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Epigenetic Embodiment of Health and Disease: A Framework for Nutritional Intervention

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Abstract

Evidence that fetal nutrition influences epigenetic profiles and adult health has heightened interest in pregnancy nutritional interventions. However, like all placental mammals, the human fetus is buffered against short-term nutritional fluctuations by maternal physiology. We review evidence that nutritional buffering reflects a broader capacity to buffer fetal biology from environmental fluctuations that varies by exposure. At one extreme are evolutionarily-novel teratogens that the placenta and mother's body have minimal capacity to shield the fetus from, making them excellent targets for intervention during pregnancy. At the other extreme are macronutrients homeostatically maintained by maternal metabolism. For macronutrients like glucose, the diet is only one of multiple sources, and temporary deficits may be redressed using maternal stores and endogenous synthesis. Fetal experience of maternal pregnancy supplementation will be tempered by these buffering mechanisms. We propose that strategies to improve fetal macronutrient delivery should strive to modify maternal metabolism, in addition to targeting her pregnancy macronutrient intake. We review evidence that sustained improvements in early life nutrition of future mothers hold promise to improve fetal nutrition and epigenetic profiles in future generations.

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I. Introduction

Recent work has highlighted the importance of prenatal nutrition as an influence on epigenetic and developmental biology in offspring (1). Glucose metabolism, blood pressure regulation, stress physiology, and immunity are among the systems shown to be modified in response to intrauterine nutrition, and which contribute to altered risk of chronic disease in adulthood (2-7). The most common approach to human work in this area has linked lower birth weight (BW), which is used as a proxy for prenatal undernutrition or stress, to cardiovascular diseases and other adult chronic degenerative conditions (1, 6). The long-term effects of early environments often involve permanent modifications in developmental biology, which recent work is tracing to changes in epigenetic markings (i.e. gene promoter methylation) that influence tissue and organ function via modified regulation of gene expression (4, 8).

Although epigenetic sensitivity persists across the life span, many systems have developmental periods of heightened sensitivity during which exposures have particularly robust long-term effects. Many of these "sensitive" or "critical" periods overlap with stages of direct resource transfer between mother and fetus across the placenta or through breast milk (9). As one example, protein restriction in pregnant rats induces epigenetic changes at regulatory genes and has important effects on offspring health (10). Similarly among a Dutch cohort whose mothers experienced famine while pregnant, offspring methylation at the IGF2 locus was found to be altered more than 60 years later (11). The model that has emerged from the developmental origins literature is one in which the mother's nutrition and her exposure to environmental factors during pregnancy and lactation can have lingering effects on the health and functional status of offspring as they grow and develop.

From a public health and policy perspective, these findings have led to hopes that the burden of disease in future generations may be reduced by improving the health and nutritional status of pregnant women (12-14). However, to date, few studies have focused on developing maternal interventions to harness these periods of heightened developmental sensitivity to improve offspring outcomes. Experimental work in animal models has almost exclusively focused on confirming that prenatal stressors contribute to adult chronic diseases (15). Although these studies provide essential details about developmental and epigenetic pathways involved in the pathophysiology of common diseases, it is presently less certain whether *enrichment* of a mother's otherwise marginal nutritional ecology improves intrauterine environment sufficient to yield long-term improvements in offspring health and human capital (16).

Although little human work has attempted to modify offspring epigenetic status or physiology through maternal nutritional supplementation, a long-standing research tradition has evaluated nutritional impacts on birth outcomes. (17). Micronutrient supplementations have had some notable successes (18-21), and can lead to increased BW and neonatal survival rates in populations with imbalanced or deficient diets (22). In contrast, studies that provide pregnant women with supplements of macronutrients (i.e. energy and protein) have generally had less impressive results. While these studies often find improvements in outcomes like maternal nutritional status and a reduced risk of stillbirth and neonatal death (23), offspring BW rarely responds robustly to maternal supplementation (23, 24). For instance, a Cochrane Review evaluating the effects of 13 balanced energy/protein supplementation trials in pregnancy reported an average increase in offspring BW of only 38 grams (23). Thus, the well-justified enthusiasm for harnessing the nutritional and epigenetic sensitivity of early development to improve the

health of future generations has outpaced efforts to test and refine effective intervention approaches.

Here we develop an evolutionary framework with the intent of stimulating new approaches to early life interventions. We begin by tracing the evolution of innovations in maternal buffering that help achieve a stable and controlled environment to support offspring development. The reproductive strategy of placental mammals represents a particularly dramatic re-organization of parental biology and care around the goal of maintaining a stable offspring rearing environment. However, even among placental mammals, fetal exposure to different factors is only buffered to varying degrees. At one extreme are harmful compounds that the mother's body and placenta have minimal capacity to neutralize or buffer , which leads to a relatively direct link between maternal and fetal exposure. At the other extreme lie factors that are regulated homeostatically by maternal metabolism and internal stores, which allow delivery to the fetus to be maintained despite fluctuations in maternal intake. We argue that maternal metabolism is adjusted gradually to chronic changes in local ecology, which helps calibrate offspring biology to local patterns of ecological change. While beneficial for buffering against transient nutritional deficiencies in pregnancy, these same mechanisms may also temper effects of macronutrient supplementation during pregnancy, thus necessitating complementary approaches.

Here our goal is not to comprehensively review the rationale for nutritional interventions, nor do we cover all previously tested or possible maternal intervention targets. Instead, we sketch a working model that differentiates several distinct pathways linking specific maternal exposures to fetal exposures in the hopes of illuminating the multiple ways that enriching maternal experience may improve offspring development and health.

II. Evolution of maternal buffering

Consider supplementing the diet of a pregnant woman. In the simplest, hypothetical scenario, the resource consumed is directly transferred to the fetus, and thus, the intervention has maximal efficacy. This type of direct connection between maternal exposure and fetal experience implies that fetal access to resources are entirely dependent upon the mother's intake in the current ecology. In fact, such examples are relatively rare, and serendipity of this sort is particularly unlikely for resources required in large and constant quantities, such as macronutrients. Indeed, the evolution of life is marked by increasingly elaborate maternal buffering strategies aimed at maintaining stability in the offspring's rearing environment despite environmental fluctuations in temperature, nutrients and environmental hazards.

The degree to which the mother's body serves as the intermediary between an environmental factor and offspring development varies markedly across taxa (25, 26), which predominately relates to differences in life span and reproductive strategy. These differences affect the ways and extent to which parental biology and behavior shape the development of offspring and potentially buffer development from fluctuations in beneficial resources and also the detrimental effects of harmful compounds. In addition, in some instances, resource flows may embody records of past maternal experience and thus allow the offspring to improve its adaptive fit with salient features of its future environment (27, 28). As we will argue below, all of these principles are important to understand when designing effective interventions.

Maternal buffering from fish to mammals

Modern day fish are descendants of the earliest vertebrates, which evolved only limited capacities for parental buffering of offspring. In early vertebrates and the majority of fish species today, eggs are formed inside the adult female's body where a flexible membrane is

constructed to encase DNA, along with a small store of nutrients, hormones and other factors needed to sustain early embryonic development following fertilization (29). Eggs are secreted into the aqueous environment in large mats, awaiting external fertilization by males who release sperm directly into the water. In many species, the vast swarm of offspring generated at fertilization are on their own, with few fish species feeding their young. Notably, some species have developed more advanced strategies of parental care and guard larva or eggs by either protecting their territory or by brooding fry in their mouths (30, 31).

Approximately 330 million years ago, the lineage leading to modern amphibians diverged from their last common ancestor with modern fish (**Fig. 1**). Some amphibians derived elaborate maternal investment strategies beyond egg laying. For instance, in some species of Caecilians (one of three forms of currently living amphibians), the offspring eat the parents' nutrient-rich skin, which is rapidly regenerated (32). However, with the exception of certain species that practice parental care in the form of egg attendance or tadpole transport and feeding (33), most amphibians simply lay eggs in water where they await external fertilization.

Between 330 and 310 million years ago the earliest amniotes evolved. These terrestrial species evolved more durable membrane-covered shells capable of surviving outside water. This group eventually gave rise to reptiles and birds in one lineage and mammals in a separate lineage. In all these species fertilization is internal, resulting in a more stable thermal, nutrient and hormonal environment during early embryonic growth. All birds and the majority of reptiles lay eggs, while mammals and some reptiles independently evolved the capacity for live birth. Of the amniotes, mammals and birds independently evolved homeothermy, or warm-bloodedness, allowing adaptive radiations of these species into higher latitudes with less consistent and colder temperatures.

Early mammals were likely similar to modern marsupials. In marsupials offspring emerge from the maternal body during early embryonic development and enter a pouch where nipples supply nutrients and hormones that support offspring growth (34). This mammalian strategy of buffering was further augmented with the evolution of placentation in eutherian mammals, such as humans. In these species a fetally-derived placenta develops and implants within the mother's uterine wall, creating a direct supply line between maternal circulation and the growing embryo. In the more invasive hemochorial forms of placentation characterizing human pregnancy, the feto-placental unit releases hormones directly into the mother's circulation, modifying maternal metabolism in ways that increase nutrient transport to support placental and fetal growth (35, 36). This physical interplay between fetus and mother helps maintain a stable fetal rearing environment in the face of variable maternal ecological conditions.

III. Pathways linking maternal and fetal environments

The above review highlights the diversity in reproductive strategies that evolution has devised to allow maternal biology to buffer the micro-environment of early offspring development. Although modern reptiles, birds and mammals are contemporaries and thus equally "evolved", placental mammals, such as humans, have particularly refined strategies that allow maternal biology to buffer the fetus from stochastic environmental variation. This basic understanding provides a starting point for considering the various types of environmental factors—both beneficial and harmful—that mammalian mothers confront, and the varying degrees to which maternal biology buffers their impact on the fetus. We now outline three distinct pathways linking maternal exposure to an external factor to the intrauterine environment experienced by offspring (**Table 1**). As we will see, the importance of a resource to development, its habitual availability in the environment or diet, and (in the case of toxins and

other harmful compounds) its degree of evolutionary novelty are key factors influencing whether it has direct effects on the fetus, or whether the mother or placenta have evolved capacities to shield or buffer fetal exposure.

Pathway A. Harmful compounds

Teratogens are chemicals or compounds that disrupt normal embryological development, and prominently include pharmaceuticals, alcohol, tobacco, metals and pesticides (37). The placenta is capable of shielding the developing fetus from some toxic compounds, while others are able to pass through readily (36). The chemical nature of individual compounds determines if and how they may be transported across the placenta (37).

One well studied teratogen that readily diffuses across the placenta is lead (38). Higher lead levels increase risk of miscarriage, stillbirth, and preterm birth (39, 40). Maternal lead is inversely associated with fetal growth rate (Jelliffe-Pawlowski et al 2006) and neurobehavioral and cognitive development of offspring (41, 42). One study found an association between maternal bone lead and umbilical cord DNA methylation, suggesting that lead exposure may impact offspring biology by modifying gene expression (43). Air pollution and particulate matter are additional sources of environmental toxicants. Studies have found relationships between air pollution, particularly carbon monoxide (CO), ground level ozone (O_3), nitrogen oxide (NO_2) and sulfur dioxide (SO_2) and risk of lower BW and preterm birth (44). Particulate matter, which is emitted from areas such as construction sites and smokestacks, is also associated with growth restriction and preterm birth

(45).

Although diverse in composition, these growth disrupting compounds share one feature in common: all are either evolutionarily-recent in origin or were only rarely encountered in

greater than trace levels by human ancestors (46, 47). Thus, there has been minimal evolutionary pressure to buffer their effects on fetal growth (**Fig. 2A**). Today, modern industries, technologies and social inequalities in environmental exposures make it challenging for high risk populations to avoid exposure to many teratogens (16). For instance, airborne pollutants released from industry can impact neighborhoods or even entire cities, while lead from lead-based paint may be present in homes, soils and water supplies. For these classes of compound to which the fetus is not biologically shielded, decreasing maternal exposure will tend benefit offspring health by directly decreasing fetal exposure.

In contrast to the exposures discussed above, some compounds with potentially disruptive developmental effects are evolutionarily ancient and thus the placenta has evolved capacities to actively shield the fetus from them (**Fig. 2A**). For example, the hypothalamic pituitary adrenal (HPA) axis produces glucocorticoids (e.g. cortisol), which are hormones with important developmental effects across a range of species (48). In humans, most maternal cortisol is deactivated by the placental enzyme 11-β-hydroxysteroid dehydrogenase 2 (11 β HSD2), in part to protect the fetus from the detrimental effects of elevated cortisol levels. While this enzyme deactivates the majority of the maternal cortisol, chronic or acute psychosocial stress exposures can elevate fetal cortisol, resulting in growth restriction or altered stress physiology (49-52). There may therefore be an upper limit to buffering even for factors that are mostly shielded by maternal or placental metabolism.

In summary, there is a broad range of compounds with harmful effects on fetal development. Maternal and fetal biology have developed mechanisms for counteracting some exposures, but at times even these mechanisms are not sufficient to completely shield developing

offspring. Policies that reduce maternal exposure to harmful compounds will often benefit fetal development by leading to immediate reductions in fetal exposure.

Pathway B. Essential nutrients - buffered by body stores only

In addition to shielding the fetus from harmful compounds, maternal biology is the sole source of nutrients and vitamins required for healthy fetal development. Strategies for maintaining availability of a nutrient vary markedly. Most macronutrients may be mobilized from stores or synthesized *de novo* when consumption falls below demand (see Pathway C below). Other nutrients required in small quantities, in particular micronutrients such as vitamins and minerals, are classified as *essential* because they are not produced within the body and thus must be consumed preformed from dietary sources. Many micronutrients serve as co-factors in metabolic or enzymatic processes, and infants born with micronutrient deficiencies are at increased risk for adverse outcomes like low BW, neural tube defects and preterm delivery (53). Some micronutrients are essential because they cannot be produced by organic chemistry (i.e. essential metals), while human ancestors lost the capacity to synthesize certain factors over the course of evolutionary history because they were required in trace quantities readily met by ancestral diets. As one well-known example, the inability to synthesize ascorbic acid (vitamin C) is thought to be due to the fact that humans evolved from fruit-eating primates, for whom vitamin C was prevalent in the diet (54).

The body has some capacity to store most essential nutrients to help ensure that needs are met should intake fall below need (**Fig. 2B**). When endogenous stores of essential nutrients are present, homeostatic regulation generally assures that circulating levels remain constant (55). Looking across species that vary in habitual diets, the capacity to store a micronutrient varies substantially (55), pointing to the fact that evolutionary selection has tended to calibrate storage

capacities to habitual patterns of availability and use. However, the storage capacity for some key micronutrients are generally modest compared to increased demands during pregnancy and lactation, when recommended intakes are generally increased (56, 57). However, when diets lack in specific nutrients, this may limit a woman's ability to meet these increased needs. For example, iron requirements across pregnancy for a 55 kg woman are approximately 1000 mg, which may exceed the quantity that can be absorbed from the diet during pregnancy. As a result, women need iron stores of at least 300 mg entering pregnancy to maintain optimal iron status (56).

Given the importance of micronutrients for fetal development and the small size of maternal stores compared to reproductive needs, it is not surprising that some maternal micronutrient supplementations in pregnancy improve pregnancy outcomes (23). In the Pune Nutritional Study in India, women regularly consuming micronutrient rich newborns almost 200g heavier than other women (58). Similar improvements in neonatal and infant health have been found with iron, folate, vitamin A, B12 and D supplementation in pregnancy and during lactation (18, 21, 53, 59-61). A recent study found that perinatal micronutrient supplementation among marginally nourished Gambian women resulted in epigenetic modifications in offspring at genes associated with resistance to infection and immune responsiveness at nine months of age, pointing to the likelihood that micronutrient supplementation could yield more durable benefit in other systems and outcomes (62).

Pregnancy induces changes in maternal metabolism that increase the efficiency with which essential nutrients are extracted from the diet and utilized, which can augment the effectiveness of interventions (63). In rats Vitamin B12 given during pregnancy is preferentially transferred to the fetoplacental unit in lieu of maternal stores, suggesting mechanisms for

ensuring micronutrient supply to the developing fetus (64). In addition the efficiency of absorption of some nutrients increases in pregnancy (65, 66).

In summary, some important nutrients are required in small quantities that must be derived from the diet. The mother's ability to buffer fetal requirements of these resources depends upon several factors, including storage capacity within the human body, adequacy of maternal intake, and any cumulative deficits from prior reproductive bouts. In populations with unbalanced or marginal nutrition, micronutrient supplementation during pregnancy will often yield direct beneficial effects on offspring outcomes.

Pathway C. Macronutrients homeostatically regulated via stores and de novo synthesis

The quantitatively most important resources required of offspring development are macronutrients: proteins, carbohydrates and fats. These provide the energy necessary for maintaining cellular function throughout the body, and are the building blocks for gene products and structures like cellular membranes. Of the macronutrients, glucose is the primary energy substrate delivered between mother and fetus and is closely associated with BW variation. Clinical work has shown that maternal glucose levels directly determine fetal glucose supply (67). This is achieved by placental glucose transporters, the density of which are sensitive to maternal nutritional status (68). Since fetal growth is insulin-driven, glucose transfer stimulates insulin production, and secondarily, fetal growth rate.

Given the pivotal role of circulating glucose to fetal growth rate, what determines maternal glucose level? Because energy substrates like glucose are required in large quantities to maintain constant functioning of every cell in the body, and since bodily requirements fluctuate across hours, weeks or even months, their availability is not relegated to chance (**Fig. 2C**). The mother's diet is only one of several potential sources of glucose called upon to sustain maternal

and fetal needs (**Fig. 3**). After a meal, foods are digested and broken down into constituent nutrients. Their presence stimulates the production of insulin, which initiates nutrient uptake by tissues and organs which use them for energy or to replenish carbohydrate, fat and protein stores. If dietary intake declines below use, stored substrates are mobilized, beginning with the body's modest glycogen stores. As glycogen stores are depleted after several hours, the body turns to the more voluminous adipose tissue stores of triglycerides, which are broken down into glycerol and free fatty acids (FFA) during fasts. Glycerol enters the liver where it is converted into glucose via gluconeogenesis. The released FFA are used as an alternative fuel source in liver, muscle and other tissues which induces insulin resistance and reduces glucose uptake in these tissues. This spares glucose for delivery to high priority non-glucose-dependent organs, including the brain, immune system and during pregnancy, the feto-placental unit (35, 69). Amino acids stored in muscle protein can also be mobilized and used as a gluconeogenic substrate, although preferential use of fats helps minimize break down of lean tissues (70). During pregnancy, maternal metabolism is adjusted to prioritize glucose delivery to the fetus, which the fetus itself helps orchestrate. The placenta uses its direct access to maternal circulation to secrete high levels of hormones that induce maternal insulin resistance. The resultant decrease in glucose uptake by maternal tissues helps prioritize glucose delivery to the fetus (35).

Although amino acids can be used as energy substrates they are also necessary for protein synthesis and accretion within the fetus (71), and maternal protein requirements are increased 30-50% during pregnancy (63). Amino acids are mainly supplied by the diet, but may also be mobilized from muscle when dietary supplies are limited (63). Critical amino acids are actively transported across the placenta (72). Reduced or elevated transport of amino acids across the placenta, for instance due to maternal smoking or diabetes, is associated with intrauterine growth

restriction or macrosomia in infants, demonstrating their importance for regulating fetal growth (72).

FFA are also delivered to offspring during gestation, either directly or as triglycerides (TG), which the placenta converts to FFA. They are used as energy sources, are essential to structures like cellular membranes, and late in gestation, are deposited in the human newborn's unusually large store of body fat (73, 74). Maternal fat accumulation predominates early in pregnancy, but maternal lipid metabolism switches to a catabolic state, resulting in increased TG and FFA concentrations in the last weeks of gestation (75). In cases of negative energy balance adipose tissue lipolytic activity increases, increasing FFA and glycerol which are converted to ketone bodies and glucose, respectively, in the liver. These substrates easily cross the placenta and supply energy for the fetus (76).

Some FFA have important structural or metabolic functions beyond serving as energy substrate. Although required in smaller quantities, some long-chain polyunsaturated fatty acids (LCPUFA) play an important role in fetal development, such as the well-known requirement of docohexaenoic acid (DHA) for brain growth (77). LCPUFAs are able to cross the placenta through active transport via transport proteins as well as through passive diffusion along the maternal-fetal concentration gradient (68). There is evidence that fatty acids like DHA, which are challenging to synthesize *de novo* and are required in large quantities late in gestation, may be mobilized from maternal or fetal fat stores if dietary intake lags behind requirements (74).

In summary, in contrast to the factors transported via Pathways A & B above, macronutrients important for fetal growth are actively regulated and in some cases synthesized *de novo* when maternal supply falls below fetal demand (**Fig. 2C**). Thus supplementing maternal

diet during pregnancy alone is unlikely to result in large effects on the fetus, since maternal metabolism is what shapes fetal macronutrient substrate availability.

IV. Implications of maternal buffering for intervention design

Above, we note that modifying maternal exposure to some harmful compounds (Pathway A) and essential micronutrients (Pathway B) can lead to relatively rapid and direct changes in fetal exposure, pointing to the utility of targeted maternal interventions during pregnancy itself. In contrast, fetal delivery of the quantitatively more important macronutrients like glucose, fatty acids or amino acids—the primary determinants of fetal growth and metabolic programming—are not passive outcomes of what the mother eats that day, but are homeostatically maintained within narrow limits by her metabolism (Pathway C). Because maternal metabolism has multiple sources beyond dietary intake to meet substrate needs, the fetus is largely buffered against temporary shortfalls in maternal macronutrient intake. But this buffering appears to work both ways: the tendency of maternal metabolism to maintain a constant internal state also minimizes the beneficial impact on the fetus of supplementing maternal diet (25).

Of course, macronutrient supplementation does benefit maternal nutritional status, health and offspring survival, and is thus well-justified (23). However, as discussed above, substantial increases in fetal growth rate and birth size have been challenging to achieve. Despite notable successes (i.e. (78), a comprehensive meta-analysis found that protein-calorie supplementation trials have modest effects on offspring BW (Kramer and Kakuma 2003). Rather than being delivered to the fetus, increases in maternal caloric intake during pregnancy appear to primarily allow increased physical activity and energy expenditure, and perhaps also to enhance maternal fat deposition (79, 80).

The discussion of pathway C illustrates that short-term supplements in essence "push" against maternal buffering systems that are designed to absorb the impact of such short-term fluctuations—whether negative or positive—and protect metabolic set points and a stable internal milieu despite them. In light of this, the question that we must confront is how to reset maternal metabolic priorities themselves, rather than work against them. As we will show, several independent lines of evidence converge on a common conclusion: we must take a long-range view and optimize the early life nutritional conditions *of future* mothers, if we hope to optimize the nutrition that the next generation receives *in utero*.

Evidence that the mother's own early life nutrition influences offspring nutrition and growth

There is a clear link between maternal body size, pelvic dimensions (81), and offspring BW across multiple species (82). This link is particularly strong in humans owing to the large cranial dimensions of our offspring, which must pass through a pelvic opening restricted in size by the mechanical constraints imposed by bipedal locomotion (83, 84). Given that maternal size places physical limits on BW, what determines maternal size? Despite strong genetic contributions to stature under favorable nutritional conditions, a large portion of global population variation in adult size is thought to trace to varying levels of nutritional stress experienced during the first 2-3 years of life (85, 86). Postnatal growth can be divided into several periods of distinct hormonal regulation that vary in sensitivity to nutritional influence, and which determine age-specific contributions to adult size (87). The first 2-3 postnatal years reflect a continuation of a hormonal regime begun *in utero* and forms the basis of a critical period in adult stature attainment. At this age, production of insulin-like growth factors (IGFs) stimulating skeletal and somatic growth are insulin-dependent, directly linking nutritional intake with growth rate (67) and attained stature (88). In many populations with nutritional growth

stunting, the majority of adult height deficits compared to healthy growth references are already present by 2-3 years of age (88, 89), reflecting deficits in length at birth combined with the impact of post-weaning nutritional stress and infectious morbidity on postnatal linear growth (85).

Consistent with this perspective, the specific components of maternal size that correlate most strongly with offspring size suggest a lingering impact of early postnatal nutrition on offspring fetal growth (90). For instance, a study of the Boyd Orr cohort in Britain found that leg length at 7 years of age was a stronger predictor of offspring BW than was adult size (91), which was similar to findings in the 1958 British birth cohort (92). Since childhood leg growth is the component of linear growth most sensitive to nutrition (93, 94), these findings suggest that nutrition in early life has lingering impacts on intrauterine nutrient transfer and fetal growth rate in offspring (95, 96).

The most widely-documented evidence for intergenerational effects of nutrition and growth comes from multi-generational cohort studies that include information on BW across multiple generations (reviewed by (97). These studies find robust relationships between maternal and offspring BW (98) which are strengthened after adjustment for gestational age, indicating that it is fetal growth rate, rather than differences in size due to prematurity, that track across generations (99). Moreover, these relationships are often independent of maternal adult stature, suggesting that there is a component of the intergenerational BW correlation that is not merely capturing an effect of birth size on later adult size (97).

While correlations between fetal growth rate in mother and offspring partly reflect an effect of shared genes, there is evidence for epigenetic and developmental contributions to these correlations, suggesting nutrition early in life can have lingering biological impacts on the next

generation (13). Studies generally report an excess in BW heritability through the matriline when compared to the patriline, showing that there is more than direct genetic effects underlying these relationships (100). Epigenetic contributions are a plausible explanation for this finding (100), and gain support from human studies. Women whose mothers experienced the Dutch Famine while pregnant gave birth to offspring who were themselves slightly smaller (101). As discussed above, prenatal famine exposure in this cohort also predicted reduced methylation near the insulin growth factor 2 gene in offspring (11), which in humans is an imprinted gene that effects metabolism and fetal growth (35). Another recent study showed that individuals *in utero* during the hunger season in rural Gambia had modified methylation at multiple loci, providing additional evidence for long-term effects of prenatal nutrition on epigenetic status (102).

Phenotypic inertia: is maternal nutrient transfer a source of ecological information?

Given the exquisite mammalian capacity to buffer the fetus against changes in *current* maternal intake, how do we make sense of the fact that fetal growth may in fact be modified in response to maternal nutritional experience decades in the *past*? Some link between maternal growth rate and offspring BW is expected in light of the fact that they are both products of the mother's expenditure of excess metabolic potential, which is first used to support her own growth before being shunted in support of offspring growth in adulthood (see (96, 103). In addition, multiple authors have speculated that some instances of nutrition-driven fetal developmental plasticity allows the fetus to prepare for conditions likely to be experienced after birth (95, 104, 105). Some of the adjustments made by the nutritionally-stressed fetus *in utero*, such as a tendency to deposit more abdominal body fat, and the reduced response of muscle to insulin that spares glucose, could provide advantages if the postnatal environment is also nutritionally stressful (for review see (69). Similarly, evidence reviewed above that offspring

birth weight is sensitive to the mother's own early life nutrition suggests a maternal capacity to recalibrate reproductive expenditure in response to early life nutritional cues (96, 106).

Pathways A, B and C discussed above all respond to different aspects of maternal (or in some cases grandmaternal) experience, thus potentially conveying information about local ecology to the developing fetus. Although directly conveyed compounds (Pathways A & B) indicate the mother's immediate exposures during pregnancy, neither pathway is likely to provide useful developmental information to the fetus (107). Teratogenic compounds are by definition disruptive of normal growth and development. Because many are evolutionarily-novel, there has also been little opportunity for human biology to evolve capacities to detect and respond to them if there was a benefit in doing so. Essential nutrients are partially or wholly buffered by maternal stores (Pathway B) and thus in theory provide information about the mother's micronutrient intake in the recent past. However, there is little evidence for adaptive developmental adjustment in response to micronutrient deficiencies, which invariably lead to developmental disruption and functional impairment in offspring (22, 58).

In contrast to pathways A and B, macronutrients that are both buffered via stores *and* produced *de novo* via maternal metabolism (Pathway C) are relatively decoupled from current intake, and as discussed above, appear to be reflective of a mother's chronic or early life nutritional conditions (95, 106, 108). Based upon this, it has been hypothesized that the flow of macronutrients to the fetus provides a long term average index of maternal nutritional experience. In an unpredictable environment this "backward looking" form of adaptation, or *phenotypic inertia* (95), provides a best guess about conditions that offspring will experience in the future (25, 109). If offspring systems that respond to these cues are better matched to their environments, this will indirectly enhance the mother's own fitness, setting in motion

evolutionary selection for maternal cues to signal environmental quality to offspring, even if the cues were initially inadvertent (110, 111).

The phenotypic inertia model implies that homeostatic systems that buffer fetal nutrition do so in part because natural selection has shaped maternal physiology to provide integrative and thus more reliable information to guide offspring development. This suggests an additional reason that maternal biology might buffer the fetus against not only nutritional stress but also nutrition that is better than average: because an unusual improvement in nutrition is likely transient, it would be unwise to plan future expenditure to expect continued abundance. So long as there are survival or other fitness costs associated with over-reaching nutritional supply, the organism should ignore temporary, short-lived increases in maternal intake when setting developmental trajectory (95). Because maternal biology and metabolic status develop in response to nutrition early in life, across the growing years, and in adulthood, maternal biology embodies a cumulative record of a lifetime of past nutritional experiences and is thus a source of more reliable historical cues of the mother's typical nutritional experience (9, 16).

Discussion

As placental mammals, humans have elaborate biological strategies to buffer early offspring development against environmental fluctuations. Since the most sensitive developmental stages occur within the mother's body, maternal physiology is capable of shielding the fetus from some potentially harmful exposures, while providing stable access to the most important nutritional resources. In many mammals, the mother's body and the placenta have evolved a capacity to shape the flow of resources to provide the fetus with ecological information. The capacity to buffer the supply of the most important nutrients implies that short-

term deviations from normal intake—whether a deficit or a supplement—will generally have attenuated effects on the fetus.

Our model points to the need to tailor interventions based upon the pathway through which a factor influences fetal development. For factors directly transferred to the fetus (Pathway A), such as teratogens, reducing maternal exposure will often result in direct reductions in fetal exposure. For instance, one study found that women who quit smoking during pregnancy gave birth to babies 167 grams heavier than babies born to women who simply reduced smoking in pregnancy, and 241 grams heavier than to women who did not reduce smoking at all (112).

In the case of factors derived strictly from the environment and which are partially buffered by maternal stores, such as essential vitamins and nutrients, supplementing women during pregnancy is likely to have substantial effects, especially when maternal nutrient status and dietary intake are marginal. This likely explains the success of some pregnancy micronutrient supplementations (53, 61). However additional research is needed to clarify which micronutrients, alone and in combination, are most effective at improving offspring outcomes, and also their long-term effects on epigenetic status and health outcomes later in life.

In contrast to the above scenarios, supplementing women with macronutrients during pregnancy alone is unlikely to achieve the full potential benefits associated with improving fetal nutrition because maternal metabolism has evolved mechanisms to buffer offspring from transient fluctuations in intake. Our model helps explain the relatively modest effects of pregnancy macronutrient supplementation on birth outcomes (23). Although available studies are few, there is evidence that sustained improvements in maternal nutrition result in relatively robust changes in offspring birth weight. For example, in a Guatemalan study, the improvement in birth weight predicted by a protein-calorie supplement (*atole*) was more than doubled if

supplementation started during the previous pregnancy and continued during the intervening period of lactation (113). In a follow up of the offspring and grandoffspring, the daughters whose mothers were supplemented with *atole* gave birth to offspring 116 grams heavier than daughters of women supplemented with a less nutritious supplement (114). These finding support the evolutionary model that we outline, and point to the need to consider nutritional interventions of young infants and children as an integral component of strategies to improve the nutritional experiences, birth outcomes and long-term metabolic programming of future generations (3).

Our coverage in this review has by necessity been selective, and we solely focused on maternal contributions to fetal nutrition and growth. Similar principles likely apply to infant metabolic programming via maternal nutrients and hormones in breast milk. Not unlike fetal nutrition, breast milk composition responds directly to maternal intake of essential nutrients (115), is unrelated to maternal macronutrient intake (116, 117), while there is some evidence for stronger links to the mother's chronic or early life nutrition (9). In addition, there is growing evidence that not only maternal nutrition, but also paternal nutrition, can have intergenerational influences on birth size and offspring health. One recent study found that manipulating the diet of adult male rats changed methylation and expression of genes affecting lipid metabolism in offspring, pointing to epigenetic inheritance via sperm (118). Although studies investigating similar questions in humans remain scarce, there is tentative evidence for transgenerational effects of paternal and grandpaternal nutrition on offspring metabolism and disease risk (119). Thus paternal diet and life course experiences likely have underappreciated effects on offspring development, pointing to the need for future research to also explore the multi-generational benefits of male nutritional supplementation.

Conclusion

In sum, we propose a model for maternal intervention that recognizes the evolution of distinct pathways linking different types of environmental resources to the intrauterine environment experienced by the fetus. While relatively unbuffered compounds that are directly conveyed to the fetus are particularly good candidates for interventions during pregnancy, optimal improvements in delivery of homeostatically regulated resources, such as most macronutrients, may require long-term approaches that modify the mother's own development in order to emulate longer timescale ecological change.

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Figure legends

Fig 1. Evolutionary innovations in maternal buffering of offspring rearing environment. Dates (MYA = million years ago) represent minimum fossil based estimate for last common ancestor for each branching point (based on Benton and Donoghue 2006). Giving birth to live young (viviparity) has evolved independently over 100 times among marsupials, eutherian mammals, reptiles and even some species of fish, pointing to the evolutionary advantages of this strategy. Of the various reproductive strategies the eutherian mammal profile of internal fertilization, having a true placenta and giving birth to live young that subsist on breast milk provides many opportunities for maternal biology to buffer environmental fluctuations and also to modify offspring development.

Fig. 2 Pathways linking maternal intake of a nutrient or compound with fetal exposure to that compound. A) Harmful compounds – when harmful compounds enter the maternal circulation, maternal and placental physiology vary in their capacity to shield the fetus from exposure ; B) Essential nutrient – a beneficial resource that the body is not capable of synthesizing *de novo*. Delivery of adequate levels of the resource to the fetus is contingent upon dietary intake and the size of the mother's bodily stores; C) Major macronutrients – internal availability is homeostatically regulated by dietary intake, mobilizing tissue stores and through *de novo* synthesis from precursors. In light of these redundant sources, nutrient delivery to the fetus is often unrelated to the mother's current dietary intake. Maternal regulatory set points that govern nutrient transfer to the fetus may be more effective targets for intervention.

Fig. 3. Redundant sources of glucose within the mother's body. Glucose levels rise after consuming a meal. During a fast, circulating glucose is first maintained by mobilizing the body's modest glycogen stores, which are sufficient to meet glucose needs for several hours. After glycogen stores are depleted, glucose is produced from mobilized amino acids (protein) and glycerol (fats). During prolonged fasts, peripheral tissues use fatty acids for energy and become insulin resistant, conserving glucose for obligate glucose-using functions and tissues. Although the brain generally only uses glucose, during starvation it may also use ketone bodies derived from mobilized fatty acids as an alternative fuel source. The shift to a predominant focus on fat metabolism with prolonged energy deficits reduces glucose requirements and thereby minimizes the need to catabolize protein in tissues and organs to provide substrate for glucose production.

Table 1. Pathways linking maternal exposures to fetal exposures

	Pathway A Harmful compound	Pathway B Essential nutrient	Pathway C Macronutrient
Examples	Metals (i.e lead, arsenic), particulate matter, elevated cortisol	Vitamins (A, C, D, E, K & B complex), minerals (i.e. iron, copper, zinc, fluoride, selenium)	Carbohydrates (i.e. glucose), protein (amino acids), fatty acids
Effect on development	Disruption of normal development, impairment, growth restriction	Co-factors in metabolic processes; deficit leads to developmental impairment	Energy substrate and building blocks of all cells and tissues; primary drivers of growth and metabolic programming
Quantity	Even trace quantities reaching fetus can often impair development	Trace quantities are typically required for healthy development	Large quantities are required
Source	External (toxicant) & internal (maternal hormone)	Diet, maternal stores	Diet, maternal stores and other metabolic precursors
Role of mother/placenta	Minimal to nearly full shielding	Buffering of dietary deficits by maternal stores	Circulating levels are homeostatically maintained with input from diet, extensive bodily stores, and metabolic interconversion between substrate types

Effect of maternal intervention on fetus	Often direct and immediate	If maternal stores depleted, can have direct/immediate effects	Dietary nutrients enter maternal metabolism which dampens direct effects on current pregnancy
Primary intervention targets	Reducing maternal exposure, especially during pregnancy	Supplementing maternal intake during and prior to pregnancy	Supplementing during mother's own early development and across life course

Fig. 1

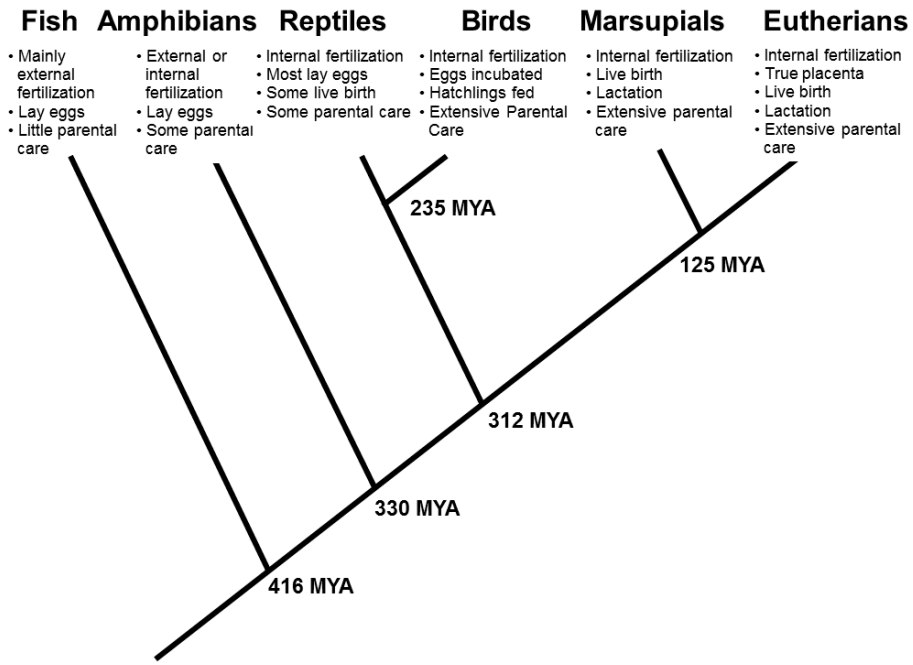

Fish
• Mainly external fertilization
• Lay eggs
• Little parental care
Amphibians
• External or internal fertilization
• Lay eggs
• Some parental care
Reptiles
• Internal fertilization
• Most lay eggs
• Some live birth
• Some parental care
Birds
• Internal fertilization
• Eggs incubated
• Hatchlings fed
• Extensive Parental Care
Marsupials
• Internal fertilization
• Live birth
• Lactation
• Extensive parental care
Eutherians
• Internal fertilization
• True placenta
• Live birth
• Lactation
• Extensive parental care
235 MYA
125 MYA
312 MYA
330 MYA
416 MYA

Fig. 2

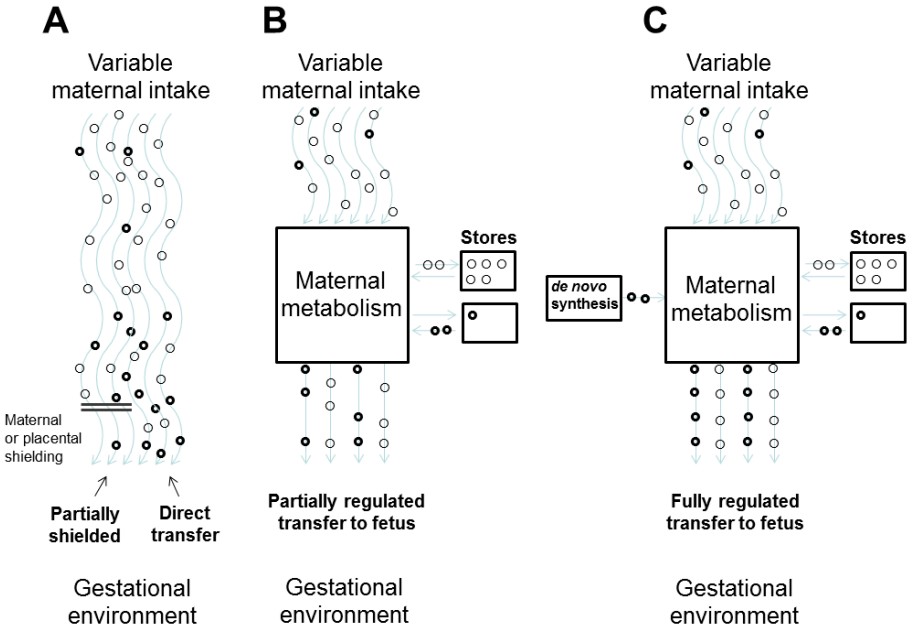
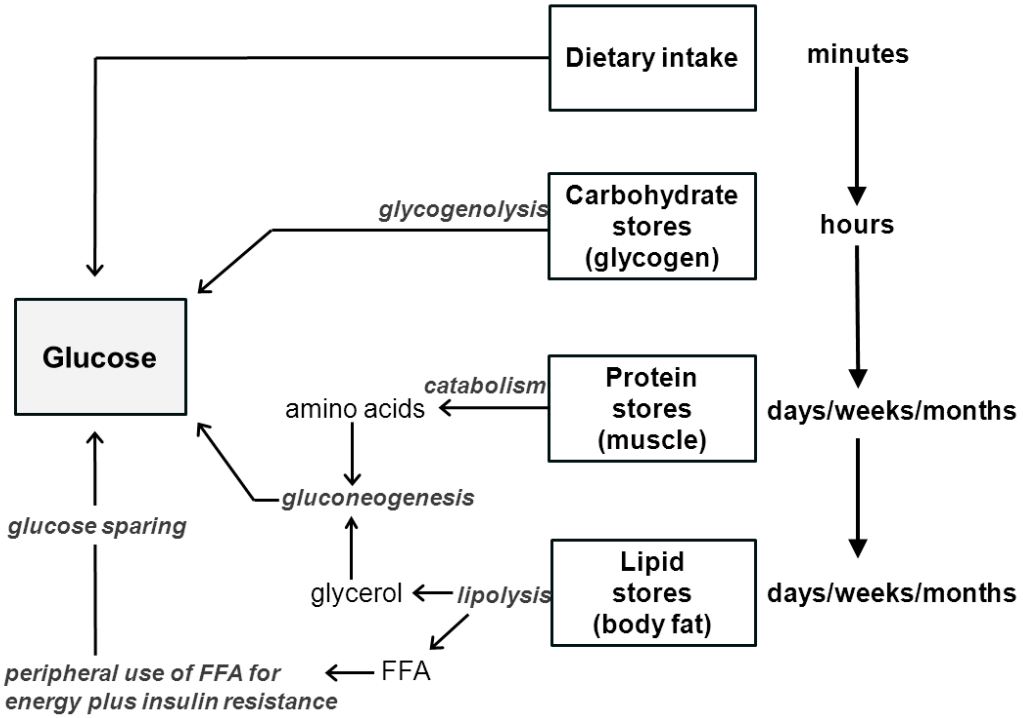

A
Variable maternal intake
Maternal or placental shielding
Partially shielded
Direct transfer
Gestational environment
B
Variable maternal intake
Maternal metabolism
Stores
Partially regulated transfer to fetus
Gestational environment
de novo synthesis
C
Variable maternal intake
Maternal metabolism
Stores
Fully regulated transfer to fetus
Gestational environment

Fig. 3


Dietary intake
minutes
glycogenolysis
Carbohydrate stores (glycogen)
hours
Glucose
catabolism
amino acids
Protein stores (muscle)
days/weeks/months
gluconeogenesis
glucose sparing
glycerol
lipolysis
Lipid stores (body fat)
days/weeks/months
FFA
peripheral use of FFA for energy plus insulin resistance