Timescales of human adaptation: the role of epigenetic processes

Human biology includes multiple adaptive mechanisms that allow adjustment to varying timescales of environmental change. Sensitive or critical periods in early development allow for the transfer of environmental information between generations, which helps an organism track gradual environmental change. There is growing evidence that offspring biology is responsive to experiences encoded in maternal biology and her epigenome as signaled through the transfer of nutrients and hormones across the placenta and via breast milk. Principles of evolutionary and comparative biology lead to the expectation that transient fluctuations in early experience should have greater long-term impacts in small, short-lived species compared with large, long-lived species such as humans. This implies greater buffering of the negative effects of early-life stress in humans, but also a reduced sensitivity to short-term interventions that aim to improve long-term health outcomes. Taking the timescales of adaptation seriously will allow the design of interventions that emulate long-term environmental change and thereby coax the developing human body into committing to a changed long-term strategy, yielding lasting improvements in human health and wellbeing.

KEYWORDS: adaptation ■ anthropology ■ critical periods ■ developmental plasticity ■ DOHaD ■ epigenetics ■ evolutionary biology ■ transgenerational effects

Christopher W Kuzawa[†1,2] & Zaneta M Thayer[1]

[1]*Department of Anthropology, Northwestern University, Evanston, IL 60208, USA*
[2]*Cells 2 Society, The Center on Social Disparities & Health at the Institute for Policy Research, Northwestern University, Evanston, IL 60208, USA*
[†]*Author for correspondence:*
Tel.: +1 847 467 4302
Fax: +1 847 467 1778
kuzawa@northwestern.edu

The nutrients and hormones experienced *in utero* or during infancy influence a wide range of biological traits, including patterns of growth, stress physiology, blood pressure, glucose metabolism, fat deposition and even reproductive biology [1–5]. This capacity to modify developmental biology in response to environmental, behavioral or other factors is defined as developmental plasticity and reflects the capacity of a single genome to generate a range of possible biological or behavioral outcomes depending upon environmental experiences [6]. As one well-known example, reduced growth rate *in utero* and after birth predicts a diverse set of outcomes that include increased risk for cardiovascular disease and diabetes and lower adult production of reproductive hormones [7–10]. Similarly, ingestion of the body fat-derived hormone leptin during brief early windows of postnatal life can permanently modify feeding behavior, weight gain and risk for diabetes [11], while there is evidence that exposure to stress hormones *in utero* modifies long-term stress reactivity after birth [12]. Interestingly, not only do many of the biological effects of early environments linger into adulthood, but some transcend the affected generation to be passed onto grand offspring and even great-grand offspring [13–16].

Some long-term impacts of early environments simply reflect impaired or disrupted development as a result of incomplete buffering against stress [17–19]. As a well-documented example, in the 1950s and 1960s, the synthetic estrogen agonist diethylstilbestrol (DES) was prescribed during pregnancy to prevent spontaneous abortions [20]. DES prescriptions were halted when it was discovered that offspring of DES-treated mothers developed a suite of adverse outcomes, including increased risk of developing a rare vaginal cancer, infertility, early menopause and immune disorders [21]. Strikingly, the children of women exposed *in utero* also went on to have children with menstrual irregularity and potential infertility, implying that some of the pathological effects of DES transcended the originally exposed generation [22].

In addition to examples of developmental disruption, other biological changes triggered by early-life plasticity are believed to help the organism adjust to environmental changes and to prepare for future experiences [3,23–25]. Indeed, as we will explore in greater depth below, many of the examples of epigenetic induction that are coming to light are complex and appear functionally integrated [26], and some perpetuate biological and behavioral traits across multiple generations of offspring. Such findings are unlikely to result from chance or simple impairment.

In this article, we review the role of developmental plasticity in human adaptation and extend these principles to the examples of

future medicine | part of fsg

transgenerational developmental plasticity that are the focus of increasing attention in the epigenetic literature. First, we briefly discuss evidence suggesting that some examples of early-life plasticity are functional rather than reflecting developmental impairment. Building on a long research tradition in biological anthropology, we then discuss the role of developmental plasticity in human adaptation to ecological, behavioral and social change. Early work on plasticity in humans clarified the adaptive advantage of altering developing biological systems in response to the environment. Current epigenetic examples add to this story by suggesting that biological settings in the present generation are often not set to the environment experienced by the developing organism itself, but to cues of historical environments experienced by ancestors in the recent past. We argue that periods of heightened epigenetic sensitivity in early development ('critical periods' or 'sensitive periods') are timed to overlap with the age of direct biological dependence on maternal metabolism and physiology, which allows the transfer of this information into the offspring's developing phenotype. We suggest that understanding the timescale of environmental change tracked by a plastic system will lead to the design of more effective interventions that mimic change at the appropriate timescale for that system, and thereby, harness these windows of sensitivity to optimally improve health across generations.

Evidence that some early-life developmental plasticity is likely to be adaptive

While not all examples of early-life developmental plasticity should be considered adaptive [17–19,27], authors such as Bateson [23] and Gluckman and Hanson [24] have argued that maternal nutrients or hormones could serve as cues of environmental conditions, and thereby, allow offspring to adaptively adjust their biological and developmental strategy. Although this hypothesis remains untested, there is intriguing circumstantial evidence in support of the idea of maternal–fetal signaling. Take for instance the diverse biological changes initiated in the fetus exposed to maternal stress hormones (glucocorticoids [GCs]), which include long-term changes in traits like stress reactivity, blood pressure regulation and metabolism [28]. The fetus is usually shielded from maternal GCs by placental expression of the enzyme 11-β hydroxysteroid dehydrogenase type 2 (11βHSD2, or 11β for short), which in humans converts biologically

active cortisol into inactive cortisone. As maternal GC levels increase, such as what occurs during acute bouts of maternal stress or during the normal course of gestation, placental expression of 11β also increases, thus bolstering this enzymatic barrier and limiting entry of cortisol into the fetal compartment [28,29]. As the feto–placental unit shields itself from exposure to maternal stress hormones by this self-reinforcing barrier, the fetus is likely to only sense an attenuated signal of the mother's day-to-day arousal and stress that are reflected in her hormonal rhythms.

Although 11β is upregulated by rising maternal GCs, the placenta also scales back this feedback-regulated shield in response to certain cues, thus demonstrating that the feto–placental unit allows fetal GC exposure in response to certain types of maternal stress. For instance, in rats the GC-stimulated rise in placental 11β is attenuated in the event of a repeat bout of maternal stress [30], suggesting a capacity to buffer transient maternal stress while allowing the programming stimulus of GC to cross the placenta in response to chronic maternal experience. The enzyme is also actively downregulated by other stressors, such as hypoxia [31] and by catecholamines and related β-adrenergic agonists [32]. Similarly, in rats, maternal protein restriction attenuates 11β [33], but this is reversed if maternal protein restriction is accompanied by the coadministration of the energy status-signaling hormone leptin [34].

The feto–placental response to these maternal cues partly reflects the need to coordinate fetal maturation in preparation for parturition, the timing of which is responsive to placental insufficiency, infection and other stressors [35,36]. However, after crossing the placenta, maternal GCs also induce a range of durable epigenetic modifications and changes in offspring physiology that modify function across the lifespan. This can be seen in examples of more severe maternal stress during pregnancy, which modifies how the offspring's body reacts physiologically to stress (e.g., regulation of the hypothalamic–pituitary–adrenal axis [HPA]) [12], how it handles and prioritizes the use of glucose within the body [37], and how it regulates specific components of immune function [38] in early adulthood. Although these authors did not evaluate epigenetic involvement in these offspring responses, imposition of stress during pregnancy in rats has been shown to change methylation patterns and mental and locomotor development in offspring [39]. Interestingly, in

this model, the direction of change in methylation and impacts on offspring behavior and locomotion depended on the intensity of the stressor, suggesting that the effects on offspring are modulated by the level of GC exposure. Although comparable studies of humans are few, there is at least preliminary evidence that prenatal stress in humans, as indicated by maternal depression, can induce changes in epigenetic markings in offspring and stress reactivity in infancy [40].

These findings suggest that hormonal changes triggered by social stressors experienced by the mother during pregnancy can modify regulatory set points of that same hormonal system in the next generation, and thereby, influence how offspring interact with and respond to similar social stimuli [41]. As the placental site of expression of the GC-blocking enzyme 11β is fetal tissue, the complex patterns of experience-dependent expression of this enzyme suggest that there is more to the programming effects of maternally derived GCs than simple impairment. Instead, these findings hint at a capacity of the fetus to at least partially control its own exposure to this programming stimulus – and thus its postnatal phenotype – in response to maternal cues and experiences.

Some examples of induced epigenetic change also appear to be too complex and functionally integrated to result from incomplete buffering of an early perturbation. Take for instance the recently published findings from an experiment in mice in which maternal separation stress was imposed during the first two weeks of postnatal life [15]. The researchers evaluated methylation in germ cells (sperm) of the males at CpG islands (genomic regions rich in cytosine–guanine dinucleotide pairs connected via phosphate) near promotors for several candidate genes influencing affect regulation. They found that methylation was modified in the vicinity of the canabinoid receptor and corticotrophin-releasing factor receptor in the sperm of the males exposed to stress as newborn pups. A similar pattern of changed methylation and changes in mRNA levels were found in the neurons of female offspring of the stress-exposed males, indicating direct germline epigenetic inheritance [15]. Early separation increased gene promoter methylation at some loci while decreasing it at others, pointing to locus-specific modifications. It seems unlikely that this complex cascade of changed epigenetic markings, which perpetuates a similar pattern of gene expression across several generations, could result from simple impairment.

Well-known examples in which maternal nurturing style in rats regulates affect and anxiety in adult offspring are similarly unlikely to reflect impairment [42]. Meaney and colleagues report that highly attentive mothers who exhibit a nurturing grooming style raise pups that, as adults, have a series of changes in gene promoter methylation and histone acetylation that modify regulation of important HPA-axis related genes [43]. These modifications are associated with heightened HPA feedback sensitivity, lower corticosterone levels and reduced anxiety. Intriguingly, partly as a result of these epigenetic modifications, female offspring are biased towards exhibiting the same style of maternal care that they experienced as pups, thereby contributing to the transgenerational transmission of an environmentally-induced behavioral phenotype [41].

In summary, plasticity can result from damage or impairment due to incomplete buffering, such as in the example of exposure to compounds with teratogenic effects. Developmental error of this sort is common and is likely to be a partial contributor to nearly all developmentally induced phenotypes [18,19]. However, other instances of epigenetic change are not easily explained as simple damage. The fact that the fetus modifies its own defensive barriers to modulate exposure to certain maternal signals suggests that the feto–placental unit has at least partial authorship of any downstream programming effects. Although there are many examples of induced phenotypes that are nonfunctional, others exhibit signs of functional integration and an increasing number are known to be perpetuated across the lifecycle, and even to offspring, via direct germline inheritance or complex phenotypic cascades that recapitulate epigenetic markings in somatic cells across generations. These examples suggest that certain types of early-life epigenetic sensitivity are functional rather than simply reflecting stress-related impairment or a failure to buffer.

Timescales of environmental change & the modes of human adaptability

To gain clues into the function of these responses, it is helpful to consider the diverse timescales of change that human beings must cope with and the repertoire of complementary adaptive processes that this requires. The question of how humans adapt to changing environments has traditionally been a subject of great interest to biological anthropologists. In the early 19th century, European anthropologists

were primarily concerned with documenting and classifying human biological variation [44]. Much of this work reified the idea that humans came in varieties or types (most classically, races) that were assumed to be stable [45,46] and that could be ordered according to divine, and later evolutionary, scales of relative social and biological advancement [47]. By the mid-20th century, this focus on description and classification ceded to an emphasis on explaining the origins of this variation as it related back to and reflected the variety of climatic and environmental conditions that human populations had adapted to [48]. The model of human adaptability that emerged from this era emphasized that human populations adapt to local environments and experiences using several adaptive modes that vary in their degrees of durability and thereby allow adjustment to different timescales of environmental change (Figure 1) [25,49]. At the slowest and most durable extreme lies natural selection as a shaper of population gene pools. When a gene variant present in a population increases the survival and/or reproductive success of its carriers, the gene will increase in relative frequency in the gene pool of the offspring generation. As a result, genes that increase survival to reproductive age or the number of offspring will, by a matter of simple arithmetic, become relatively more common than other alleles present in the population. Over many generations this will tend to shape organisms with lifecycles, reproductive strategies, morphology, metabolism and behavior well suited to the most stable features of environments encountered by members of that population.

Although adaptation by 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 frequencies. This would require many generations, and hundreds if not thousands of years in a long-lived species such as humans to accrue in the gene pool. Human biology therefore includes additional, more rapidly acting adaptive processes to cope with such change [25,49,50]. The most rapid ecological fluctuations (e.g., fasting between meals, temperature changes when stepping into the cold, or the increase in nutrients needed when running) are handled primarily via homeostatic systems, which respond to changes or perturbations in a way that offsets, minimizes or corrects deviations from an initial state (negative feedback). Operating not unlike a thermostat that maintains a constant temperature by cycling the air conditioning unit or furnace on and off, homeostatic systems modify physiology, behavior and metabolism to maintain relatively constant internal conditions despite fluctuations in features such as 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 biological changes that they coordinate are not permanent but reversible.

Although homeostatic processes are powerful buffering mechanisms, it is easy to see how a sustained environmental change might overload these flexible capacities if this were the only means available to help the organism cope with it [51]. Take, for example, an individual who has recently moved to high altitude where oxygen pressure is lower than his or her lungs can efficiently extract. One immediate response will be an elevated heart rate, which increases the volume of blood and thus the number of oxygen-binding red blood cells that pass through the lungs. By engaging a homeostatic system – heart rate – the body has found a temporary fix to help compensate for the low oxygen pressure. However, this comes at a cost, for flexibility in heart rate is finite and can be 'used up'. If heart rate is already high under resting conditions, there is less leeway to increase heart rate further to deal with new challenges that require bursts of high heart rate, such as the need to run from a predator. With time, additional changes ease the burden on the heart, such as increasing the number of oxygen-binding red blood cells, but these too come with costs. Increasing hemoglobin also increases blood viscosity and requires elevated blood pressure, which if chronic, can lead to organ and tissue damage. Homeostatic changes may work as short-term

Cycle duration		Adaptation	
Years		Mode	Process
0.00000001	Seconds		
0.0001	Hours	Physiologic	Homeostasis
0.001	Days		
0.1	Months		
1	Years	Developmental	Plasticity
10	Decades	Intergenerational	Inertia
100	Centuries		
1000	Millenia	Genetic	Natural selection
1,000,000	Millions		

Figure 1. Timescales of human adaptability.
Adapted from [5].

solutions, but are generally a poor means of coping with a condition such as high altitude hypoxia if this is the new baseline environmental state.

This is where the value of developmental plasticity becomes clear. Individuals raised at a high altitude have a more efficient strategy for coping with low oxygen availability, for they simply grow larger lungs during childhood, thus obviating the need for these fixes [52]. This is an example of how developmental plasticity allows organisms to adjust biological structure on timescales too rapid to be dealt with through genetic natural selection, but too chronic to be efficiently buffered by homeostasis. These mechanisms can be viewed as allowing the organism to fine-tune structure, function and regulatory set points to match the needs imposed by an individual's idiosyncratic behavioral patterns, nutrition, stress and other environmental experiences, none of which can be anticipated in detail by the genome inherited at conception. Other classic examples of experience-driven plasticity include the development of the skeletal, central nervous and immune systems, all of which internalize ecological information via the proliferation of redundant variants (e.g., osteoblasts, neurons/synapses and antibodies) and use or disuse driven stabilization or pruning of those variants [53–55].

Human adaptability extended: transgenerational effects

While the lasting effects of early environments on epigenetic settings and developmental biology are clear examples of nongenetic environmentally-induced developmental variation, they have properties that distinguish them from previously documented human examples of developmental plasticity. As illustrated earlier, classic examples of developmental plasticity involve permanently modifying a trait in response to the organism's own environmental experiences during growth and development [49,56]. In the many new examples of early-life epigenetic sensitivity, in contrast, the biological system is not modified in response to the environment itself, but to signals or cues of past environments as experienced by ancestors, most notably the mother [24,25,57]. From this perspective, what makes fetal developmental plasticity distinct from conventional plasticity is the time depth of the information to which the developing body responds (FIGURE 2).

How might this 'backward-looking' plasticity serve the adaptive needs of a long-lived organism [58]? Ecological conditions can change on many timescales, as reflected for instance in abundant and lean seasons or years. Historical records

of the price of rye in various regions of Germany illustrate this well (FIGURE 3). Although trending gradually upward with time in some regions, the value of rye fluctuated widely around that trend on a shorter timescale. Temporary spikes and dips in price tracked transient influences, such as volcanic eruptions that altered climate and agricultural productivity, periods of temporary and severe drought, or periods of abundance when this confluence of factors was absent. More generally, the paleoclimate record demonstrates that variability has characterized the climate experienced during much of early human evolution. In contrast to the relative climate stability of the past 10,000 years, much of the preceding millions of years were marked by larger shifts that led to locally rapid ecologic change (reviewed elsewhere [59]). Data from lake sediments, ocean sediments and glacial ice cores show large and irregularly timed climate shifts that occurred on the scales of centuries and even decades, and that altered vegetation, landscape productivity, streamflow and other environmental conditions important for human survival.

Although natural selection operating on gene frequencies can adjust a population to changing conditions, this process is slow in comparison to these shifts. On top of this, humans have excelled as a colonizing species, implying that our ancestors survived by moving between niches and ecologies [60]. Thus, our ancestors would have required more rapid modes of biological adaptation than the slow sifting of gene frequencies by natural selection to cope with ecologic variability [59]. At the same time, however, given the substantial year-to-year and seasonal environmental variability that humans have also faced, the utility of adjusting strategy for life, based upon conditions during a few short early months, is not obvious. After all, what benefit would be gained by preparing the body for a life of abundance, based upon the chance event of being born during an especially bountiful season or year?

Sensitive periods, which overlap with maternal phenotype rather than the fluctuating ecology itself, have the potential to facilitate the flow of more reliable, maternally derived phenotypic information that is less sensitive to such short timescale processes [25,61]. We believe that this helps explain why developing organisms set biological strategies in response to cues during brief early developmental windows, for many of these periods overlap with maternal buffering and the direct provisioning of nutrients and hormones, which transfer more reliable information reflecting the mother's cumulative experiences via
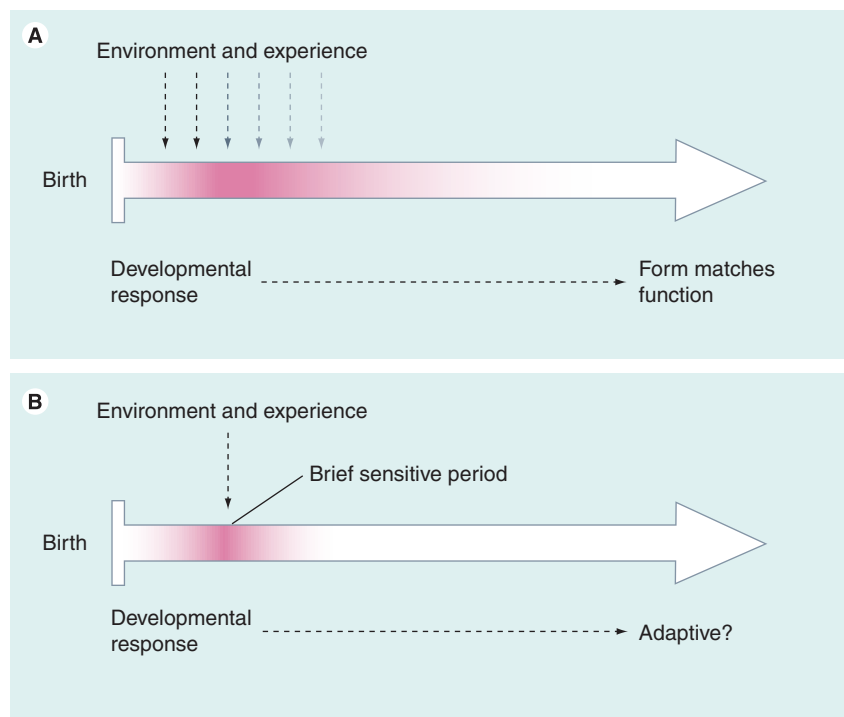
Figure 2. Two contrasting types of developmental plasticity. Plasticity that **(A)** accommodates via interaction with environment across the period of growth and development, and **(B)** that sets the strategy for life in response to cues of past environments conveyed during a brief early-life sensitive period.

the placenta and breast milk [25], and also via behaviors such as rearing style and attachment quality [42,62–64].

Take as an example the many downstream biological effects of fetal nutrition, as illustrated by the finding that birthweight relates inversely to blood pressure and metabolic disease risk in humans [65,66], and by animal model work that replicates similar findings by experimentally modifying the nutritional milieu of the fetus *in utero* [7,33,67,68]. If fetal nutrition is the cue (partly) responsible for initiating these durable changes in offspring biology, what in the mother's experience determines fetal nutrition? The answer to this question should provide clues into what the fetus 'sees' in this stream of resources, or equivalently, what aspects of maternal experience developing fetal systems pay attention to and 'track' during the brief window of gestation [25].

At the outset, it is important to underscore the distinction between fetal nutrition and maternal nutrition, which are by no means equivalent [69,70]. We see this clearly in the fact that most pregnancy macronutrient supplementation trials often have minimal or even negligible effects on offspring birthweight [70–76], showing that short-term increases in maternal nutrient intake are not likely to be sensed by the fetus [25]. A recent review found that balanced protein–calorie pregnancy

supplementation trials on average yielded a mere 38 g mean increase in offspring birthweight [76]. The authors concluded that we lack evidence that balanced protein and energy supplementation trials in pregnancy confer long-term benefits with respect to offspring growth, cognition or cardiovascular health.

While there is little evidence for strong impacts of nutritional intervention during pregnancy on fetal development, larger effects have been documented in relation to maternal nutrition and nutritional status prior to pregnancy [77], and at various ages that potentially extend back to the mother's gestational environment, and by inference, the grandmother's nutritional history [78,79]. As one example of the latter, in one British cohort the mother's leg length when she was a child, which is an age when leg growth is especially sensitive to nutrition, was a stronger predictor of her offspring's future birthweight than was her concurrent stature or leg length during pregnancy [80]. Similarly, it has long been hypothesized that the transfer of nutrients to offspring *in utero* is partly set in response to that woman's own nutritional experiences when she was a fetus [78]. The epigenetic or developmental pathways that might link a woman's past or early-life nutritional experiences with the nutrients conveyed to the fetus remain unknown [81]. However, what these findings suggest is that if fetal nutrition is indeed influenced by aspects of the local nutritional ecology, it is tracking a chronic or integrated signal of several decades of nutrition as experienced across several generations (for more detail see [25]).

One example of a longer-term intervention that may have provided a more sustained signal of maternal nutritional quality is the Institute of Nutrition of Central American and Panama (INCAP) Oriente Longitudinal Study in Guatemala. Martorell and colleagues have reported on the biological effects of two types of nutritional supplements that were provided to women and children in four rural Guatemalan villages from 1969–1977 [82–84]. Villar and Rivera found that women who consumed supplements continuously across two successive pregnancies gave birth to newborns that were 267 g heavier than women who consumed less than this amount [85]. When the researchers compared women who only received supplementation for the second pregnancy the effect was intermediate, with an increase in offspring birthweight of 100 g. This implies that longer periods of supplementation are more effective at improving offspring birth outcomes [85].

Studies of the growth rate of offspring in the next generation (the children of women who were themselves supplemented *in utero* and/or during infancy or childhood) report that the offspring of women who themselves were supplemented as older children grew faster compared with offspring of women supplemented during infancy and early childhood [83]. Women supplemented with atole (the more nutritionally dense of the two supplements) during early-life gave birth to babies that were 116 g heavier, with sons being relatively more sensitive to their mother's prior supplementation than their daughters were [84]. Viewed alongside the evidence reviewed earlier, these findings suggest that longer-term interventions are more effective at influencing offspring health outcomes when compared with short term interventions aimed solely at modifying maternal nutrition in pregnancy [74–76].

Sensitivity in the development of metabolism and physiology appears to continue after birth, as indicated for instance by the lower risk of obesity and diabetes among adults who were breast-fed as infants [86]. Evidence from both animal experiments and human populations points to a similar capacity of the infant to entrain development to signals that reflect the mother's history of experience in that environment [87]. After birth, signals are likely to be conveyed in part via breast milk, which is a conduit not only for nutrients, but for an expanding list of maternal immune components, growth factors and hormones with short- and long-term effects on offspring developmental biology [88]. The hormone leptin, which is produced by fat cells in proportion to their lipid content, is a fascinating example. Leptin is present in breast milk and when the infant consumes milk the hormone passes across the still 'leaky gut' and enters the circulation, where it is biologically active. Milk leptin levels are inversely related to the rate of infant weight gain [89] and in one study infants who consumed mother's milk with higher leptin at 1 month were found to be thinner at 2 years of age [90].

In light of these apparent effects of orally ingested leptin on infant appetite regulation, growth and metabolism, what determines the level of leptin that a mother secretes into the milk that her body produces and that her infant consumes? One important factor appears to be the size of the mother's own energy stores – her body fat – which is the primary source of adult leptin levels. Indeed, the leptin concentration in breast milk was found to be positively related to measures of the mother's body fat and level of

circulating leptin [91]. Consistent with an important role of maternal leptin as a source of infant leptin, the mother's adiposity was the strongest predictor of her infant's circulating leptin levels, but only if her infant was breastfed [92].

Research on the maternal determinants of birthweight and breast milk leptin hints at a capacity for biological 'learning' in which the offspring does not modify metabolism and growth in response to the environment itself, but instead entrains to maternal cues conveyed via nutrients or other signals across the placenta *in utero* and via breast milk during lactation. This tendency for plasticity to respond not to current ecological signals, but to parental cues, which tend to integrate past environmental experience, has been
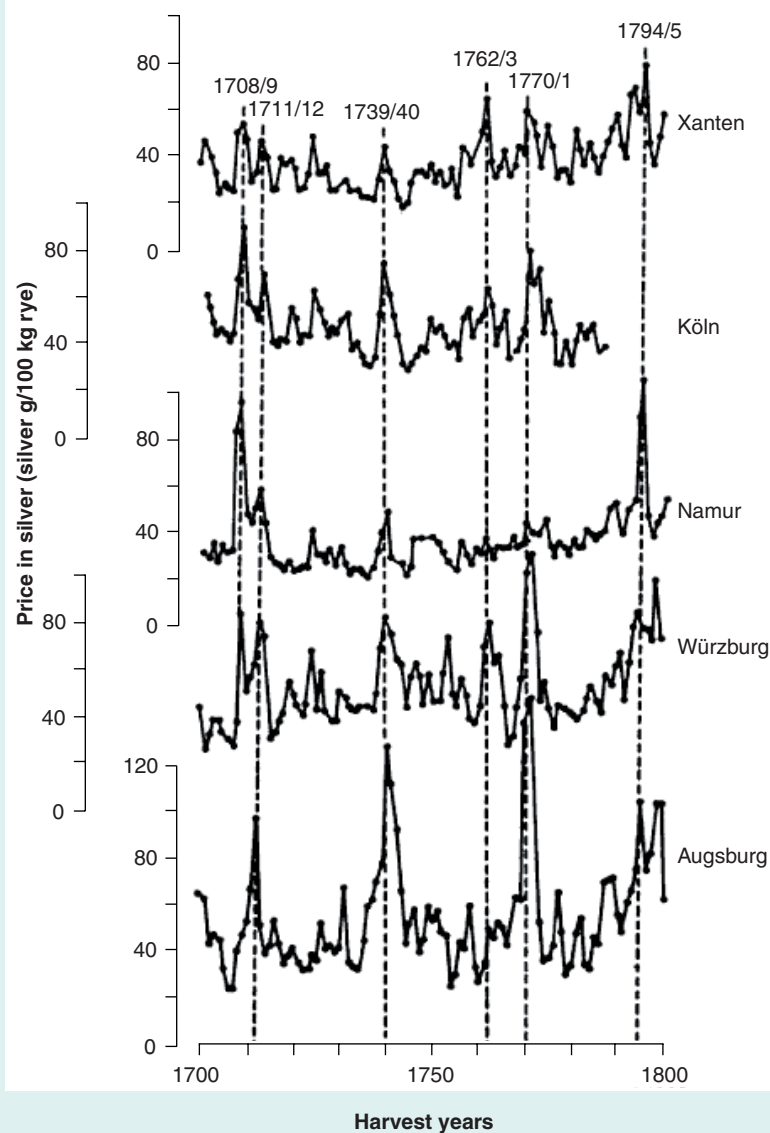

Figure 3. Historical rye prices in Germany.
Reproduced with permission from Cambridge University Press [105].

defined as phenotypic inertia [25]. The value of this transgenerational system is that it calibrates offspring biology to something akin to a running average of conditions experienced in the recent past, which in an unpredictable environment provides a best guess of average conditions likely to be experienced in future years.

Although the function of offspring metabolic changes triggered *in utero* or during infancy is not certain, they hint at a sensible metabolic strategy in light of the stressors and selection pressures that humans face. In both instances, signals that indicate maternal nutritional stress predict that her offspring's metabolism will place higher priority on depositing fat and especially in the more rapidly mobilized visceral depot [26]. In light of the high risk of nutritional stress and mortality during infancy and weaning, this may be an appropriate response among populations facing a nutritional deficit [24,93,94]. However, these modifications might also heighten risk of developing diabetes or cardiovascular disease under adult conditions of chronic positive energy balance [24].

Although we have focused narrowly on the example of nutritional programming, other examples in which maternal cues signal average historical experiences are coming to light. In one well-described example alluded to above, psychosocial stress appears to have cumulative effects on epigenetic markings and hormone-regulatory set points in the mother's body, which can modify gestational and postnatal rearing environments for offspring, and thereby, perpetuate stress phenotypes across generations [40,46,95]. In this example, offspring stress physiology may be calibrated in anticipation of the predicted strength, severity and frequency of stressor exposures, which can have downstream effects on patterns of growth, development and reproduction in offspring [4,18].

Why do some interventions fall short & how do we design improved interventions?

The principles of adaptation reviewed here tell us that adaptable biological systems are calibrated to buffer unstable features of the environment and to adjust developmental trajectory only in response to more stable, reliable trends. If there is truth in this framework, it may not be surprising that pregnancy supplementations often fall short. Pregnancy supplementation trials often modify the nutritional ecology of a mother for a period of weeks or months [72], which is an ecological change on a timescale that the body copes with using rapid and reversible homeostatic buffering mechanisms (Figure 1, top). The biological system

targeted by intervention, in the earlier example fetal nutrition (Figure 1, middle), is likely designed to ignore such transient 'spikes' in nutritional intake. When a supplementation mimics a short-term deviation from that individual's typical experiences, it is bound to have modest influence, because it fails to send a signal that a durable change in biological or developmental strategy is needed [25]. And sustained biological improvement is of course what we aim to achieve by intervening. To gain leverage and modify developmental pathways that are recalibrated on an intergenerational timescale, we must adopt a long-term view with long-range goals and search for new and creative ways for our interventions to either sustain, or at the very least mimic, longer timescale change.

How might this goal be achieved? One possibility that gains some support 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 to the mother, have greater effects on the offspring than would be expected based upon the additive effects of supplementing during only one of these windows? Similarly, might the pronutritional signal conveyed to breastfed infants via breast milk nutrients or hormones be enhanced if the mother received supplements during or prior to pregnancy? Results from the INCAP study, discussed earlier, suggest that such an approach holds promise [70,83–85].

Although buffering of short-term fluctuations could attenuate immediate impacts of supplementation on offspring, viewing adaptation through the lens of timescale underscores the need to take a long-term view when evaluating the benefits of an intervention. In light of the evidence that nutrition has effects that persist across the lifecycle and even across generations, an intervention with modest effects today may nonetheless be essential to laying a firmer foundation for improved health in future generations.

Findings in model species such as rats and mice provide hints of interactions between pre- and post-natal conditions, along these lines [96]. Although such precedents are essential to motivate additional research, when addressing issues of adaptation we must use caution when extrapolating between species that vary in lifespan and reproductive strategy. While enormous insights into human biology have come from work using mammalian species as analogs, mammalian

biological systems have evolved to serve vastly different goals across species. Since humans are a long-lived species, a larger share of human reproductive output and, thus, Darwinian fitness, is achieved at later ages. It follows that our biological strategies are future oriented and geared not simply towards reproducing now but also building a body that is robust enough to survive to reproduce well into the future [97,98], including a critical role of provisioning and providing care for offspring and grand offspring for several decades beyond the years of active reproduction [99].

Since humans typically live decades rather than months, this implies that the types and magnitudes of environmental change that are relevant when orienting an individual human life will be quite different than for a member of a smaller, short-lived species. The severity of the particular season during which a mouse happens to be born will dominate conditions during its short life, but may be little more than environmental noise from the perspective of a human lifetime [25]. It follows that human biology should be designed to buffer out or ignore timescales of change that are critical to a developing mouse or rat.

There is in fact evidence for such species-level differences in the fetal response to maternal nutritional stress during pregnancy. For instance, in the human cohort exposed *in utero* to the well-documented Dutch Famine Winter during World War II, studies have typically found modest or no long-term effects on many biological or disease outcomes that exhibit large changes in animal models involving comparable levels of nutritional stress [100,101]. FIGURE 4 presents a selection of studies that illustrate species-level variation in offspring physiological outcomes induced by a similar magnitude of macronutrient restriction. To the extent that estimated caloric deficits experienced by pregnant women during the Famine are accurate, these comparisons suggest that human offspring may be less affected by transient nutritional perturbations than the shorter-lived species that serve as animal models, even when strictly comparing the gestational exposure period associated with the most significant long-term effects in humans.

These differences across species are likely to reflect several factors. For one, metabolic processes, including nutritional requirements and reproductive expenditure, scale with body mass such that they are lower per unit mass for larger-bodied species [102]. This implies that a nutritional deficit must be greater in the large-bodied human to generate a comparable change in nutritional transfer to the developing fetus [103]. In addition, the total weight of the products of conception relative to the mother's weight is often higher in smaller species, with the rat ratio being approximately 25–35% as opposed to 6–10% in the sheep and 3–5% in humans. Thus, reproductive expenditure also often accounts for a larger percentage of total metabolism in small species, suggesting that deficits in maternal intake will likely have larger impacts on the developing fetus or litter.

It may be that the differences documented in FIGURE 4 largely trace to simple metabolic scaling relationships of this sort. However, it also seems likely that smaller species have an incentive to change strategy in response to a stress or deficit experienced by the mother during gestation itself. A mouse will live 24–36 months [104] and thus being born in a bad season or a lean year predicts limiting conditions across a large percentage of that individual's lifespan. Because a human will experience many dozens of seasons and years in a lifetime, average conditions measured on the scale of decades, rather than months, may best approximate experiences in the future and thus provide a more reliable basis for setting long-term strategy [25]. For a long-lived species such as humans, the phenotypes and epigenomes of parents, which have been modified cumulatively by lifetimes of local experience, may be the only available source of reliable information regarding longer-term conditions. As we have emphasized in this article, the brief windows of many early-life sensitive periods, which overlap with direct maternal supply of nutrients and hormones, may allow the developing offspring to calibrate biology and development to these maternal historical cues.

Future perspective

Principles of evolutionary biology and adaptation lead us to hypothesize that many short-term interventions that trigger large biological changes in short-lived species will have comparably smaller effects in humans. If correct, this implies that humans will generally be less severely impacted by transient early-life stressors, but conversely, that short-term improvements, as reflected in many interventions, may similarly have modest long-term beneficial effects. This does not imply that humans are not sensitive to early conditions; rather, it proposes that some of our systems will be sensitive to longer timescale signals as 'remembered' in and conveyed by parental – and especially maternal – phenotypes, which reflect average past experience rather than only present or recent experience. Embracing the principles of evolutionary biology, and the concepts of adaptation and timescale, will help uncover the rules that govern developmental responsiveness
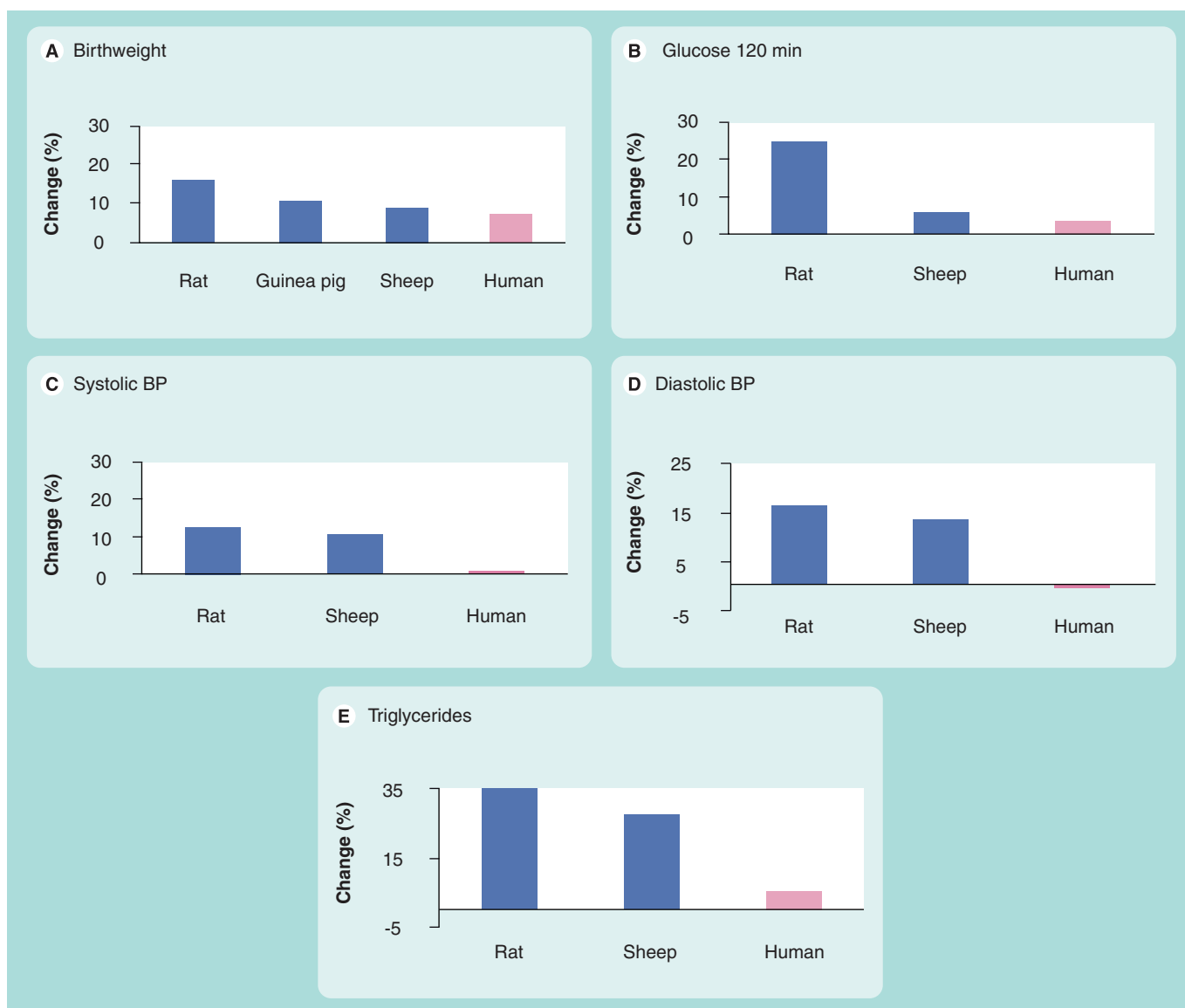
Figure 4. Magnitude of change in offspring outcomes induced by maternal diet restriction during pregnancy, ordered by species. All animals born to mothers who experienced caloric restriction during early gestation (30–50% caloric restriction). All values are calculated as the percentage difference between the control group and the case group and represent averaged male and female values. **(A)** Birthweight. Rat: [106]; guinea pig: [68]; sheep: [107]; human: [108], value represents conceived after famine control group versus conceived in middle or late gestation. **(B)** Glucose. Rat: [109], values represent difference at 14 weeks of age; sheep: [107], value represents difference at 3 years of age; human: [108], value represents conceived after famine control versus early gestation exposure, measured in adulthood. **(C & D)** Systolic and diastolic blood pressure. Rat: [106], value represents difference at 200 days postnatal; sheep: [107], value represents difference at 3 years of age; human: [108], value represents conceived after famine control versus early exposure, measured in adulthood. **(E)** Triglycerides. Rat: [106], value represents difference at 200 days postnatal; sheep: [110], value represents difference at 1 year of age; human: [108], value represents conceived after famine control versus early exposure, measured in adulthood.
BP: Blood pressure.

across species. Moving forward, we suggest that it will be useful to envision many interventions as attempts to mimic signals of sustained environmental change.

Executive summary

▪ The function or adaptive role of early-life developmental and epigenetic sensitivities is a topic of increasing interest.

Some early epigenetic changes are likely to be adaptive

▪ Although examples of stress-induced impairment of development are common, many examples of early-life plasticity appear too complex and integrated to reflect simple impairment, and instead, suggest an adaptive function.

▪ As an example, the feto–placental unit partially regulates its own exposure to maternal hormones, hinting at a fetal capacity to modify any downstream developmental effects.

▪ Other examples involve complex epigenetic cascades that maintain a behavioral or biological phenotype across multiple generations, which is an unlikely outcome of simple damage or impairment.

Timescales of environmental change & the modes of human adaptability

▪ Anthropology has a long history of studying environmental contributions to human biological variation.

▪ Humans adapt to multiple timescales of environmental change, from short-term fluctuations that are buffered by homeostatic processes to long-term adjustments facilitated by natural selection operating on population gene frequencies.

▪ Developmental plasticity involves changes of intermediate durability, which allow adaptation to environmental dynamics that are relatively stable for decades or several generations.

Human adaptability extended: transgenerational effects

▪ In classic examples of plasticity the organism modifies developing structures as it interacts with the environment, whereas in many new examples of developmental plasticity and epigenetic sensitivity the organism responds instead to cues of past environments as experienced by parents, especially the mother.

▪ This 'backward looking' form of plasticity, described as phenotypic inertia, may allow the organism to access integrated information embodied in the mother's phenotype.

▪ This helps the organism sense and respond to average conditions as experienced by the mother, and perhaps, the grandmother. This is a more stable cue than could be achieved by responding directly to the environment itself, which is variable for timescales shorter than a human lifespan.

Why do some interventions fall short (& how do we design improved interventions?)

▪ Interventions that are short in duration may mimic the type of short-term environmental fluctuations that human biological systems may be designed to buffer.

▪ Interventions that are more sustained and span multiple sensitive periods, or that mimic environmental change over a longer timeframe, may be more effective at inducing the desired response in offspring.

▪ Differences in size and lifespan across species mean that the magnitude of the offspring response to a particular maternal experience will vary by species; thus, animal models serve as precedents for the presence of specific patterns of developmental sensitivity but are poor gauges of the magnitude of human biological responses to early-life interventions.

▪ Consistent with the expectation that transient exposures during pregnancy will induce smaller physiological changes in humans than in shorter-lived species, humans exposed to the Dutch famine *in utero* exhibit modest long-term effects compared with animal models involving similar levels of nutritional restriction.

▪ Current pregnancy supplementation strategies commonly augment maternal diet for weeks or months, mimicking the type of short-term environmental fluctuations that an organism with a human lifespan should buffer rather than modify biological and developmental strategy in response to.

▪ In order to improve human health outcomes, we need to provide more sustained interventions – or learn to mimic environmental signals that reflect longer-term trends.

Future perspective

▪ We suggest that many interventions may be best viewed as attempts to mimic signals of sustained environmental change.

Bibliography

1   Barker D: The fetal origins of adult disease. *Fetal Maternal Med. Rev.* 6(2), 71–80 (1994).

2   Gluckman PD, Hanson MA, Cooper C, Thornburg KL: Effect of *in utero* and early-life conditions on adult health and disease. *N. Engl. J. Med.* 359(1), 61–73 (2008).

3   Cameron NM, Shahrokh D, Del Corpo A *et al.*: Epigenetic programming of phenotypic variations in reproductive strategies in the rat through maternal care. *J. Neuroendocrinol.* 20(6), 795–801 (2008).

4   Kuzawa CW: Developmental origins of life history: growth, productivity, and reproduction. *Am. J. Hum. Biol.* 19(5), 654–661 (2007).

5   Kuzawa CW, Pike IL: Introduction. Fetal origins of developmental plasticity. *Am. J. Hum. Biol.* 17(1), 1–4 (2005).

6   West-Eberhard M: *Developmental Plasticity and Evolution.* Oxford University Press, NY, USA (2003).

7   Mcmillen IC, Robinson JS: Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol. Rev.* 85(2), 571–633 (2005).

8   Symonds ME, Sebert SP, Budge H: The impact of diet during early-life and its contribution to later disease: critical checkpoints in development and their long-term consequences for metabolic health. *Proc. Nutr. Soc.* 68(4), 416–421 (2009).

9   Jasienska G, Ziomkiewicz A, Lipson SF, Thune I, Ellison PT: High ponderal index at birth predicts high estradiol levels in adult women. *Am. J. Human Biol.* 18(1), 133–140 (2006).

10   Kuzawa CW, McDade TW, Adair LS, Lee N: Rapid weight gain after birth predicts life history and reproductive strategy in Filipino males. *Proc. Natl Acad. Sci. USA* 107(39), 16800–16805 (2010).

11   Sanchez J, Priego T, Palou M, Tobaruela A, Palou A, Pico C: Oral supplementation with physiological doses of leptin during lactation in rats improves insulin

sensitivity and affects food preferences later in life. *Endocrinology* 149(2), 733–740 (2008).

12   Entringer S, Kumsta R, Hellhammer DH, Wadhwa PD, Wust S: Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. *Horm. Behav.* 55(2), 292–298 (2009).

13   Pembrey ME, Bygren LO, Kaati G *et al.*: Sex-specific, male-line transgenerational responses in humans. *Eur. J. Hum. Genet.* 14(2), 159–166 (2005).

14   Pembrey ME: Male-line transgenerational responses in humans. *Hum. Fertil.* 13(4), 268–271 (2010).

15   Franklin TB, Russig H, Weiss IC *et al.*: Epigenetic transmission of the impact of early stress across generations. *Biol. Psych.* 68(5), 408–415 (2010).

■   Demonstrates stress-induced patrilineal transmission of epigenetic and gene regulation changes across several generations in mice.

16   Anway MD, Cupp AS, Uzumcu M, Skinner MK: Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 308(5727), 1466–1469 (2005).

17   Ellison PT, Jasienska G: Constraint, pathology, and adaptation: how can we tell them apart? *Am. J. Hum. Biol.* 19(5), 622–630 (2007).

18   Gluckman PD, Hanson MA, Spencer HG, Bateson P: Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proc. Biol. Sci.* 272(1564), 671–677 (2005).

19   Schell LM, Magnus P: Is there an elephant in the room? Addressing rival approaches to the interpretation of growth perturbations and small size. *Am. J. Human Biol.* 19(5), 606–614 (2007).

20   Prins GS: Estrogen imprinting: when your epigenetic memories come back to haunt you. *Endocrinology* 149(12), 5919–5921 (2008).

21   Newbold RR, Padilla-Banks E, Jefferson WN: Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. *Endocrinology* 147(6), S11–S17 (2006).

22   Titus-Ernstoff L, Troisi R, Hatch EE *et al.*: Menstrual and reproductive characteristics of women whose mothers were exposed *in utero* to diethylstilbestrol (DES). *Int. J. Epidemiol.* 35(4), 862–868 (2006).

23   Bateson P: Fetal experience and good adult design. *Int. J. Epidemiol.* 30(5), 928–934 (2001).

24   Gluckman PD, Hanson M: *The fetal matrix: Evolution, Development, and Disease.* Peter Gluckman PD, Hanson M (Eds). Cambridge University Press, NY, USA (2005).

▪▪   Proposes the concept of 'predictive adaptive response' to explain adaptive value of fetal developmental plasticity.

25   Kuzawa CW: Fetal origins of developmental plasticity: are fetal cues reliable predictors of future nutritional environments? *Am. J. Human Biol.* 17(1), 5–21 (2005).

▪▪   Develops the concept of transgenerational 'phenotypic inertia'.

26   Kuzawa C, Gluckman P, Hanson M, Beedle A: Evolution, developmental plasticity, and metabolic disease. In: *Evolution in Health and Disease.* Stearns S, Koella J (Eds). Oxford University Press, Oxford, UK, 253–264 (2008).

27   Martorell R: Body size, adaptation and function. *Human Organization* 48(1), 15–20 (1989).

28   Seckl JR, Holmes MC: Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nat. Clin. Pract. Endocrinol. Metab.* 3(6), 479–488 (2007).

29   Schoof E, Girstl M, Frobenius W *et al.*: Course of placental 11β-hydroxysteroid dehydrogenase type 2 and 15-hydroxyprostaglandin dehydrogenase mRNA expression during human gestation. *Eur. J. Endocrinol.* 145(2), 187–192 (2001).

30   Welberg LA, Thrivikraman KV, Plotsky PM: Chronic maternal stress inhibits the capacity to up-regulate placental 11β-hydroxysteroid dehydrogenase type 2 activity. *J. Endocrinol.* 186(3), R7–R12 (2005).

31   Alfaidy N, Gupta S, Demarco C, Caniggia I, Challis JR: Oxygen regulation of placental 11 β-hydroxysteroid dehydrogenase 2: physiological and pathological implications. *J. Clin. Endocrinol. Metab.* 87(10), 4797–4805 (2002).

32   Sarkar S, Tsai SW, Nguyen TT, Plevyak M, Padbury JF, Rubin LP: Inhibition of placental 11β-hydroxysteroid dehydrogenase type 2 by catecholamines via α-adrenergic signaling. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 281(6), R1966–1974 (2001).

33   Langley-Evans S: Fetal programming of cardiovascular function through exposure to maternal undernutrition. *Proc. Nutr. Soc.* 60, 505–513 (2001).

34   Stocker C, O'Dowd J, Morton NM *et al.*: Modulation of susceptibility to weight gain and insulin resistance in low birthweight rats by treatment of their mothers with leptin during pregnancy and lactation. *Int. J. Obes. Relat. Metab. Disord.* 28(1), 129–136 (2004).

35   Pike IL: Maternal stress and fetal responses: evolutionary perspectives on preterm delivery. *Am. J. Hum. Biol.* 17(1), 55–65 (2005).

36   Wada H: Glucocorticoids: mediators of vertebrate ontogenetic transitions. *Gen. Comp. Endocrinol.* 156(3), 441–453 (2008).

37   Entringer S, Wüst S, Kumsta R *et al.*: Prenatal psychosocial stress exposure is associated with insulin resistance in young adults. *Am. J. Obstetr. Gynecol.* 199(5), 498. e1–e7 (2008).

38   Entringer S, Kumsta R, Nelson EL, Hellhammer DH, Wadhwa PD, Wüst S: Influence of prenatal psychosocial stress on cytokine production in adult women. *Dev. Psychobiol.* 50(6), 579–587 (2008).

39   Mychasiuk R, Ilnytskyy S, Kovalchuk O, Kolb B, Gibb R: Intensity matters: brain, behaviour and the epigenome of prenatally stressed rats. *Neuroscience* (2010) (Epub ahead of print).

40   Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM: Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress responses. *Epigenetics* 3(2), 97–106 (2008).

41   Champagne FA: Epigenetic mechanisms and the transgenerational effects of maternal care. *Front. Neuroendocrinol.* 29(3), 386–397 (2008).

42   Weaver ICG, Cervoni N, Champagne FA *et al.*: Epigenetic programming by maternal behavior. *Nat. Neurosci.* 7(8), 847–854 (2004).

43   Zhang T-Y, Meaney MJ: Epigenetics and the environmental regulation of the genome and its function. *Ann. Rev. Psychol.* 61(1), 439–466 (2010).

44   Stocking GW: *Race, Culture and Evolution: Essays in the History of Anthropology.* Free Press, NY, USA (1968).

45   Boas F: Changes in the bodily form of descendents of immigrants. *Am. Anthropol.* 14(3), 530–562 (1912).

■   Widely credited as the first anthropological study of human developmental plasticity.

46   Kuzawa CW, Sweet E: Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. *Am. J. Hum. Biol.* 21(1), 2–15 (2009).

47   Gould SJ: *The Mismeasure of Man.* WW Norton and Company, NY, USA (1981).

48   Washburn S: The new physical anthropology. *Trans. NY Acad. Sci.* 13(7), 298–304 (1951).

49   Lasker G: Human biological adaptability. *Science* 166(3912), 1480–1486 (1969).

50 Ellison PT: Evolutionary perspectives on the fetal origins hypothesis. *Am. J. Human Biol.* 17(1), 113–118 (2005).

51 Bateson G: The role of somatic change in biological evolution. *Evolution* 17, 529–539 (1963).

52 Frisancho A: Developmental adaptation to high altitude hypoxia. *Int. J. Biometerol.* 21(2), 135–146 (1977).

■ Well-studied example of developmental adaptation in response to a particular stress exposure, in this case high-altitude hypoxia.

53 Edelman GM: Neural Darwinism: Selection and reentrant signaling in higher brain function. *Neuron* 10(2), 115–125 (1993).

54 Changeux J-P: *Neuronal Man: The Biology of Mind.* Oxford University Press, NY, USA (1986).

55 McDade TW, Worthman CM: Evolutionary process and the ecology of human immune function. *Am. J. Human Biol.* 11(6), 705–717 (1999).

56 Bogin B: *Patterns of Human Growth, (2nd Edition)*. Cambridge University Press, Cambridge, UK (1999).

57 Wells JC: The thrifty phenotype as an adaptive maternal effect. *Biol. Rev. Camb. Philos. Soc.* 82(1), 143–172 (2007).

58 Kuzawa C: The developmental origins of adult health: intergenerational inertia in adaptation and disease. In: *Evolutionary Medicine: New Perspectives*. Trevathan ES, Mckenna J (Eds). Oxford University Press, Oxford, UK, 325–349 (2008).

59 Potts R: Environmental hypotheses of hominin evolution. *Am. J. Phys. Anthropol.* (Suppl. 27), 93–136 (1998).

60 Wells JC, Stock JT: The biology of the colonizing ape. *Am. J. Phys. Anthropol.* (Suppl. 45), 191–222 (2007).

61 Wells JC: The thrifty phenotype hypothesis: thrifty offspring or thrifty mother? *J. Theor. Biol.* 221(1), 143–161 (2003).

62 Belsky J, Steinberg L, Draper P: Childhood experience, interpersonal development, and reproductive strategy: and evolutionary theory of socialization. *Child Dev.* 62(4), 647–670 (1991).

63 Chisholm JS: Death, hope, and sex: life-history theory and the development of reproductive strategies. *Curr. Anthropol.* 34(1), 1–24 (1993).

64 Ellis B, Figueredo A, Brumbach B, Schlomer G: Fundamental dimensions of environmental risk. *Hum. Nat.* 20, 204–268 (2009).

65 Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME: Growth *in utero*, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 298(6673), 564–567 (1989).

66 Newsome CA, Shiell AW, Fall CHD, Phillips DIW, Shier R, Law CM: Is birthweight related to later glucose and insulin metabolism? A systematic review. *Diabetic Med.* 20(5), 339–348 (2003).

67 Kind KL, Clifton PM, Grant PA *et al.*: Effect of maternal feed restriction during pregnancy on glucose tolerance in the adult guinea pig. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 284(1), R140–R152 (2003).

68 Kind KL, Simonetta G, Clifton PM, Robinson JS, Owens JA: Effect of maternal feed restriction on blood pressure in the adult guinea pig. *Exp. Physiol.* 87(4), 469–477 (2002).

69 Harding JE: The nutritional basis of the fetal origins of adult disease. *Int. J. Epidemiol.* 30(1), 15–23 (2001).

70 Rasmussen KM, Habicht J-P: Maternal supplementation differentially affects the mother and newborn. *J. Nutr.* 140(2), 402–406 (2010).

71 Adair L, Pollitt E: Outcome of maternal nutritional supplementation: a comprehensive review of the Bacon Chow study. *Am. J. Clin. Nutr.* 41(5), 948–978 (1985).

72 Abu-Saad K, Fraser D: Maternal nutrition and birth outcomes. *Epidemiol. Rev.* 32(1), 5–25 (2010).

73 Osrin D, Prost A: Perinatal interventions and survival in resource-poor settings: which work, which don't, which have the jury out? *Arch. Dis. Childhood* 95(12), 1039–1046 (2010).

74 Merialdi M, Carroli G, Villar J *et al.*: nutritional interventions during pregnancy for the prevention or treatment of impaired fetal growth: an overview of randomized controlled trials. *J. Nutr.* 133(5), 1626S–1631S (2003).

75 Villar J, Merialdi M, Gülmezoglu AM *et al.*: Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials. *J. Nutr.* 133(5), 1606S–1625S (2003).

76 Kramer MS, Kakuma R: Energy and protein intake in pregnancy. *Cochrane Database Syst. Rev.* 3, 1–74 (2010).

■■ Reviews the limited efficacy of pregnancy nutritional supplementation trials in humans.

77 Medicine IO: *Nutrition During Pregnancy. Part I, Weight Gain.* National Academy Press, Washington, DC, USA (1990).

78 Ounsted M, Scott A, Ounsted C: Transmission through the female line of a mechanism constraining human fetal growth. *Ann. Hum. Biol.* 13(2), 143–151 (1986).

79 Morton S: Maternal nutrition and fetal growth and development. In: *Developmental Origins of Health and Disease*, Gluckman PD, Hanson MA (Eds). Cambridge University Press, NY, USA, 98–129 (2006).

80 Lawlor DA, Davey Smith G, Ebrahim S: Association between leg length and offspring birthweight: partial explanation for the trans-generational association between birthweight and cardiovascular disease: findings from the British Women's Heart and Health Study. *Paediatr. Perinat. Epidemiol.* 17(2), 148–155 (2003).

81 Rutherford JN: Fetal signaling through placental structure and endocrine function: illustrations and implications from a nonhuman primate model. *Am. J. Hum. Biol.* 21(6), 745–753 (2009).

82 Lechtig A, Habicht J-P, Delgado H, Klein RE, Yarbrough C, Martorell R: Effect of food supplementation during pregnancy on birthweight. *Pediatrics* 56(4), 508–520 (1975).

83 Stein AD, Barnhart HX, Hickey M, Ramakrishnan U, Schroeder DG, Martorell R: Prospective study of protein-energy supplementation early in life and of growth in the subsequent generation in Guatemala. *Am. J. Clin. Nutr.* 78(1), 162–167 (2003).

■ Study of rural Guatemalans found that long-term nutritional supplementation of mothers during early life increases the height of offspring.

84 Behrman JR, Calderon MC, Preston SH, Hoddinott J, Martorell R, Stein AD: Nutritional supplementation in girls influences the growth of their children: prospective study in Guatemala. *Am. J. Clin. Nutr.* 90(5), 1372–1379 (2009).

85 Villar J, Rivera J: Nutritional supplementation during two consecutive pregnancies and the interim lactation period: effect on birth weight. *Pediatrics* 81(1), 51–57 (1988).

86 Arenz S, Ruckerl R, Koletzko B, Von Kries R: Breast-feeding and childhood obesity – a systematic review. *Int. J. Obes. Relat. Metab. Disord.* 28(10), 1247–1256 (2004).

87 Kuzawa C, Quinn E: Developmental origins of adult function and health: evolutionary hypotheses. *Ann. Rev. Anthropol.* 38, 131–147 (2009).

88 Savino F, Liguori SA, Fissore MF, Oggero R: Breast milk hormones and their protective effect on obesity. *Int. J. Pediatr. Endocrinol.* 2009, 327505 (2009).

89 Doneray H, Orbak Z, Yildiz L: The relationship between breast milk leptin and neonatal weight gain. *Acta Paediatr.* 98(4), 643–647 (2009).

90   Miralles O, Sanchez J, Palou A, Pico C: A physiological role of breast milk leptin in body weight control in developing infants. *Obesity (Silver Spring)* 14(8), 1371–1377 (2006).

91   Ilcol YO, Hizli ZB, Ozkan T: Leptin concentration in breast milk and its relationship to duration of lactation and hormonal status. *Int. Breastfeed J.* 1, 21 (2006).

92   Savino F, Liguori SA, Oggero R, Silvestro L, Miniero R: Maternal BMI and serum leptin concentration of infants in the first year of life. *Acta Paediatr.* 95(4), 414–418 (2006).

93   Kuzawa CW: Adipose tissue in human infancy and childhood: an evolutionary perspective. *Am. J. Phys. Anthropol.* (Suppl. 27), 177–209 (1998).

94   Kuzawa CW: Beyond feast-famine: brain evolution, human life history, and the metabolic syndrome. In: *Human Evolutionary Biology.* Muehlenbein M (Ed.). Cambridge University Press, Cambridge, UK (2010).

95   Mcgowan PO, Sasaki A, D'Alessio AC *et al.*: Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat. Neurosci.* 12(3), 342–348 (2009).

96   Gluckman PD, Lillycrop KA, Vickers MH *et al.*: Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. *Proc. Natl Acad. Sci. USA* 104(31), 12796–12800 (2007).

97   Trivers RL: Parent-offspring conflict. *Am. Zoologist* 14(1), 249–264 (1974).

98   Haig D: Genetic conflicts in human pregnancy. *Q. Rev. Biol.* 68(4), 495–532 (1993).

99   Hawkes K: Colloquium paper: how grandmother effects plus individual variation in frailty shape fertility and mortality: guidance from human–chimpanzee comparisons. *Proc. Natl Acad. Sci. USA* 107(Suppl. 2), 8977–8984 (2010).

100   De Rooij SR, Painter RC, Phillips DIW *et al.*: Hypothalamic-pituitary-adrenal axis activity in adults who were prenatally exposed to the Dutch famine. *Eur. J. Endocrinol.* 155(1), 153–160 (2006).

101   De Rooij SR, Painter RC, Holleman F, Bossuyt PM, Roseboom TJ: The metabolic syndrome in adults prenatally exposed to the Dutch famine. *Am. J. Clin. Nutr.* 86(4), 1219–1224 (2007).

102   Calder WA: *Size, Function, and Life History.* Harvard University Press, Cambridge, MA, USA (1984).

103   Mccance R, Widdowson E: Glimpses of comparative growth and development. In: *Human Growth. A Comprehensive Treatise, Volume 1. Developmental Biology, Prenatal Growth.* Tanner J, Falkner F (Eds). Plenum, NY, USA, 133–151 (1986).

104   Rollo CD: Growth negatively impacts the life span of mammals. *Evol. Devel.* 4(1), 55–61 (2002).

105   Flohn H: Short-term climate fluctuations and their economic role. In: *Climate and History. Studies in Past Climate and their Impact on Man.* Wigley T, Ingram M, Farmer G (Eds). Cambridge University Press, Cambridge, UK, 310–336 (1981).

106   Ozaki T, Nishina H, Hanson MA, Poston L: Dietary restriction in pregnant rats causes gender-related hypertension and vascular dysfunction in offspring. *J. Physiol.* 530(1), 141–152 (2001).

107   Gopalakrishnan GS, Gardner DS, Rhind SM *et al.*: Programming of adult cardiovascular function after early maternal undernutrition in sheep. *Am. J. Physiol.* 287(1), R12–R20 (2004).

108   Roseboom TJ, Van Der Meulen JHP, Ravelli ACJ, Osmond C, Barker DJP, Bleker OP: Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Mol. Cell. Endocrinol.* 185(1–2), 93–98 (2001).

▪▪   **Provides an overview of some of the health outcomes that have been studied in the Dutch Famine Birth Cohort.**

109   Franco Mdo C, Arruda RM, Dantas AP *et al.*: Intrauterine undernutrition: expression and activity of the endothelial nitric oxide synthase in male and female adult offspring. *Cardiovasc. Res.* 56(1), 145–153 (2002).

110   Gardner DS, Tingey K, Van Bon BWM *et al.*: Programming of glucose-insulin metabolism in adult sheep after maternal undernutrition. *Am. J. Physiol.* 289(4), R947–R954 (2005).