Chapter 2
Intergenerational Memories of Past Nutritional Deprivation: The Phenotypic Inertia Model

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Abstract Human and animal model research shows that prenatal nutrition influences early development and has long-term effects on adult biology and chronic disease. Much of this literature has emphasized the limited maternal capacity to buffer the fetus from stressors that negatively impact development. An alternative perspective recognizes that a subset of prenatal biological responses reflect an ability to adaptively change how the body regulates metabolism, hormone production, and other biological functions in anticipation of postnatal environmental conditions. The applicability of this concept to humans has been challenged on the basis of the long duration of the human life span and the imperfect correlation between environmental conditions during early and later life. The phenotypic inertia model proposes a solution to this problem: if maternal physiology and metabolism transfer nutrients or hormones in relation to the mother's average life experience, rather than to the specific conditions experienced during that pregnancy, this could provide a more reliable basis for the fetus to adjust its long-term strategy. This hypothesis is supported by evidence that fetal nutrition is buffered against short-term fluctuations in maternal intake during pregnancy in women who are not on the extreme ends of energy balance, while showing evidence of sensitivity to a mother's early developmental and chronic nutritional experience. Maternal buffering of fetal nutrition in humans is predicted to limit the deleterious impact of nutritional stress experienced by the mother during pregnancy while also attenuating the long-term health benefits of short-term dietary supplements consumed during pregnancy. According to this model, maternal interventions aimed at improving the health of future generations via fetal nutritional programming will be most effective when they emulate sustained, rather than transient, nutritional improvement.

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2.1 Introduction

There is now much evidence that constrained fetal nutrition has effects on a broad array of functional capacities and disease outcomes (Barker 1994; Barker et al. 1989; Roseboom et al. 2001, 2006). Birth weight is commonly measured and recorded and as a result has frequently served as a proxy for prenatal nutrition, hormone exposure, and other gestational conditions. Low birth weight (LBW) is a global health concern as it predicts elevated risk of cardiovascular disease and metabolic syndrome and also contributes to infant mortality and leads to deficits in indices of human capital, such as body size, strength, lung capacity, educational attainment, and even wages (Hancox et al. 2009; Levitt et al. 2000; Yliharsila et al. 2007). In addition, there is growing evidence that maternal overnutrition, as demonstrated by maternal obesity and type II (non-insulin-dependent) diabetes, leads to increased risk of cardiometabolic disease in offspring (see Armitage et al. 2008; Dörner et al. 1988). These findings linking infant and adult well-being to both under- and overnutrition during pregnancy underscore the need to understand the underlying biological processes and targets for intervention (Gluckman and Hanson 2005; Kuzawa and Thayer 2012).

From a public health or policy perspective, the finding that fetal nutrition has long-term effects on adult health and functional capacities has led to a hope that modifying the diets of pregnant women will result in benefits for future generations. Perhaps the strongest evidence for a benefit of supplementing the dietary intake of pregnant women comes from an intervention in the Gambia in which women in mid-gestation received an additional daily allotment of 1028 kcal, along with calcium and iron (Ceesay et al. 1997). This intervention yielded a sizeable 201 g increase in offspring birth weight during the hungry season, when nutritional status deteriorates due to negative energy balance secondary to food scarcity, high workloads, and high burdens of infectious disease due to the heavy rains. During the harvest season, the same intervention yielded a 94 g increase (roughly 4 oz).

The Gambian study suggests that substantial and sustained improvement in maternal dietary intake can improve fetal nutrition and growth, with the greatest benefits experienced during acute bouts of energetic and nutritional stress. Unfortunately, few other similar interventions have yielded comparable levels of success in improving birth outcomes. In a systematic review of balanced protein/calorie pregnancy supplement trials, Kramer and Kakuma (2003) found a reduced risk of giving birth to small-for-gestational age offspring. However, these macronutrient supplementation trials did not yield significant increases in offspring birth weight, length, or head circumference. As illustrative examples, increases in birth weight of 51 and 41 g, and a decrease of 40 g, were reported in three of the larger dietary supplementation trials of undernourished women in Guatemala (Mora et al. 1978), New York City (Rush et al. 1980), and India (Kardjati et al. 1988), respectively. Among the five studies that provided balanced protein/energy supplements to adequately nourished women, birth weight increased in two but declined in three, with a weighted-average nonsignificant increase of around one ounce.

These findings underscore a paradox and also a policy dilemma: *fetal* nutrition apparently has large effects on future health, but increasing *maternal* macronutrient intake during pregnancy only nudges fetal growth and birth outcomes. To the extent that fetal growth is a useful proxy for the nutrients that cross the placenta, this suggests that current intervention strategies (that generally augment a woman's dietary intake during pregnancy) are not likely to yield large improvements in fetal nutrition and downstream metabolic programming. What might account for this apparent disconnect between the foods that the mother consumes during pregnancy and the nutrients that the fetus receives across the placenta?

The present chapter integrates principles from biological anthropology and evolutionary biology to shed light on the possible origin and function of developmental responses to early nutritional environments. It has been known for over 50 years that developmental plasticity, or the capacity of developmental biology to be modified in response to the environment, is an important way by which human populations adapt to changing environments (Lasker 1969). The literature documenting long-term effects of early environments expands the concept of human developmental plasticity by pointing to pathways of communication between mother and offspring, such as nutrients and hormones passed across the placenta and via breast milk (Bateson 2001; Bateson et al. 2004; Gluckman and Hanson 2005; Kuzawa and Pike 2005). An evolutionary framework highlights the need to consider the timescale of ecological change that these flexible systems are likely built to accommodate (Kuzawa 2005). Using an evolutionary approach, we argue that finding ways to communicate cues (e.g., nutrients, hormones) intergenerationally that mimic *sustained* environmental change, in contrast to the short-term, transient changes represented by most nutritional supplementation trials, will prove key to designing interventions that improve long-term functional and health outcomes in future generations.

2.2 Intergenerational Effects and the Human Adaptability Framework

To gain insights into effective strategies for modifying early developmental plasticity to improve long-term health, it is helpful to first consider the fundamental question of why the body modifies its biology in response to early life experiences. For some outcomes, the simple explanation is that environmental stressors impair healthy development, as illustrated by the fact that fetal nutritional stress can impair the growth of organs (Harrison and Langley-Evans 2009; Nwagwu et al. 2000). This is thought to explain some of the links between smaller birth size and poor adult health, such as the fact that LBW babies tend to have smaller kidneys with fewer nephrons, which predisposes them to hypertension and renal failure later in life (Iliadou et al. 2004; Lampl et al. 2002).

While some effects of early environmental conditions result in impairment or damage, other physiological outcomes influenced by fetal nutrition are not as easily explained. Instead, they appear to result from changes in regulatory set points that influence how the body prioritizes specific functions or responds to

experiences over the life course. For example, in children and adults born with a lower birth weight, weight is preferentially deposited in the form of fat accumulation in the abdominal or "visceral" region. The fat cells in this region are innervated with sympathetic nerve fibers that secrete adrenaline, thus allowing the body to rapidly mobilize a usable source of energy from these cells when faced with a stressful challenge (Hucking et al. 2003). The free fatty acids that are released by the visceral depot when the body is faced with a stressor have additional cascading biological repercussions. The very act of mobilizing reserve energy stores sends a signal to the liver that the body is under duress and that glucose should thus be spared for use in more critical functions, such as brain metabolism. This is achieved by reducing the sensitivity of tissues like muscle and liver to the effects of insulin (i.e., insulin resistance) (Kuzawa 2010). Not only do low birth weight individuals deposit more fat in this rapidly mobilized depot, but there is also evidence that their fat cells mobilize *more* stored fats when exposed to the same dose of adrenaline, making this stored fuel rapidly available for use (Boiko et al. 2005).

There is nothing about the development and function of the fat deposits of these individuals that hints at either damage or impairment. Unlike the example of impaired kidney growth, there is no shortage of cells in the affected organ or tissue. Instead, these findings suggest that prenatal nutrition can change regulatory set points to alter the priorities with which scarce resources are used within the body: in this example, the body preferentially deposits any excess energy in fat deposits that are more easily and rapidly accessible when the body is faced with stress (Boiko et al. 2005). Many of the changes that are triggered in response to prenatal conditions appear to have similar origins in altered regulation, suggesting that they are examples of adaptive adjustments in developmental biology rather than simple impairments of organ growth (Kuzawa and Thayer 2011).

2.3 Developmental Plasticity as a Means of Adaptation

The concept of adaptation is one of the organizing principles of evolutionary biology and refers broadly to changes in organismal structure, function, or behavior that improve survival or reproductive success. Genetic adaptation more specifically refers to the process by which gene variants (alleles) that code for beneficial traits become more common within a population's gene pool through the mechanism of natural selection. Although natural selection is a powerful mode of adjustment at the population level, many environmental changes occur more rapidly than can be efficiently dealt with by changes in gene frequency, which require many generations to accrue. To cope with more rapid change, human biology includes additional, more rapid adaptive processes (Kuzawa 2005; Lasker 1969). The swiftest ecological fluctuations (e.g., fasting between meals or the increase in nutrients that our bodies need when we run) are handled primarily via

homeostatic systems, which respond to changes or perturbations in ways that offset, minimize, or correct deviations from an initial state. Operating not unlike a thermostat, which maintains a constant temperature by turning the furnace on and off, homeostatic systems modify physiology, behavior, and metabolism to maintain relatively constant internal conditions despite fluctuations in features like ambient temperature, dietary intake, and physical threat. The distinctive features of homeostatic systems include their rapid responsiveness, their self-correcting tendencies, and the fact that the changes they induce are reversible.

Some environmental trends are chronic enough that they are not efficiently buffered by homeostasis, but also do not persist for long enough for substantial genetic change to occur. As such, organisms may not rely on homeostasis and natural selection to adjust biological strategies to these intermediate timescale trends. A simple example illustrates how a sustained change in experience might overload the flexible capacities of a homeostatic system if this was the only means available to help the organism adapt (Bateson 1963). In this case, imagine an individual that has recently moved to high altitude where oxygen pressure is lower, resulting in an elevated heart rate that increases blood flow and thus the rate that oxygen-binding red blood cells pass through the lungs. By engaging a homeostatic system (heart rate), the body has activated a temporary fix to help compensate for the low oxygen pressure. However, this is only a short-term solution that comes with a cost: not being able to increase heart rate further if the need arises, like when fleeing from a predator. Thus, the homeostatic strategy of elevating heart rate may work for short-term acclimation, but is a poor means of coping with chronic high-altitude hypoxia.

Over longer time spent at high altitude, additional biological adjustments ease the burden on the heart, such as increasing the number of oxygen-binding red blood cells in circulation. However, individuals who grow and develop at high altitude exhibit an even better strategy for coping with hypoxia. They grow larger lungs, a developmental response that increases the lung's surface area for oxygen transfer, thus obviating the need for temporary and more costly short-term adaptations (Frisancho 1993). This change in developmental biology is an example of *developmental plasticity*, which allows organisms to adjust biological structure on timescales too rapid to be dealt with through natural selection, but too chronic to be efficiently buffered by homeostasis (Kuzawa 2005).

These mechanisms can be viewed as allowing the organism to fine-tune structure and function to match the needs imposed by their idiosyncratic behavioral patterns, nutrition, stress, and other environmental experiences that cannot be "anticipated" by the genome (West-Eberhard 2003). Unlike homeostatic changes that are transient, growth and development occur only once, and thus plasticity-induced modifications tend to be irreversible once established. In this sense, developmental plasticity is intermediate between homeostasis and natural selection in both the phenotypic durability of the response and the timescale of ecological change that it accommodates.

2.4 The Phenotypic Inertia Model

Because some of the biological changes induced by intrauterine or infancy cues appear to reflect modifications of regulatory set points rather than developmental damage, it has been speculated that some components of developmental plasticity might be initiated to help the fetus prepare for conditions likely to be experienced after birth (Bateson 2001; Gluckman and Hanson 2005; Kuzawa 2005) (see Fig. 2.1). Some of the adjustments made by the nutritionally stressed fetus in utero (such as the aforementioned tendency to deposit more abdominal body fat and the glucose-sparing effects of muscle insulin resistance) could provide the advantage of saving scarce glucose for use in more essential functions after birth (e.g., brain metabolism) if the environment remains nutritionally stressful after birth (Gluckman and Hanson 2005; Kuzawa 2010). By this reasoning then, nutrition, hormones, and other gestational stimuli experienced by the developing fetus might convey information about local ecological conditions, thereby allowing the fetus to adjust priorities in anticipation of the postnatal reality that s\he is likely to experience (Bateson 2001). Bateson (2001) describes this as the mother sending a "weather forecast" to the fetus, while Gluckman and Hanson (2005) label this a "predictive adaptive response."

One challenge to this notion of long-term anticipatory adaptation comes from the fact that humans have long life spans. Because humans typically live many decades, any conditions experienced during a few months of early development, such as gestation or early infancy, may not serve as reliable cues of environments likely to be experienced in adult life (Kuzawa 2005; Wells 2003). We have argued that it is precisely the brief and early timing of many of the body's periods of heightened developmental sensitivity that paradoxically could *help* the developing organism overcome the challenge of reliably predicting future conditions (Kuzawa 2005; Kuzawa and Thayer 2011). The mother's physiology could buffer the fetus against the day-to-day, month-to-month, or seasonal fluctuations in the environment while passing along more integrative information on average conditions experienced by the mother in recent decades or the grandmother prior to the moth-

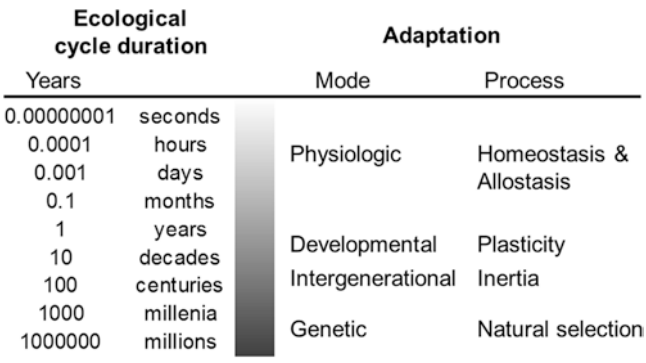

Fig. 2.1 The timescales of human adaptation (modified after Kuzawa 2008)

er's birth and during lactation. Because the mother's biology and behavior have been modified by her lifetime of experiences (including her own gestational environment, and thus her offspring's grandmother's experience), the nutrients, hormones, and other resources that she transfers to the fetus in utero or to her infant via breast milk could correlate with average local conditions and experiences rather than to the vagaries of what the mother happens to experience during any given week or month of gestation itself (Kuzawa 2005; Wells 2003). If maternal physiology buffered out transient, short-term nutritional variations while conveying more reliable average information, this could provide the fetus with a more useful basis for adjusting characteristics such as growth rate, body composition, and/or nutritional requirements as environmental conditions gradually shift across decades of his/her lifetime or over several generations (Kuzawa 2005).

There is accumulating evidence that the mother's body does convey average, rather than transient, ecological information to the fetus. As noted above, despite the general tendency for populations faced with low socioeconomic conditions and chronic nutritional stress to have reduced birth weights, supplementing the diets of pregnant women in these populations generally has minimal effects on the birth weight of immediate offspring (Kramer and Kakuma 2003). In contrast, studies provide evidence that a mother's own early life nutrition, or nutrition across development, may be a strong predictor of the birth weight of her future offspring. In most studies that evaluate this, fetal growth of the mother is a stronger predictor of offspring birth weight than is the father's birth weight, pointing to possible maternal effects, either indirect genetic or epigenetic (for review see Kuzawa and Eisenberg 2012). Similarly, in a pooled sample of five large cohort studies in low- and middle-income countries, both maternal and paternal birth weight and early postnatal growth were found to be significant predictors of offspring birth weight, but these relationships were more consistent (and stronger) among females, pointing to a possible intergenerational effect of the mother's developmental nutrition (Addo et al. 2015).

Leg growth is particularly sensitive to nutritional conditions during infancy and early childhood and thus provides a useful retrospective proxy of developmental conditions experienced by the mother (Frisancho et al. 2001). In the United Kingdom, a woman's adult leg length was a stronger predictor of offspring birth weight than was her trunk length (Lawlor et al. 2003). In a similar study, a woman's leg length measured during her own childhood (around 7 years of age) was the strongest maternal anthropometric predictor of her future offspring's birth weight, even after adjusting for adult size and stature (Martin et al. 2004). Most recently, a study in the Philippines found leg length to be the strongest predictor of both offspring birth weight and placental weight, whereas trunk length was only weakly related to birth weight and unrelated to placental weight (Chung and Kuzawa 2014). Because leg growth is among the most nutritionally sensitive components of stature growth, these studies suggest that a mother's own infancy or early childhood nutrition can have lingering intergenerational effects on offspring fetal growth, which likely manifests in part through alterations in placental growth and size.

Collectively, these studies, viewed alongside the relatively modest success of nutritional supplementation trials during pregnancy, suggest that long-term or chronic nutritional history may be an important influence on the resources transferred in support of fetal growth and birth size (secondarily impacting the many traits and functions that are sensitive to and "downstream" of prenatal experience), while fluctuations in the mother's intake during pregnancy itself (though important) have comparably modest effects. This *phenotypic inertia* in fetal nutrient transfer—reflecting the lingering biological but nongenetic effects of the mother's average experiences in the past—could allow the fetus to track those dynamic features of environments that are relatively stable on the timescale of decades or even several generations (see Kuzawa 2008; Kuzawa 2005).

2.5 Mechanisms of Intergenerational Phenotypic Inertia

The mechanisms linking maternal-fetal nutrient transfer to the mother's developmental or chronic nutrition are unknown, but there are interesting potential candidates. First, it has been hypothesized that modifying the mother's growth rate during early critical periods in skeletal growth (when long-term growth trajectories are set) could set the mother's "productivity" and thereby have carryover effects on offspring fetal growth once productivity is reallocated from self-growth to supporting offspring growth (Kuzawa 2007). The greater nutritional sensitivity of leg growth during this early critical period and the finding of strong relationships between leg growth and offspring birth weight are consistent with this idea.

In addition, because maternal glucose levels during pregnancy are important predictors of offspring fetal growth and birth weight (Metzger et al. 2008), any effects of early life metabolic programming that the mother experiences could have secondary impacts on her pregnancy glucose status and thus the fetal growth of offspring. Once female offspring develop into reproductive adults, these phenotypic effects could linger and even accumulate across multiple generations (Drake and Liu 2010; Kuzawa and Eisenberg 2014; Kuzawa and Sweet 2009). Epigenetic changes are likely candidate pathways for such life course, inter- or multigenerational effects (for review see Kuzawa and Eisenberg 2014). For instance, in human populations, individuals exposed to famine while in utero exhibit alterations in methylation at genes (like IGF2) that are related to glucose metabolism and cardiovascular disease risk (Heijmans et al. 2008). Studies demonstrate the transmission of environmentally-induced epigenetic changes across one or more generations in other mammals (Franklin et al. 2010; Guerrero-Bosagna and Skinner 2012). At present, little is known about how common germline epigenetic inheritance might be in humans, but intriguing evidence has emerged from the creative use of historical records. In northern Sweden, harvest yields during the grandparents' childhood predicted mortality in matched-sex grand offspring, pointing to possible multigenerational, epigenetic, and sex-linked effects of nutritional experiences (Pembrey et al. 2006).

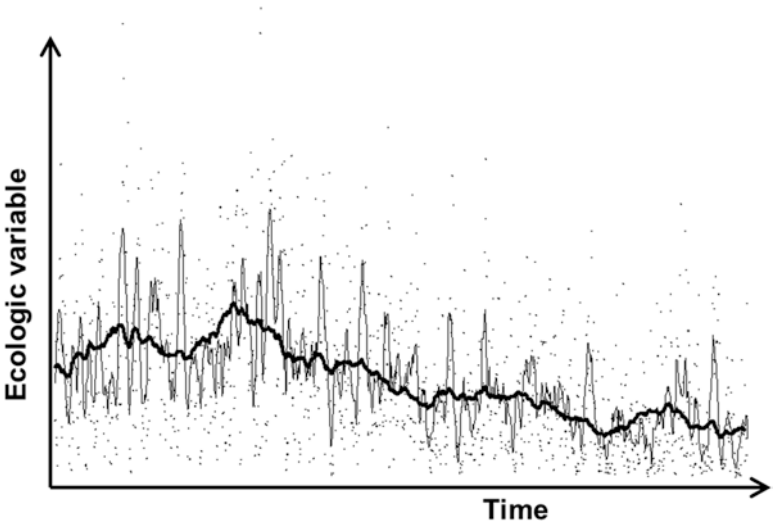

Fig. 2.2 The value of averaging as a means of identifying a trend in a noisy signal, in this case representing the availability of a hypothetical ecological resource. The two lines are running averages calculated across 10 time units (*thin line*) and 100 time units (*dark line*). As the window of averaging increases, an underlying long-term trend is uncovered. Intergenerational influences of maternal and grandmaternal nutritional history on fetal nutrition may help achieve a similar feat (from Kuzawa and Quinn 2009, with permission)

While the mechanistic specifics remain to be demonstrated, if the mother's (or father's) body or epigenome pass along biological "memories" that "sample" (and thus mirror) chronic local nutritional experiences, this could allow the fetus to make developmental adjustments in response to conditions that have dominated in recent generations and, thus, serve as a "best guess" of conditions likely to be experienced during the lifetime of the offpsring (see Fig. 2.2).

2.6 Why Do Some Nutritional Interventions Fail?

We have argued that long-lived organisms will tend to buffer or ignore transient features of their environments, but are sensitive to environmental features that are stable over longer time periods (i.e., a generation or more). We conclude by considering the implications of this idea for two research and policy domains: the biomedical use of animal experiments as models for developmental processes in humans and the design of human interventions aimed at improving long-term health.

First, what is "transient" or "stable" for individual species is inherently relative. We should expect that adaptively relevant timescales of environmental change for a human will be markedly longer than those of a rat or other short-lived species. Thus, humans should be expected to "ignore" the types of environmental changes mice or rats will modify their life trajectory in response to. After all, if a rat is born during a

stressful season or year, those conditions are likely to predominate during its entire brief life. Because humans will live through hundreds of seasons, what a mouse would consider as an environmental "signal" would simply be "noise" to be buffered out by a developing human.

This perspective may help explain why individuals in the World War II Dutch Famine Winter cohort, who were exposed in utero to caloric restriction of a similar magnitude as in many animal experiments, experienced comparably small changes in birth weight followed by more modest long-term effects on metabolism and adult cardiovascular disease risk factors (Lussana et al. 2008; Painter et al. 2006) (see Fig. 2.3). Because biological processes and responses scale with traits like

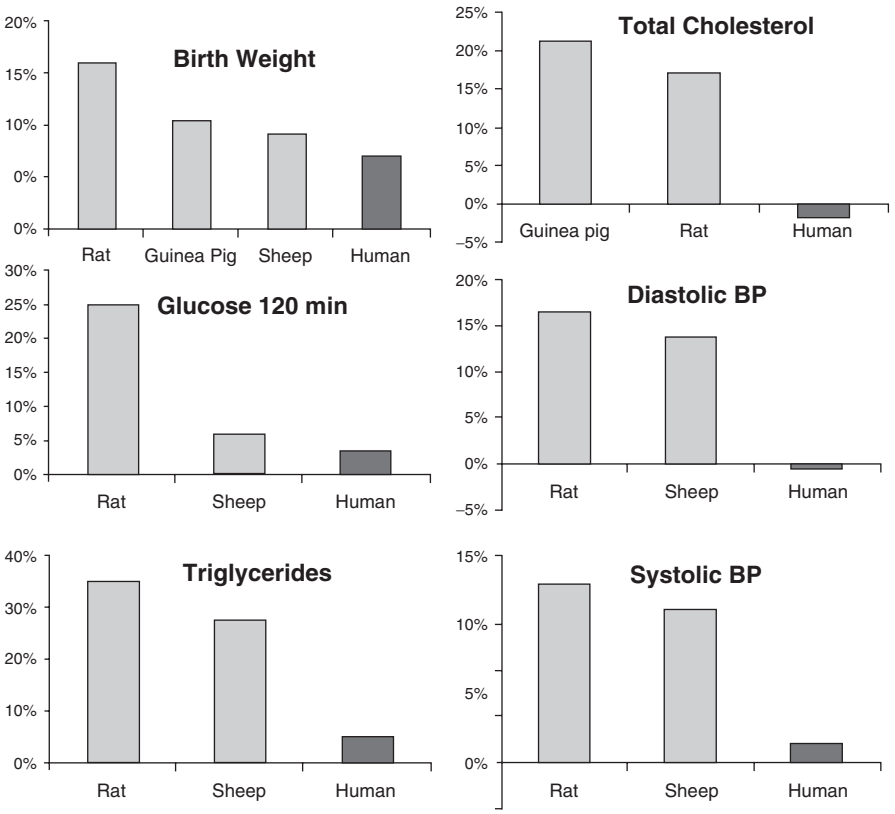

Fig. 2.3 The magnitude of change in offspring biology triggered by maternal diet restriction during pregnancy across species varying in life span (modified after Kuzawa and Thayer 2011; see original for references). All animals born to mothers who experienced caloric restriction during early gestation (30–50 % global caloric restriction). All values are calculated as the percent difference between the control group and the case group and represent averaged male and female values. All human data are from the Dutch Famine Winter adult cohort with those who experienced famine in middle or late gestation compared to the control group of those conceived after the famine (Roseboom et al. 2001)

body size and life span, mice and rats can provide a precedent for how programming might work mechanistically in humans, but remain poor guides to the magnitude of health impacts of early stressors for humans.

More specifically, the differences in findings in humans and rodents suggest that maternal nutritional stress will generally have attenuated negative impacts on offspring biology in humans, compared to other species commonly used as experimental models in biomedical research. By the same token, it seems likely that short-term improvements, as reflected in the typical design of many interventions, may yield comparably modest long-term benefits. Pregnancy supplementation trials often modify the nutritional ecology of a mother for a period of weeks or months, which represents a timescale of change that a human body should be expected to simply buffer. It would not be advantageous for a human to adjust its strategy *for life* based upon such a short-term and likely transient change in the mother's experience.

Ideally, the knowledge of the long-term benefits that accrue with favorable early life nutrition would motivate economic and health policies that improve the nutrition of entire populations to optimize health over the course of two or three human generations. In the absence of such policies, the principles of biological adaptation, and of timescale, may lead us to effective shortcuts. To "convince" the biology of future generations to modify lifelong developmental trajectories—that is, to improve long-term offspring health via intergenerational interventions—we must strive to develop interventions that sustain, or at least mimic, longer timescale environmental change.

How might this goal be achieved? One possibility, which has gained some empirical support (see Kuzawa and Thayer 2011), is that intervening at several ages will have synergistic effects on offspring outcomes. For instance, the flow of nutrients and hormones across the placenta and in breast milk both appear to influence metabolism, growth, and long-term biological settings in offspring. Might supplementing the mother's diet during pregnancy *and* lactation, sending a signal of consistently improved conditions, have effects that are greater than the sum of their independent parts? Similarly, might the programming effects of favorable nutritional signals conveyed to breastfed infants via breast milk be enhanced if the mother received supplements during or prior to pregnancy, rather than during lactation alone? Recognizing that fetal growth is more directly contingent upon maternal metabolism than her dietary intake suggests yet other potential strategies. Although not without potential risks, directly manipulating maternal metabolism during gestation (for instance, by raising or lowering blood glucose) should have relatively direct and potentially large effects on fetal nutrient transfer and metabolic programming.

The notion of adaptive timescales underscores that interventions aimed at improving the gestational flow of resources across generations need to broaden the window of intervention to include the mother's own development, a point recently emphasized in the public health literature (Victora et al. 2008). Given evidence that early life nutrition has intergenerational effects, public health efforts to improve health and nutrition during early development, for instance, by supplementing nutritional intake or reducing the burden of common infections, can be understood as not only benefiting the infant but also the future offspring of that individual, who we may hypothesize will experience more favorable fetal nutrition and growth conditions as a result.

In a unique supplementation trial in Guatemala, young girls who were provided high-protein/calorie supplements as infants and young children, when compared with peers who received only a high calorie supplement, went on to give birth to larger babies decades later, pointing to the potential intergenerational power of a long-term developmental approach to nutritional intervention (Behrman et al. 2009).

The literature and ideas that we review here suggest that it is prudent to envision that the goal of our interventions is not only to alleviate stress in the present but also to find creative ways to mimic cues of sustained environmental improvement in the recent past (Kuzawa and Thayer 2011). By producing signals that indicate sustained nutritional improvements, we can hope that future generations of our long-lived species will alter developmental trajectories in ways that help limit the rising burden of chronic disease.

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