2018). In specific countries, such as Ecuador, there is a high prevalence of stunting that has been linked to household economic status and dietary diversity (Weigel et al. 2018). In Brazil, the prevalence of growth retardation has improved greatly in recent years, partly due to economic development that has reduced the number of families living in poverty and partly due to national nutrition programs that have promoted nutrition and education in lower income communities (Yokoo et al. 2018). It is imperative to highlight the differences regarding the prevalence of stunting among different countries in Latin America. For example, 48% of children under the age of 5 in Guatemala are stunted compared to 2% of children in Chile (World Health Organization 2018). Still, one cannot generalize as to why some children become stunted and others do not within specific countries, regions or continents, but rather evaluate the prevalence individually to better plan policies and other interventions for each country (Corvalán et al. 2017).

1.4.3 Stunting in Africa

Countries in Africa and Asia tend to have a high prevalence of both wasting and stunting resulting from poor maternal nutrition as well as ongoing food insecurity due to political unrest, economic disparities, and poverty. For example, while in 2015 there were 98.5 million fewer stunted children under 5 years of age than in 1990, the global prevalence is partly reflected by gains in some regions, but not others as the number of stunted children in sub-Saharan Africa increased by 12.4 million in the past 25 years (Campisi et al. 2017). In Kenya, approximately 30% of children under two years of age were stunted (Ndemwa et al. 2017) while in South Africa, 26% of boys and 19% of girls under two years were stunted (Hanson et al. 2018). In summary, great advances have been made in many countries to improve nutrition and lower the prevalence of growth retardation, but many countries still face serious challenges and an increasing prevalence of stunting that has the potential to limit educational attainment and economic advances for members of the lowest income groups or in marginalized communities.

1.4.4 First 1,000 Days Concept

Extending the concept of DOHaD to include growth after the "first 1,000" days, essentially considering nutritional insults that impact linear growth and results in chronic growth retardation, is an important consideration given the vast number of children worldwide who are classified as stunted (de Onis et al. 2018). Stunting, as well as more moderate growth retardation, affects upwards of 150 million children worldwide, with the majority residing in low- and middle-income countries (de Onis et al. 2011). For decades, stunting was associated with poverty and lack of access to adequate nutrition, generally thought to be a problem of insufficient calories and micronutrients. However, in the mid 1990s, a study of four countries found that stunting in adolescence was a risk factor for obesity in adulthood (Popkin et al. 1996), a new paradox given the conventional thinking that obesity was a problem of wealth and excess caloric intake. Subsequent clinical studies of stunting and obesity support this initial finding and offer potential biological explanations for the relationship between stunting and fat deposition. One study of adolescent girls in Senegal who were stunted before the age of 2 years, accumulated more subcutaneous fat on the trunk and arms compared to non-stunted girls, even when adjusted for BMI (Bénéfice et al. 2001). Likewise, a separate study of Guatemalan children who were stunted had a BMI above the median for US children of the same age, but low extremity fat assessed using skinfold measurements (Schroeder and Martorell 1999). When adults from the same cohort had anthropometric measures conducted, those who were severely stunted as children had greater central fat, even when adjusted for total FM and other confounding factors, compared to those who were moderately or never stunted (Schroeder et al. 1999).

To further explore and understand the relationship between stunting and obesity, a clinical study of stunted children in Brazil was conducted to assess metabolic adaptations that may promote excess adiposity. Briefly, stunted children were recruited from the same shantytowns as normal height control children, the gain of truncal fat mass was greater during a four-year period, independent of total fat mass (Hoffman et al. 2007). It should be noted that the method to assess adiposity in this study involved the use of imagining, a far more accurate methodology than anthropometrics alone. Nonetheless, there are other studies that have reported divergent results. For instance, longitudinal analyses of the Bt20 cohort found that stunting at age 2 years was not associated with a high BMI or central adiposity (Cameron et al. 2005). As well, one study of indigenous children in Bolivia reported that stunting was associated with a lower BMIZ and body fatness assessed using skinfold measurements (Tanner et al. 2014). Still, in a separate Brazilian cohort, there were no significant associations between indices of undernutrition (such as WHZ or HAZ) and adiposity (Gigante et al. 2009). One important caveat to this cohort from Brazil is that the proportion of children who were found to be undernourished was relatively low (less than 10%), but poor growth early in life was associated with shortness later in life, a significant predictor of poor health outcomes and other factors associated with poverty, but not with excess adiposity or obesity. Moreover, a recent study from Nepal found that

stunted children in a low-income and less developed region, have poor lean tissue accretion and less fat mass compared to normal height children (Wells et al. 2018). To best understand the complementary and conflicting results presented in these studies, despite the fact that subject characteristics or inclusion criteria may have bee similar, the differences in methods used to assess outcomes, sample size, and socio-economic environment of the study sample all contribute to potential differences in associations and conclusions. Certainly, investigators may make the best attempt to control for all possible confounding factors, but interactions between a any number of factors is bound to influence associations that do not allow for a consensus on the question being studied.

Based on the studies discussed above, there is clearly an abundance of research that has provided solid evidence that poor nutrition in the "first 1,000 days" has an impact on body composition and body fat distribution later in life, phenotypes that may increase the risk for metabolic disorders and other nutrition-related chronic diseases. Certainly, it is wise and prudent to consider that growth continues well after the first 1,000 days and future research needs to consider the dynamic events during later childhood and puberty that may either interact with or exacerbate, maybe even attenuate, the nutritional insults during early development. As well, as a child grows, their dietary and activity patterns, along with exposure to a number of environmental toxins, contribute to their life course and influence their initial risk of chronic diseases, along with their gestational and early life exposures. Still, the ability to greatly control and influence a child's exposure to unhealthful diet or environment are greatest during the first 1,000 days.

1.4.5 Stunting and Metabolic Adaptations

While most of the studies discussed in this chapter were epidemiological or clinical, one of the criteria for assessing causality in epidemiology is the existence of plausible biological mechanisms that support results from population studies. Yet, studies of humans complement other animal studies and appear to suggest specific metabolic mechanisms behind the association between in utero or post-natal under-nutrition and adult health. In fact, studies of human energy expenditure, including resting metabolic rate (RMR) and substrate oxidation, have reported that metabolic adaptations may increase the risk for greater adiposity later in life. Two such studies found no significant differences in RMR between stunted children and normal height children (Hoffman et al. 2000a; Wren et al. 1997). Yet, two studies reported a significantly lower RMR in growth retarded children compared to normal height children (Aidam et al. 2005; Said-Mohamed et al. 2012). Apparent differences in human studies of body composition or energy metabolism may easily be attributed to differences in methodologies used or the statistical analyses used. For example, for those studies that reported no significant finding related to RMR, investigators used ratios for energy metabolism per unit body composition and it is generally accepted that the more appropriate analysis would have use linear regression analyses where

body composition is entered as a confounding variable. Regardless, there is substantial data that either support the hypothesis that nutritional insults early in life program metabolic adaptations that may increase the risk for chronic diseases under obesogenic conditions, such as high dietary fat intake or low physical activity, but conflicting studies do not negate these results, rather they create an impetus for more refined research to be conducted.

Given these methodological differences, it is still important to address impact of poor growth on energy metabolism and body composition, but perhaps employing a more nuanced approach to studying specific elements of energy metabolism, such as substrate metabolism, a key metabolic risk factor for fat deposition. Studies on substrate oxidation in growth retarded children are generally more consistent compared to studies of energy expenditure. A number of clinical studies have reported specific metabolic adaptations associated with low birth weight or growth retardation. As discussed above, the study of stunted children in Brazil measured basal substrate oxidation and found that stunted children metabolized fat at a lower rate than normal height children, independent of fat mass and macronutrient intake (Hoffman et al. 2000b). Along those lines, a study of men from the Hertfordshire Cohort reported that men who were born small had a lower rate of 24-h fat oxidation compared to those men born with a higher birth weight (Kensara et al. 2006). In addition, a study of the Buryat in southern Siberia found that adults who were significantly shorter than their peers following the fall of the Soviet Union had a lower rate of fat oxidation (Leonard et al. 2009). Finally, North Korean children who were either stunted or short for age had a significantly lower rate of fat oxidation compared to North Korean children who were not growth retarded (Lee et al. 2015). It is important to consider that these similar results come from studies of adults and children with vastly different cultural and genetic differences. Thus, one could conclude that that poor growth, either in utero or during childhood, is associated with a metabolic adaptation that promotes fat storage and under the right environmental conditions. A challenge to understanding more intricate aspects of metabolism in growth retarded children is the ethical issues related to invasive methods. Obviously, studies on rodents are able to provide great insight into potential metabolic mechanisms that may develop following growth retardation and are discussed in detail in a number of review papers beyond the scope of this chapter (Goldstein et al. 2017; Tain and Hsu 2017; Tain et al. 2017a, b).

1.4.6 Social Determinants of Growth and Role in DOHaD

Poor growth associated with poor dietary intake or intrauterine exposure to stress hormones or other environmental factors is generally a reflection of poverty and other structural factors that may be difficult to modify. Yet, when one considers the biology of DOHaD and the implications for lifelong health, it is important to consider the number of social and economic factors that may interact with dietary intake and and environmental exposure. Such factors may range from maternal education, household

income, access to nutritious food, air quality and sanitation, all of which have great potential to adversely influence maternal and paternal health, nutrient availability, and fetal growth.

Perhaps the most insightful study to date that has the ability to address social and economic influence on the biology of DOHaD comes from the Bt20 cohort. One salient study from this cohort reported that socio-economic status was protective against risk for hypertension independent of size at birth (Hoek et al. 1998). It was also found that a high degree of social support and income were associated with greater bone mineral content, adjusted for body composition and pubertal development (Crookston et al. 2010). Returning to the study of the Chinese famine, adults who were born during the famine and live in high income areas had a greater risk of T2D, suggesting that prosperity may further increase the risk for specific chronic disease previously thought to be attributable to famine exposure only (Wang et al. 2015). In terms of interactions between social and biological factors, in utero famine exposure was found to increase the risk of T2D, yet those adults exposed to the famine who ate a "Western" diet were even more likely to have T2D compared to those who ate a "traditional" diet, illustrating the intricate interaction between in utero and environmental exposures on chronic disease development (Li et al. 2011).

Birth weight is often used to reflect the intrauterine growth experience, but studies of post-natal growth report that the impact of socio-economic status on risk and/or recovery from growth retardation play very significant roles in the biological outcomes studied. For example, a higher birth weight was associated with a lower risk of stunting, but higher maternal education was protective only in girls while a higher SES was protective for boys (Sokolovic et al. 2014). In terms of cognitive development, children who recover from stunting by 5 years of age experienced greater cognitive challenges compared to normal height children. In fact, the cognitive problems in children recovered from stunting were estimated to be as severe as those measured in stunted children who remained stunted (Sokolovic et al. 2014). While single country studies are subject to criticism given the number of social and cultural differences between various countries can impact the variables being studied, it is useful to consider multi-country studies. To that end, based on data from a large multi-country study of growth and human capital, children born with a higher birth weight or a rapid gain in height by age 2 years, had a higher level of education that was estimated to increase adult income by 5% (Sokolovic et al. 2014). Moreover, in terms of economic productivity, it was found that height at 2 years of age was the greatest predictor of overall human capital. Clearly, the negative effects of growth retardation are physiological and threaten the long-term health of an individual, but it is important and necessary to consider the impact of cognitive damage associated with poor nutrition as these outcomes may interact with general health to limit a person reaching their full human potential, in both biological and social terms.

1.5 Summary and Conclusions

In summary, while DOHaD began with a series of epidemiological studies, the exact mechanisms to explain and support the results presented were scarce. However, over the past 20–30 years, substantial evidence from additional cohort, small mammal, and even epigenetic studies have proposed plausible and consistent mechanisms linking poor nutrition in early life to risk of chronic diseases in adulthood. Given the studies reviewed, it is apparent that particular physiological and behavioral adaptations following acute and chronic undernutrition, either in utero or during early childhood, have significant impacts on adult health. However, it remains a challenge for future research to design cohort studies using new technologies in proteomics, metabolomics, and epigenetics to refine the knowledge of potential mechanisms of DOHaD. Perhaps even more important is that the research community remains cognizant of the social and economic conditions in which children are exposed to poor nutrition and incorporate interventions that not only lower the risk of chronic diseases in adulthood, but also actually improve education and nutrition of women in lower and middle income countries.

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