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The "Early Life" Origins of Obesity-Related Health Disorders: New Discoveries Regarding the Intergenerational Transmission of Developmentally Programmed Traits in the Global Cardiometabolic Health Crisis

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ABSTRACT Popular media reports concerning the causes of the current global obesity pandemic and its related sequelae—the cardiometabolic syndrome—are often couched in terms of dramatic changes in diet and lifestyle around the world; namely, drastically increasing dietary intakes of high energy foods and plummeting levels of daily physical activity—the hallmarks of the so called "nutrition transition." Far less attention is generally drawn to the important role phenotypic plasticity during early life (i.e., "developmental programming") plays in the cardiometabolic health crisis. Recently, however, researchers working within the field of the developmental origins of health and disease (DOHaD) and epigenetics have extended our understanding of the role played by these developmental processes and capacities in health and disease even further by investigating the transmissible nature of developmentally programmed cardiometabolic traits to subsequent generations. In this review, after briefly revisiting the fundamental discoveries of first-generation DOHaD research, I consider how recent discoveries regarding the transmissibility of developmentally acquired traits are providing new insights into the current global cardiometabolic pandemic, and how a better understanding of developmental programming—including transmissibility—are essential for the conceptualization and implementation of public health initiatives aimed at stemming this global health crisis. Am J Phys Anthropol 57:79–93, 2013.

A recent study describing the shifting global burden of disease from 1990 to 2010 reports that global mortality due to malnutrition and infectious diseases, such as tuberculosis, had fallen sharply during the report's twenty year study period, while death from diseases that typically strike in older age and wealthier societies, such as heart disease, showed dramatic increases (Lozano et al., 2012). The report cites improvements in sanitation, childhood immunization programs, and access to food as largely responsible for the shift. As infant mortality and infectious diseases have fallen around the world, however, deaths due to obesity-related diseases have risen sharply; diabetes mortality, for example, doubled during the study period. This, even as malnutrition (due to poor quality diets) remains an intractable problem in much of the economically developing world (FAO, 2012), often existing side by side with (energy) over-nutrition, a situation commonly referred to as the "dual burden of malnutrition" (Doak et al., 2004). These recently identified shifts in mortality reflect, in part, the health consequences of the two co-existing patterns associated with the global "nutrition transition" (Popkin, 2006): one characterized by low quality/low variety diets consisting of starchy, low fat, high fiber foods, and coupled with labor intensive physical activity and stunting (Fig. 1 [Stage 3]); the other by diets and lifestyles marked by highly processed inexpensive foods—high in energy, simple sugars, and saturated fat, while low in fiber—coupled with sharply declining levels of physical activity in both work and leisure settings, and increasing levels of obesity (Fig. 1, [Stage 4]). While the mortality risk associated with more modest levels of adiposity (corresponding to the common body mass index classifications of "overweight/preobese" [BMI of 25–29.9] and "class 1 obesity" [BMI of 30–34.9]) may have been overstated (Flegal et al., 2013), obesity remains a major risk factor for Type 2 diabetes, cardiovascular disease, and hypertension—the major components of the cardiometabolic syndrome. This is problematic given that, according to the World Health Organization, "an escalating global epidemic of overweight and obesity—'globesity'—is taking over many parts of the world" (WHO, 2013), in some cases, paradoxically, even in contexts of "food insecurity" (Velásquez-Melendez et al., 2011).

Obesity was first recognized as an important chronic disease risk factor in the 1970s (Keys et al., 1972) when its association with cardiovascular disease was first noted, and by the late 1990s obesity-related metabolic diseases like Type 2 diabetes were viewed as a major threat to global health (King et al., 1998). In the earliest stages of what would later become known as the global obesity pandemic, many scientists believed that the

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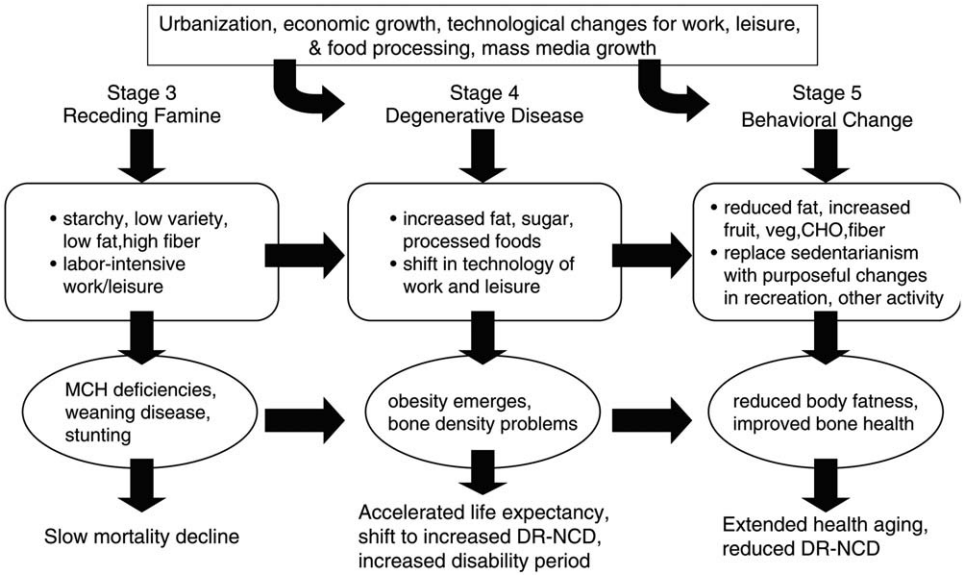

Fig. 1. Stages 3–5 of the nutrition transition. Stage 3 and Stage 4 currently characterize the two dietary, physical activity, and morbidity patterns associated with the "dual burden" of malnutrition. (Reproduced with permission from Popkin, Am J Clin Nutr, 2006, 84, 289–298© American Society for Nutrition).

propensity to accumulate excess body fat (among other dysregulated "thrifty" metabolic features) was strictly determined by the interaction of genotype and "lifestyle" (i.e., dietary and physical activity) risk factors (Neel, 1962, 1982, 1999; Ritenbaugh and Goodby, 1989). The relative frequency of the so called "thrifty genotype" in human populations was thought to vary largely along racial/ethnic lines, and was believed to reflect the different nutritional histories and food economies of these groups over many millennia. Natural selection, it was thought, would have favored thrifty genotypes among human groups experiencing regular and severe "feast or famine" cycles of food availability, due to their hunter–gatherer food economies, harsh local ecology, or lengthy and arduous migrations (Diamond, 1992, 2003). As a result, by the 1980s, several "thrifty genotype" populations including American Indians, Pacific Islanders, and Aboriginal Australians had been identified, and their staggering and growing prevalence of obesity and Type 2 diabetes were seen by most human biologists and geneticists as the direct consequence of their common genetic predisposition for a thrifty metabolism that would preferentially "store fat and spare glucose." The genetic predisposition that once ensured their ancestors' survival, the theory suggested, now predisposed their descendants to obesity and Type 2 diabetes even as they transitioned to obesogenic western diets and lifestyles (Neel, 1999). Twenty years after its original formulation, the thrifty genotype hypothesis was embraced by most members of the scientific and medical communities, and it remains widely cited today[1].

Beginning in the late 1980s, an alternative view to the narrowly construed genetic predisposition model of the thrifty genotype hypothesis emerged, one that could better account for the extent and pace of shifts in global morbidity and mortality patterns that would eventually be recognized as the global obesity/cardiometabolic pandemic. This was the "thrifty phenotype hypothesis," which, by recognizing the importance of critical windows of growth and development in human health and disease during adulthood, offered an alternative explanation for what may only have appeared to be a (genetically) heritable component to obesity and cardiometabolic health problems among the highest risk populations. This ultimately opened the door for a new paradigm for understanding chronic disease risk that moves beyond simplistic (and inadequate) genetic or lifestyle explanations, and instead offers a more integrated approach that incorporates genetic heritability and lifestyle factors such as diet and activity levels into the analysis of human health, but that also recognizes the role played by a powerful capacity in nature—*developmental plasticity*—the ability of a gene to generate a range of possible phenotypes depending on environmental experience.

THE DEVELOPMENTAL ORIGINS OF CARDIOMETABOLIC DISEASE

Although the relationship between deprivation in childhood and increased adult mortality had been noted decades earlier (see Kermack et al., 1934; Forsdahl, 1977), the association between poor maternal diet during pregnancy (expressed as low birth weight offspring) and adult cardiometabolic dysfunction (especially when diet had improved in adulthood) was only being discovered at this time by researchers in England. Drawing on supportive data from both retrospective epidemiological studies and experimental animal research, Hales and Barker's (1992) "thrifty phenotype" hypothesis offered

[1]At the same time, the shortcomings of the model have increasingly become apparent. Although recent genomic research does provide some evidence of population-specific and metabolically-based genetic variants, as predicted by the model, these specific alleles have very small effect sizes. Thus, while some findings from genomic analyses have proven to be consistent with the thrifty genotype model, the "thrifty genes" identified by genetics research appear to fall well short of accounting for population-based differences in cardiometabolic functioning and morbidity/mortality predicted by the hypothesis (see Laland et al., 2010).

an alternative explanation for the population-based (i.e., ethnic/race/class) differences in incidence and prevalence of Type 2 diabetes, cardiovascular disease (and other cardiometabolic disorders [Weiss et al., 1984]) that could not be explained by differences in diet and lifestyle risk factors alone. According to the thrifty phenotype hypothesis, at least some population differences in susceptibility to adult cardiometabolic disease could now be seen as the downstream effect of a fetal developmental response to inadequate nutritional conditions *in utero*—an example of a phenomenon often referred to today as "developmental programming"[2]. The thrifty phenotype hypothesis focused attention on bio-physiological capacities, processes, and consequences associated with phenotypic or developmental plasticity, already well known to life history theorists in evolutionary ecology and comparative biology (Stearns, 1992; West-Eberhard, 2003)—but largely ignored in biomedicine.

This awakening of interest in human developmental plasticity within a biomedical context, a paradigm now referred to as the Developmental Origins of Health and Disease (DOHaD), includes researchers from a broad range of disciplines, and has been especially informative in understanding the etiology of obesity and related cardiometabolic disorders.

The developmental origins of obesity-related cardiometabolic disease: Human cohort studies and experimental animal models

Since the thrifty phenotype hypothesis was first proposed, an impressive number of human cohort and experimental animal studies have confirmed the associations between low birth weight, which is generally viewed as a proxy for the quality of maternal diet during pregnancy/nursing (i.e., the "early" nutritional environment), and offspring growth, body composition, and cardiometabolic capacity/functioning under varying postnatal (e.g., adult) nutritional conditions. Maternal undernutrition has been investigated in the form of total energy (i.e., global undernutrition), macronutrient (e.g., protein), and micronutrient (e.g., iron) deficiencies in both experimental animals (including mice, rats, guinea pigs, rabbits, sheep, pigs, and non-human primates) and humans cohort studies (see Armitage et al., 2004; Alfaradhi and Ozanne, 2011; Li et al., 2011). It has since been noted, however, that while birth weight continues to serve as an easily identifiable proxy for poor maternal nutrition, some forms of prenatal undernutrition do not result in low birth weight offspring (Eriksson, 2006; Morton, 2006). The same can be said for the timing of the maternal dietary restriction. Offspring whose mothers experienced severe dietary restrictions during the Dutch "hunger winter" during early (rather than mid or late) gestation were shown to be at increased risk for cardiovascular disease in adulthood, even though birth weight was unaffected in this group (Roseboom et al., 2001). Indeed, in epidemiological and animal studies the effects of maternal undernutrition on cardiometabolic capacity and function can be seen in adult offspring across the full range of birth weight (Armitage et al., 2004; Morton, 2006). The extremes of the birth weight continuum, however, remain reliable indicators of relative increased risk of adult cardiometabolic dysfunction (Eriksson et al., 2003; Eriksson, 2011).

To date, a tremendous amount of DOHaD research has investigated the life course nutritional sequence identified with the various iterations of the global nutrition transition in developing and developed countries. Most of the early DOHaD research investigated what has been characterized as the "famine" developmental pathway to cardiometabolic disorders, one of two primary pathways associated with the developmental origins of cardiometabolic disease; the other being the "feast" pathway (Benyshek, 2007). The "famine" pathway is characterized by poor nutritional conditions in early life (e.g., maternal undernutrition during pregnancy and while nursing), followed by calorically adequate (or more than adequate) offspring diets years later in adulthood. This life course diet sequence has been noted in rapidly developing and urbanizing countries such as India (Popkin, 2006), and among a wide array of disadvantaged minority populations in developed countries (Benyshek, 2007). The growth and adult phenotype hallmarks of the famine developmental pathway include low birth weight (especially < 2.5 kg), "catch-up" growth and an earlier adiposity rebound in childhood, abdominal obesity, dyslipidemia, hypertension, insulin resistance, and glucose intolerance in adulthood (Eriksson, 2006; Benyshek, 2007).

As the global obesity epidemic has worsened in recent years, more research has also been brought to bear on the "feast" developmental pathway to cardiometabolic disorders, typified by early life environments associated with nutritional excess (e.g., maternal high fat/sugar/energy diets) followed by a high energy/low fiber "western" diet among offspring in adulthood (Benyshek, 2007; Alfaradhi and Ozanne, 2011; Rkhzay-Jaf et al., 2012). Indeed, recent research has shown that the critical factors that comprise the "early" nutrition/metabolic environment for this pathway extend far beyond maternal nutrition during pregnancy and nursing/formula feeding (Dewey et al., 1993; Singhal et al., 2004; Stettler et al., 2005) that have been known for some time. For example, prepregnancy obesity has now been shown to be an independent risk factor for offspring overweight and abdominal obesity (Pirkola et al., 2010). In further support of these findings, a recent clinical study by Guénard et al. (2013) found that, as adults, children born to women after gastrointestinal bypass surgery were less obese with fewer cardiometabolic risk factors compared to siblings born before maternal bypass surgery. Other studies have shown an independent relationship between maternal BMI and offspring BMI, adiposity, and insulin resistance (Whitaker, 2004; Koupil and Toivanen, 2008; Mingrone et al., 2008), and between weight gain during pregnancy and greater offspring adiposity (Reynolds et al., 2010). Obesity during pregnancy has also long been linked to increased risk for developing gestational diabetes, which is itself independently associated with a greater risk of diabetes and obesity

[2]It should be noted that while the quality of the "early environment" most often refers to maternal nutrition during the prenatal/nursing period in DOHaD-oriented studies (as it does for the current review), a steadily expanding list of other early life conditions associated with developmental programming have been identified and investigated, including early exposure to toxicants (e.g., tobacco smoke), geography (e.g., high altitude environments), seasonality, and maternal stress, among others (Gluckman and Hanson, 2006). Nutrition, across the life course, however, remains the primary focus of DOHaD research, not only because of its obvious relevance in the era of the global nutrition transition, but to the essential role food availability and diet has played in shaping human evolution.

among the offspring of mothers with gestational diabetes (Dabelea, 2007; Vohr and Boney, 2008; Poston, 2010).

The nutrition transition sequence associated with the "feast" developmental pathway (pre- and postnatal overnutrition) is increasingly evident in both urban populations in developing countries, and across social strata and minority ethnic boundaries in developed countries (Popkin, 2006), although populations affected concomitantly by the "dual burden" of both under- and overnutrition are being increasingly identified (Grijalva-Eternod et al., 2012). The growth trajectory and adult phenotype associated with the feast developmental pathway includes both low and high birth weight (especially > 4.0 kg), adolescent and adult obesity, dyslipidemia, hypertension, insulin resistance, and glucose intolerance (Boney et al., 2005; Benyshek, 2007; Cnattingius et al., 2012; Yu et al., 2013). In both the "feast" and "famine" developmental pathways, developmentally programmed adjustments to early nutritional conditions represent pathological cardiometabolic traits in the context of their adult nutritional environments, and represent key factors in recent world-wide epidemiological shifts that are not explicitly acknowledged in the "nutrition transition" model, or in current, mainstream efforts to stem the tide of the global obesity epidemic (Gluckman et al., 2011).

Over the course of the last decade, DOHaD research has moved beyond simply identifying the links between maternal under- and overnutrition during pregnancy/nursing, with prenatal/postnatal growth, and the subsequent risk of cardiometabolic dysfunction in the context of a "western" diet and lifestyle. Today, most research investigates the possible causal mechanisms and processes behind these well-established associations. Literature reviews in peer-reviewed journals and edited volumes are now dedicated to developmental origins research which aim to identify any number of regulatory systems, organs, and tissues effected by developmental programming and which play important roles in cardiometabolic functioning, including: hormone regulatory systems (e.g., the secretion and action of key hormones such as insulin and leptin and their neurotrophic actions on appetite regulation and energy metabolism) (Breton, 2013); the hypothalamic–pituitary–adrenal axis (Sloboda et al., 2006); adipose tissue signaling and metabolism (Feng et al., 2013); cellular mitochondria (McConnel, 2006), the structure and function of the pancreas (Reusens et al., 2006; Portha et al., 2011) and vascular system (Napoli et al., 2006; Thompson and Regnault, 2011), and altered placental function (Myatt and Roberts, 2006), among others.

Beyond these important studies, one of the most productive and exciting areas of research into the DOHaD is the investigation of the mechanisms that provide the primary basis for developmental programming: epigenetics.

While the fundamental principles of epigenetics were first proposed by Waddington (1942) well over a half century ago (he also coined the term), the importance of the ideas he first formulated have only recently begun to be fully appreciated. Today, epigenetics is the rapidly maturing study of gene expression—the system that turns genes on and off in plants and animals—and has become a cornerstone in the study of the DOHaD.

Epigenetics works through a variety of mechanisms, including modifications to chromatin (the complex of nucleic acids and histone proteins that make up chromosomes)—such as DNA methylation and histone modification. In addition, changes to noncoding RNAs have also recently been implicated in epigenetic effects (see Lim and Brunet, 2013). While much currently remains unknown, at present, one of the better understood epigenetic mechanisms is DNA methylation (Suzuki and Bird, 2008). Methyl groups are organic compounds that attach to DNA and tell a cell to either use or ignore a particular gene. The process whereby methyl groups adhere to DNA (or to histone proteins that order and compact DNA into structural units) is called methylation—which effectively blocks the attachment of transcription factors and other signaling proteins, thus keeping a gene turned off (Bannister and Kouzarides, 2011). The process of demethylation, by contrast, turns a gene on. Presently, a tremendous amount of research is being focused on the precise role of methylation, histone modifications, and other epigenetic mechanisms in the DOHaD in particular, and phenotypic plasticity in general (see Burdge and Lillycrop, 2010; Thayer and Kuzawa, 2011), and a detailed account of this body of research is beyond the scope of this review. The discussion of epigenetics that follows is instead limited to the latest research implicating the transmission of developmentally programmed traits to subsequent generations.

EPIGENETICS AND THE INTERGENERATIONAL TRANSMISSION OF DEVELOPMENTALLY ALTERED CARDIOMETABOLIC TRAITS

Recent research from both human and animal studies suggests that the effects of developmentally programmed traits are not limited to the directly exposed generation, but may be transmitted to subsequent generations (Francis et al., 1999; Drake and Walker, 2004; Drake and Liu, 2010). In rodent models, many of these traits (e.g., insulin resistance) are induced by direct exposure to early environmental conditions (e.g., poor quality maternal diet), and are then observed in the subsequent "unexposed" (e.g., adequate maternal diet) generations of offspring, although often steadily diminishing in magnitude (Benyshek et al., 2006, 2008). These characteristics suggest a relatively stable and heritable phenotypically plastic response (i.e., epigenetic), rather than one mediated by changes in DNA sequence (i.e., genomic change). Drake and Lui (2009) outline three possible mechanisms that underlie these multigenerational observations: those due to persistent environmental exposures (i.e., generation after generation) during early development; a single "maternal environment" exposure that is nevertheless able to produce a multigenerational phenotype; and epigenetic effects that are transmissible through the germline.

Maternal exposure to persistent environmental conditions

In some cases, developmentally programmed traits may simply be the result of persistent or replicated exposure during critical periods of development generation after generation. Several researchers have suggested that the history of severe socio-political disruptions, prejudice, and economic disadvantage suffered by ethnic/racial minority populations in the US and elsewhere, represent such recurring, multigenerational environmental insults (including chronic food insecurity) that may have led to developmentally programmed traits that contribute significantly to the cardiometabolic health disparities seen in these populations (Wells, 2010,

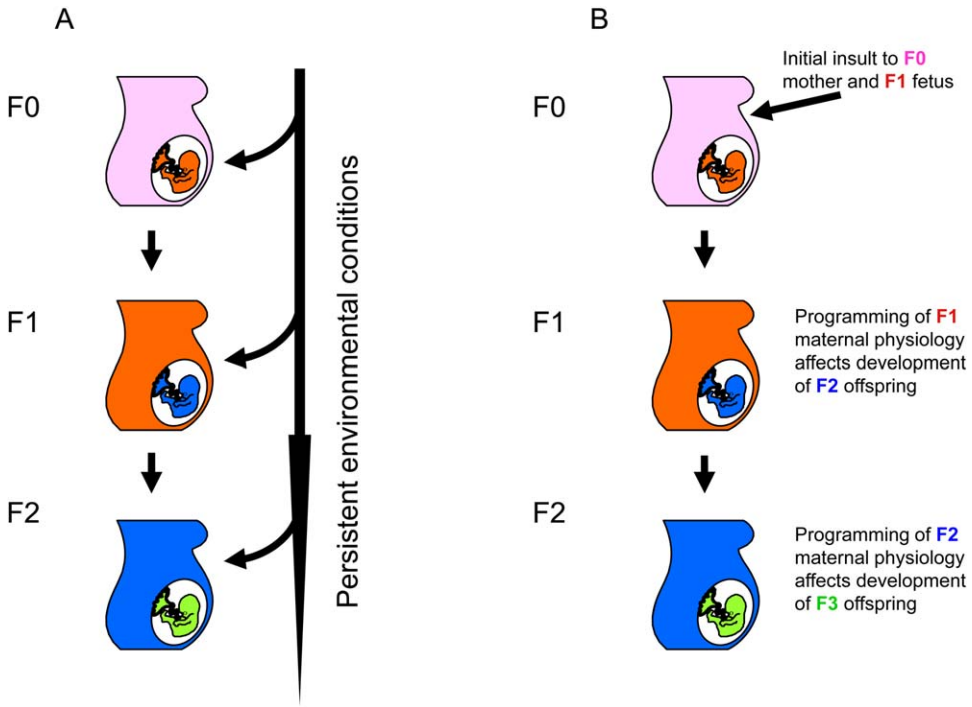

Fig. 2. Mechanisms for the intergenerational transmission of programming effects. (**a**) Persistence of an adverse external environment can result in the reproduction of the phenotype in multiple generations. (**b**) The induction of programmed effects in the F1 offspring following *in utero* exposure (e.g., programmed changes in maternal physiology or size) results in programmed effects on the developing F2 fetus and so on. Reproduced with permission from, Drake AJ, Liu L. 2010. Intergenerational transmission of programmed effects: public health consequences. Trends in Endocrinology & Metabolism 21:206–213. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

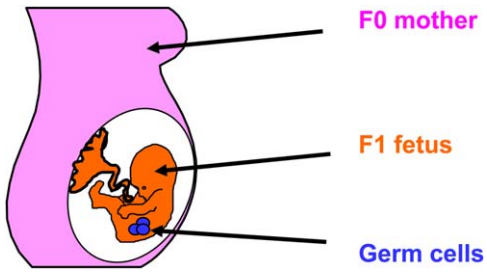

Fig. 3. Multigenerational exposure to an environmental effect. An environmental insult during pregnancy to a mother (F0 generation) might affect not only the developing fetus (F1 generation) but also the germ cells which will go on to form the F2 generation. Reproduced with permission from, Drake AJ, Liu L. 2010. Intergenerational transmission of programmed effects: public health consequences. Trends in Endocrinology & Metabolism 21:206–213.[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2012). Benyshek et al. have argued that the sociopolitical marginalization, severe economic hardship, and nutritional inadequacy common to many Native American communities in the US during the reservation era reflect the environmental conditions consistent with the developmental origins of cardiometabolic disease, and may help explain the Type 2 diabetes epidemic among Native Americans (Benyshek et al., 2001). Kuzawa and Sweet (2009) similarly argue that the disproportionate burden of cardiovascular disease among African-Americans in the US may trace to similar longstanding, adverse social and economic environmental conditions. (Fig. 2a represents this mechanism schematically). Thus, persistent, "external" (e.g., ecological, economic) environmental conditions "program" the same developmentally plastic traits in each successive generation. These same authors have argued that this creates a trend that looks heritable and, therefore, genetically based, but which may be largely developmental and, as a consequence, potentially preventable.

Comparable generational effects have also been demonstrated in experimental animal studies in which environmental stressors are reintroduced to offspring over successive generations. In a multigenerational mouse study, under persistent high fat diet feeding conditions, the F2 male offspring of F0 grandmother and F1 mothers similarly fed a high fat diet during pregnancy and lactation were also shown to be especially susceptible to developing obesity and hepatic steatosis (Li et al., 2012). In another animal study utilizing a rat model of neonatal overfeeding, Plagemann et al. (2009) propose an epigenetic model of obesity and the metabolic syndrome that is underpinned by the developmentally programmed dysregulation of hypothalamic body weight regulation. Based on their findings, they suggest that if left unchecked (by maternal diet modification during the nursing period), the "vicious intergenerative circle" of obesity and cardiometabolic disorders remains closed (2009, p 4974).

Maternal environment effects

Research has also identified the effects of the maternal (i.e., intrauterine) environment that are capable of

producing effects in F1 and F2 generation offspring via developmental programming in response to a single maternal (F0) environmental exposure. Skinner (2008) has proposed that when such developmentally programmed changes are observed only in the generations of offspring that are exposed to the perturbed maternal environment, they should be referred to as a "multigenerational phenotype," and should be distinguished from "transgenerational inheritance" that is transmitted epigenetically via the germline (see below). For example, when a pregnant mother is suffering from a low protein diet, three generations are effectively being exposed simultaneously to this dietary insult; the pregnant mother (F0), her fetal offspring (F1), and the primordial germ cells (PGCs)—the precursors of sperm and eggs—within the F1 fetuses (Fig. 3).

As discussed previously, the links between low birth weight and subsequent adult risk for the cardiometabolic syndrome have been well established in the experimental animal and epidemiological literatures. Smallness at birth has been shown to increase adult risk of cardiometabolic disease, including hypertension/CVD, glucose intolerance, and abdominal obesity (Gluckman and Hanson, 2006; Benyshek, 2007). One of the first "maternal effects" to be studied by researchers was "maternal constraint." The maternal constraint of birth weight has been described in both maternal "supply" and "demand" terms (Gluckman and Hanson, 2004a). Maternal constraint, due to limitations of supply, may be due to decreased uteroplacental blood flow, reduced blood volume, decreased oxygen carrying capacity, prenatal nutrition, teratogens, and short birth intervals; while the demand factors limiting fetal growth include such things as multiple gestations (Hendrix and Berghella, 2008). In a classic crossbreeding study utilizing artificial insemination techniques to cross "miniature" Shetland horses and large, draft, Shire horses, Walton and Hammond (1938) demonstrated that offspring size at birth was primarily determined by the size of the gestating mother; smaller Shetland mothers gave birth to small foals irrespective of parental genotype. Consistent with this experimental finding, a recent epidemiological study analyzing birth weight in Norway between 1967 and 2004 found that genetic factors accounted for only 31% of birth weight variation (Lunde et al., 2007), a finding consistent with other estimates of the genetic heritability of for birth weight (Whitfield et al., 2001). In addition, several other population based studies have investigated the relative strength of the relationships between maternal and paternal birth weight and offspring birth weight, and have found a significantly stronger maternal effect (Coutinho et al., 1997; Magnus et al., 2001; Lunde et al., 2007; Kuzawa and Eisenberg, 2012), although a minority of contrary findings have also been reported (Agnihotri et al., 2008; Veena et al., 2004). Consistent with other studies of intergenerational predictors of birth weight, Kuzawa and Eisenberg also found a stronger maternal effect between maternal and offspring birth weight. Their study did not find that maternal intergenerational birth weight correlations were stronger among taller women, however. As a result, they conclude, they did not find any direct evidence that a history of nutritional insufficiency—as reflected in reduced adult stature—led to increased constraint of offspring birth weight. The authors go on to discuss several possible mechanisms that might explain their findings, including sex-linked genetic effects, indirect genetic, epigenetic, and shared environmental/cultural effects, but emphasize that in every case the mechanism exerted its effect on birth weight for both mother and child *in utero* (Kuzawa and Eisenberg, 2012). Thus, maternal effects that disproportionately affect birth weight are complex, and are likely influenced by a host of factors that extend well beyond adult maternal size and stature.

Human cohort studies have also provided supportive evidence for multigenerational maternal environment effects. In the Dutch "hunger winter" studies mentioned previously, researchers not only found that adult female offspring of mothers exposed to the famine during pregnancy (when official rations fell to as little as 500 kcal/-day), had dysregulated lipid profiles (i.e., cholesterol and triglycerides) compared to unexposed siblings (Lumey et al., 2009), but that their offspring exhibited higher neonatal adiposity, and were nearly 2.0 times more likely to suffer from cardiometabolic disease than the unexposed controls (Painter et al., 2008).

A large number of experimental animal studies have also demonstrated such multigenerational (i.e., F1, F2) effects (see Drake and Liu, 2010). Primarily utilizing rodent models, researchers have shown cardiometabolic programming effects on F1 and F2 animals derived from a single (F0) maternal exposure. Many of these studies subjected (F0) mothers to protein and/or energy restricted diets during pregnancy and/or lactation and observed programmed effects in both F1 and F2 generation animals on insulin sensitivity and glucose tolerance (Martin et al., 2000; Zambrano et al., 2005; Jimenez-Chillaron et al., 2009), birth weight, blood pressure, kidney structure (Harrison and Langley-Evans, 2009), and obesity (Jimenez-Chillaron et al., 2009). Other studies exposed F0 mothers to excess glucocorticoids (Drake et al., 2005), or made surgical alterations to the placenta (Anderson et al., 2006) and observed developmentally programmed effects on birth weight, glucose tolerance, and blood pressure.

Multigenerational effects due to prenatal diet exposures are not exclusively found in restrictive maternal diet models, however. As discussed above, many animal studies investigating the effects of maternal overnutrition and/or obesity prior to conception, during pregnancy, and/or while nursing (i.e., the "feast" pathway) on cardiometabolic structure and function have been conducted (see Rkhzay-Jaf et al., 2012). In instances where the F2 generations have been included in the research design, initial (F0) "excess" maternal nutritional environments have been shown to lead to multigenerational effects on obesity and other cardiometabolic traits. Animal studies have shown that F0 maternal high fat diets during pregnancy influence body size and insulin sensitivity in both F1 and F2 offspring (Dunn and Bale, 2009). Gniuli et al. (2008) report that in mice, a prenatal high fat diet, especially if followed by a maternal high fat diet during the suckling period, induces a "Type 2 diabetes phenotype," which can be directly transmitted to their F2 progeny, even in the absence of additional dietary insults. Indeed, similar to single generation experimental animal studies, the importance of the perinatal maternal nutritional environment alone should not be underestimated. Srinivasan et al. (2008) found that female rat pups fed a high fat formula diet during the suckling period became obese as adults, as did their adult (F2) offspring, even though the F1animals had been maintained on a standard chow diet after weaning.

The mechanisms responsible for the intergenerational transmission of these developmentally programmed

traits remain unclear. It is possible that, at least in some cases, the multigenerational programming effects of both the F1 and F2 generations, as in the studies above, are not due to the same, single maternal intrauterine exposure (e.g., F0 maternal low protein diet) (Fig. 3). Instead, it may be that cardiometabolic dysfunction resulting from the early environment exposure of the F1 female gives rise to an altered intrauterine environment during her own pregnancy that is distinct from the one in which she was gestated (F0), but that also leads to the same developmentally programmed trait in her (F2) offspring. Indeed, some animal models of multigenerational transmission of glucose intolerance from F1 to F2 generations point to such a sequence. Several rodent studies have shown that glucose intolerant, adult F1 animals whose mothers (F0) were fed a low protein diet during pregnancy are insulin sensitive but have insufficient insulin secretory capacity as adults, which in turn results in glucose intolerance (Dahri et al., 1991). The glucose intolerant adult (F2) offspring of these (F1) females, on the other hand (whose F1 mothers consumed a control diet during gestation/lactation), are insulin resistant (rather than insulin sensitive) and hyperinsulinemic (as opposed to insulin deficient) (Martin et al., 2000). In this example, both F1 and F2 generational animals are glucose intolerant, but apparently due to different developmental disruptions in glucose-insulin metabolism, and due to distinct developmental programming pathways in the intrauterine environment. In this scenario, the intrauterine perturbation in one generation causes a metabolic cascade that leads to another (similar or dissimilar) cascade in the subsequent generation, and so on (Fig. 2b).

Importantly, in most of the aforementioned multiple generation animal studies, the research design did not include an F3 generation. Of the two studies that did include an F3 generation in their research design (Drake et al., 2005; Harrison and Langley-Evans, 2009) no evidence of transmission to F3 animals was found. The lack of F3 inheritance might suggest that the observed F1 and F2 effects were due to direct exposure (of the F1 fetus and F2 PGCs) in the (F0) intrauterine environment—lending some support to Skinner's notion of a "multigenerational phenotype" (Skinner, 2008). Both types of developmental programming inheritance may occur (Figs. 2b and 3).

Epigenetic, cardiometabolic traits transmissible through the germline (F3 and beyond)

For developmentally programmed cardiometabolic traits to be transmitted to the F3 generation and beyond (i.e.,"transgenerational inheritance"), information about paternal and/or maternal experience/exposure must be transmitted through the germline, as no direct exposure of the initial insult could exist for F3. Recent research in the field of epigenetic inheritance is revealing how such non-genomic inheritance may be possible in the germline in the absence of alterations in genetic structure (i.e., base pairs of DNA).

While the epigenetic regulation of gene expression has been recognized for some time (e.g., through the relatively rare process of genomic imprinting discovered in the 1980s [Reik et al. 1987]), the possibility and importance of the transgenerational inheritance of epigenetic marks is only now beginning to be widely accepted—and its mechanisms understood. The reason for the delay is that the common understanding in developmental biology and genetics has been that, in each generation, epigenetic marks are "reset" or erased in the PGCs. The general rule of epigenetic germline "erasure" thus allows the genetic regulatory system to be reestablished in each generation, and, until recently, this well-known process cast considerable doubt on the frequency and importance of epigenetic inheritance. New research discoveries, however, have begun to change the standard view. Hackett et al. (2013) recently discovered not only how methylation marks are erased in mouse PGCs (through a process of chemical conversion and subsequent dilution during cell division), but also how some (rare) methylation marks escape erasure, thus providing a potential mechanism for true transgenerational epigenetic inheritance. In another recent landmark study, researchers showed that a small number (~1%) of histone marks—located at key sequences with gene regulatory functions—remain in mouse sperm after cell differentiation, furthering our burgeoning understanding of the mechanisms underlying epigenetic inheritance (Erkek et al., 2013).

Discoveries such as these may provide clues to understanding several epidemiological research findings that appear to reflect such processes at work in human populations. In one fascinating recent study, three birth cohorts born in northern Sweden in the late 1800s and early1900s who experienced a fluctuating food supply were analyzed to see if food availability during the slow growth phase (8–12 years of age) of paternal grandfathers and grandmothers was associated with the risk of diabetes, cardiovascular disease, and longevity in their children and grandchildren. Analysis revealed that low food intake by fathers during their slow juvenile growth phase was associated with the reduced risk of diabetes and cardiovascular disease of sons, while increasing food availability during the paternal grandfather's slow growth period was associated with increased risk for diabetes among grandsons (Kaati et al., 2002, 2007). Paternal grandfathers' food supply during the slow growth phase was associated with longevity in grandsons, while paternal grandmothers' food supply during fetal/infant life or the slow growth period was associated with granddaughters' longevity (Pembrey et al., 2006).

In another recent study, researchers set out to investigate the relationship between paternal obesity and DNA methylation patterns for a known obesity susceptibility gene. In this study, Soubry et al. (2013) sought to determine whether associations exist between parental obesity and DNA methylation at the insulin-like growth factor II (IFG-II) gene—known to play a role in the risk for obesity, gestational diabetes, and some forms of cancer—in their children. DNA from the umbilical cords of the newborn children was analyzed for its methylation patterns and compared to information about parental obesity before conception. The results showed that DNA methylation at the IGF-II gene in the offspring of obese fathers was significantly lower than in the children of non-obese fathers, providing some additional evidence for the paternal transmission of epigenetic effects associated with obesity, to offspring.

Similar transgenerational effects have also been modeled in some, but not all, animal studies. Chewing betel nuts (which contain nitrosamines—a known toxin) is a popular practice throughout India, Southeast Asia, and Polynesia, and is known to increase the risk for the cardiometabolic syndrome (Lin et al., 2008). In an effort to

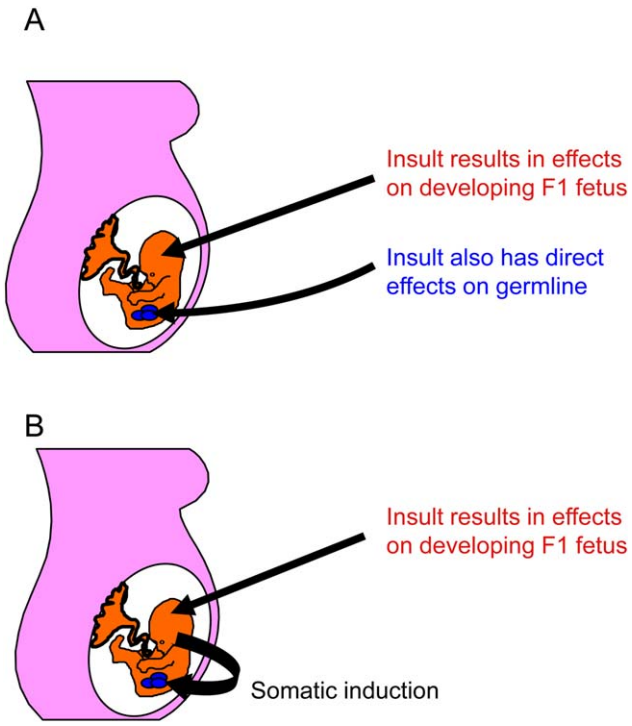

Fig. 4. Transmission of epigenetic effects through gametes. (**a**) An environmental exposure affects the developing F1 fetus, but also has direct effects on the developing germ cells which form the F2 generation. (**b**) Alternatively, effects induced in the developing F1 fetus can be transmitted to the germ cells which will form the F2 generation (somatic induction). Reproduced with permission from, Drake AJ, Liu L. 2010. Intergenerational transmission of programmed effects: public health consequences. Trends in Endocrinology & Metabolism 21:206–213. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

model the effects of betel nut consumption on blood glucose across three generations of experimental animals, Boucher et al. (1994) fed young mice betel nut in their standard chow for 4–6 days. Glucose tolerance tests were administered to the F0 animals in adulthood. Betel nut consumption was found to significantly increase the risk of developing glucose intolerance in F0 animals, and in the F1 and F2 offspring of males that consumed betel nuts in their chow before mating.

In another rodent study, researchers investigated the effects of a (F0) maternal high fat diet on offspring body size and glucose-insulin metabolism over three consecutive generations through both the maternal and paternal lines. Results of the study revealed that both F1and F2 generation animals were insulin resistant and had increased body length, compared to control animals, even though they were consuming control diets, and that these effects were seen in both the paternal and maternal lineages. In the F3 generation, animals were no longer insulin resistant, but females inherited increased body length through the paternal line (Dunn and Bale, 2011).

In another three generational study with rats, Benyshek et al. (2006) found that feeding F0 rat dams a low protein diet throughout pregnancy and lactation resulted in reduced insulin secretory capacity in F1 animals and insulin resistance in their F2 offspring through the maternal line. F3 generation males also exhibited insulin resistance compared to controls, although it was of diminished severity compared to F2 animals. As in the previous study, the alterations in glucose-insulin metabolism in the F1–F3 generations were the result of a single maternal dietary manipulation in F0 females. All animals were fed control diets after weaning, and pregnant F1 and F2 dams were similarly maintained on control diets throughout pregnancy and lactation, indicating that at least some epigenetic alternations associated with insulin glucose metabolism survived germline epigenetic mark erasure by the F3 generation.

Other experimental animal studies that have shown evidence of inherited epigenetic effects in the F2 generation,have found no evidence of transgenerational effects in F3 animals. These investigations have included studies that subjected pregnant F0 females to glucocorticoid overexposure (Drake et al., 2005), and low protein diets during gestation (Harrison and Langley-Evans, 2009).

The presence of F3, transgenerational epigenetic effects in some studies but not others requires explanation. As mentioned previously, the lack of F3 effects in some studies may reflect their modeling of Skinner's "multigenerational phenotype" (2008) that is due to direct exposure (Fig. 3), while the experimental conditions in other studies allowed researchers to capture "transgenerational inheritance" through the germline, due either to direct effects on the developing germ cells *in utero* (Fig. 4a), or indirectly via "somatic induction" of the developing fetus (Jablonka and Raz, 2009) (Fig. 4b). Alternatively, it is possible that an epigenetic threshold effect which calibrates to the type, intensity, duration, and/or timing of the initial F0 exposure determines the durability of epigenetics marks undergoing intergenerational epigenetic reprogramming, and in some studies this threshold was reached, while in others it was not. Relatedly, it may be that under some conditions, epigenetic marks that initially accumulate in the F1 and manage to evade complete epigenetic erasure in F2, are adequately "diluted" or erased in subsequent generations such that the phenotypic traits are no longer identifiable. This might explain the diminution of programmed effects seen in some transgenerational studies from F2 to F3 (e.g., Benyshek et al., 2006). Whatever the reason(s), a clear explanation of the mechanistic differences between multigenerational phenotypes and epigenetic transgenerational inheritance awaits future, multiple (3+) generation studies, of which there are very few to date.

THE INTERGENERATION TRANSMISSION OF DEVELOPMENTALLY PROGRAMMED CARDIOMETABOLIC TRAITS: IMPLICATIONS FOR INTERVENTIONS

In the context of the developmental origins of cardiometabolic disease reviewed here—including its intergenerational transmission—the rapidly shifting dietary patterns world-wide (Popkin 2006), and the concomitant global obesity pandemic (WHO, 2013) that exists alongside persistent undernutrition and stunting (FAO, 2012), are sobering realities indeed. The current global trends unquestionably present major challenges to public health professionals and policy makers. The question is; can the principles and observed effects of the developmental origins of cardiometabolic disease be leveraged to slow or reverse the currents trends?

During the twenty years since the "thrifty phenotype" hypothesis was first proposed, many researchers have

seized on what the developmental programming of cardiometabolic traits might mean for public health interventions. If increased risk for Type 2 diabetes and cardiovascular disease can be traced to the hijacked capacity for developmentally programmed adjustments made early life, then there may be great promise in "reverse engineering" the same capacities (e.g., by optimizing maternal nutrition during pregnancy) in order to improve fetal growth and health outcomes via primary prevention interventions (Benyshek et al., 2001; Gluckman and Hanson, 2004b; Forrester, 2006). Indeed, the DOHaD literature is replete with references to the possible development of such intervention programs during pregnancy and the early postnatal period as a means of cardiometabolic disease prevention.

But evidence from dozens of observational studies and randomized controlled trials supplementing maternal diet during pregnancy with targeted macro- and micronutrients in efforts to improve fetal growth and maternal and child health outcomes have been mixed, and with only very modest improvements in the successful interventions (see Merialdi et al., 2003; Morton, 2006; Kramer and Kakuma, 2010; Stein et al., 2003). While there is reason to believe some of these approaches do hold some promise (Behrman et al., 2009), one of the likely reasons for their limited and modest successes thus far are due to the species-specific timescales on which the developmental pathways reviewed in this article, are calibrated. As Kuzawa and Thayer point out, the "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 small effects in humans" (Kuzawa and Thayer, 2011, p 229). The authors go on to show that differences in body size, lifespan, and reproductive strategy of various mammalian species (e.g., rodents, guinea pigs, sheep, and humans) exert significant influence on the magnitude of developmentally programmed effects due to early life environments (e.g., maternal dietary restrictions during pregnancy).

Acknowledging these differences provides a serious challenge to one of the central tenets of one of the most influential concepts in developmental origins research, the "predictive adaptive response" (PAR)—which posits poor health outcomes when early life and adult environments are "mismatched" (e.g., poor maternal nutrition during pregnancy followed by overnutrition in adulthood) (Gluckman and Hanson, 2004c). Although there is a great deal of epidemiological and experimental animal evidence that is consistent with this PAR concept, several authors have challenged the notion that environmental cues during early life (e.g., maternal nutrition during gestation) are reliable predictors of future adult environments for long-lived species like humans (Kuzawa, 2005; Kuzawa and Quinn, 2009; Wells, 2007). Instead, these authors argue, the entire maternal phenotype—expressed as nutrients, hormones, metabolites, and growth and immune factors, communicates an integrated and averaged signal of generations of matrilineal experience that is transmitted to the developing offspring through the placenta and lactation during critical periods of development. If this view is correct, and the maternal/paternal epigenomes, along with other aspects of the maternal phenotype during critical periods of early life do transmit longer term (i.e., multigenerational) information that influences developmental programming, this in turn is likely to have important implications on the structure and content of interventions aimed at improving adult health.

One possibility might have future interventions designed to be sustained over longer periods of time and/or target multiple ages across reproductive life in order to gain more leverage for efforts to improve birth weight and other neonatal and maternal health outcomes that have proven to be so refractory to short-term maternal diet supplement interventions. If, as Kuzawa and others have suggested, an integrated signal that reflects longer-term nutritional conditions is transmitted to offspring during critical periods in early life (Kuzawa, 2005; Wells, 2007; Kuzawa and Thayer, 2011), perhaps a more sustained intervention—possibly even targeting multiple generations in high risk communities—may prove effective. Precedents for this kind of approach do exist, and have yielded promising results (Behrman et al., 2009). In nutritional supplement interventions for women, this might also include the period immediately prior to conception, and during lactation, as well as throughout pregnancy. Innovative interventions might also consider targeting boys' nutrition during the slow growth phase of preadolescence, as well as interventions aimed at nutrition and body weight/composition among fathers in the preconceptual period. Other studies might focus on critical elements of metabolism—energy expenditure and physical activity during multiple sensitive periods of development. Little is known about how effective such interventions might be with humans, but there is reason to believe they hold significant potential based on recent animal modeling (Huber et al., 2009; Miles et al., 2009).

Future efforts aimed at prevention might also seek to intervene with exogenous hormones and growth factor treatments that might provide shortcuts to the type of long-term trend signals being transmitted to offspring during critical periods of early development (Kuzawa and Thayer, 2011). Research with animal models has provided important insights on how this might be accomplished (Vickers and Sloboda, 2012). Leptin is a protein hormone secreted by adipose tissue that plays an especially critical role in regulating long-term energy balance, appetite, and metabolism. Research with rodent animal models has shown that administration of leptin during neonatal life normalizes many of the cardiometabolic abnormalities associated with the maternal low protein, growth restricted phenotype (Vickers et al., 2005), and in some studies has been shown to protect offspring of normally nourished dams from developing diet-induced obesity (Stocker et al., 2007; Pico et al., 2011). Animal studies have also provided evidence that maternal supplementation with methyl donors (e.g., folic acid and choline) improves some features of developmentally programmed cardiometabolic abnormalities associated with maternal low protein diet restriction (Lillycrop et al., 2005; Bai et al., 2012). Still other animal models have investigated the effects of administering the glucagon-like peptide analogue Exendin-4 on the diminution, resolution, and prevention of developmentally programmed cardiometabolic abnormalities, with some promising early findings (Park et al., 2008; Raab et al., 2009). Whether or not the findings from these animal model treatment studies will provide the conceptual and empirical basis from which analogous interventions might be developed for humans remains an open question. The results of these studies do provide some reason for optimism, however.

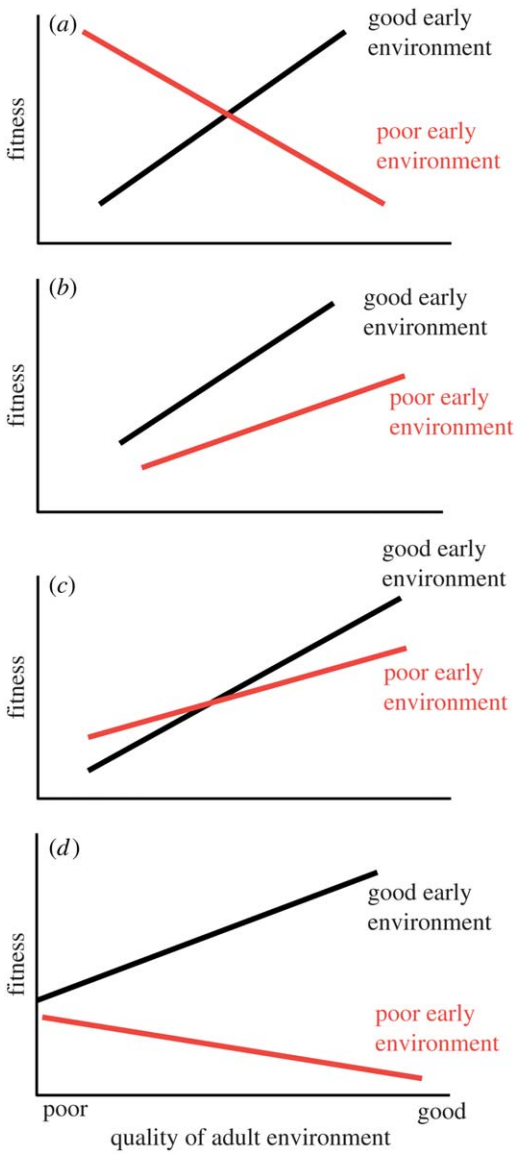

Fig. 5. Developmental programming hypotheses. (**a**) PAR. Here the adult environment changes in relation to levels of a particular parameter, e.g. food resource low to food resource high. Lines are shown for individuals developing at the low and high ends of the environmental spectrum. For those developing in both good and poor environments, fitness is the highest when the adult and developmental environments "match". (**b**) Silver spoon effects. Here there is no environmental matching. Fitness always improves with improvement in the adult environment, and those born in poor conditions always have lower fitness than those born in good conditions. (**c**) Thrifty phenotype. Fitness always increases with resources in the adult environment, but when these are low, those born in such an environment have a fitness advantage over those not born in such conditions. (**d**) A combination of the silver spoon and PAR. For both those born in the good environment, fitness improves as the quality of the adult environment improves; for those born in the poor environment, fitness declines as the resources in the adult environment increase; however, whatever the adult environment, those born in the good environment always have higher fitness. (Reproduced and modified with permission from Monaghan, Philos Trans R Soc Lond B Biol Sci 2008, 363:1635–1645; ©The Royal Society.) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The need for research capable of discriminating between competing developmental programming hypotheses

The ultimate success of DOHaD-oriented interventions will also depend on gaining a better understanding of the fundamental evolutionary principles on which developmental programming rests. Beyond continuing efforts to refine existing primary prevention efforts and develop new interventions based on encouraging animal models as outlined above, there is also a need to produce clinical, epidemiological, and experimental (animal) data that can help distinguish between competing hypotheses, as DOHaD researchers strive to gain a clearer understanding developmental programming evolutionary underpinnings. Currently, there is no shortage of evolutionary hypotheses that provide testable and predictive frameworks with which such an understanding might be achieved. One of the most influential and widely cited of these is the PAR hypothesis, mentioned above.

The PAR hypothesis, like its predecessor, the thrifty phenotype hypothesis, proposes that the cardiometabolic abnormalities associated with global obesity pandemic are actually misplaced adaptations. For example, for most proponents of the thrifty phenotype hypothesis, developmentally programmed traits are adaptations made by the fetus that are variously identified with improved survival during fetal life (Hales and Barker, 1992), infancy (Kuzawa, 2005) or childhood (Wells, 2003, 2007), but which, under altered adult conditions, lead to increased cardiometabolic morbidity and mortality. PAR hypothesis proponents also assume adaptations are made by the fetus, but these adaptations that are calibrated to "forecasted" or expected conditions in adulthood (Gluckman and Hanson, 2004c) that do not materialize. But as Ellison (Ellison, 2005; Ellison and Jasienska, 2009) has astutely asked: "how do we know 'thrifty' cardiometabolic developmentally programmed traits represent adaptations?" It is also possible they reflect nothing more than the effects of throttled development (i.e., "constraint"), or broken physiology (i.e., "pathology"). To be sure, there are several hypotheses capable of accounting for the bulk of DOHaD-oriented epidemiological, clinical, and experimental animal study findings—largely because nearly all of this research has focused on the original "thrifty phenotype" sequence—poor conditions in early life followed by good or "rich" environments in adulthood (Fig. 5). These include the "PAR hypothesis" (Fig. 5a), the "silver spoon hypothesis" (Fig. 5b), the "thrifty phenotype hypothesis" (Fig. 5c), and a combination of the PAR and silver spoon hypotheses (Fig. 5d). The silver spoon hypothesis, for which there is considerable evidence from studies in evolutionary biology, is a "constraint" hypothesis (Monaghan, 2008). Alternatively, Figure 5d might conceptually represent a "pathology" hypothesis. As can be seen in Figure 5, these hypotheses make very different predictions regarding "fitness" (i.e., morbidity/mortality) based on early life and adult conditions. Indeed, the few studies that have tested these alternative hypotheses—especially those investigating the effects of poor conditions in both early and later life among human populations—have provided conflicting results (Forrester et al., 2012; Hayward et al., 2013). Until more work is done, and researchers are able to devise additional new and innovative ways of explicitly testing these alternative models, the evolutionary basis of the developmentally programmed traits associated

with the cardiometabolic pandemic will remain unknown. And until we have a better understanding of the evolutionary basis on which developmental programming rests, devising and implementing interventions capable of reversing the global cardiometabolic health crisis will likely remain out of reach.

New sources of DOHaD data

Generating the data necessary to distinguish between current (and future) hypotheses that might illuminate the fundamental evolutionary principles that shape developmental programming will also require fresh and refined methods and data sources. There are now likely important new opportunities to study captive primates (and perhaps even household pets), as the same obesity-related health problems facing humans are increasingly evident in zoos and among other captive animal populations (Natterson-Horowitz and Bowers, 2013). These captive zoo populations—especially primates—may present unique opportunities to track and study the intergenerational transmission of obesity-related, cardiometabolic disorders among these animals and subsequent generations of their offspring in captivity.

While laboratory animal studies can also provide profound insights into the DOHaD, too many questions remain about precisely how, and under what circumstances, developmental programming differs in humans compared with other animal species. As a consequence, better methods and new data sources are needed to further explore the unique dimensions of the developmental programming of cardiometabolic abnormalities in humans, and its intergenerational transmission.

Currently, much of what we know about the developmental programming of cardiometabolic disease in humans come from marginalized populations suffering from recent or ongoing social and economic disruptions and/or undergoing rapid lifestyle transitions (Benyshek, 2007; Kuzawa and Sweet, 2009; Wells, 2010). This presents significant challenges to DOHaD researchers working in these populations and communities. While longitudinal, prospective cohort studies remain an incredibly powerful research design for DOHaD research, vital information about developmental programming is also rooted in the past. New and refined (already-established) methods to assess developmental program retrospectively are currently needed.

One critical challenge to retrospective DOHaD studies is growth assessment. Birth weight records and recall have been used extensively and to great effect in developmental programming studies, but more detailed and comprehensive markers of early growth are required. Several innovative approaches have recently been developed and utilized, and might be extended and refined further. Kahn et al. have pioneered an early growth measure that utilizes finger-tip ridge counts differences to assess human growth in the first weeks of pregnancy (Kahn et al., 2001, 2008) in the service of developmental programming studies, and several researchers have used leg length and body proportion to retrospectively assess childhood growth (see Bogin and Varela-Silva, 2010).

As the field of epigenetics matures, there may also be new opportunities to do retrospective studies with "banked" epigenomic information, much the same way that birth weights and other measurement records have been utilized in DOHaD research in the past. Guthrie cards are a potential resource for retrospectively analyzing epigenetic marks established *in utero* in regions found to be associated with disease in affected individuals (Beyan et al., 2012) and that may change over the course of person's lifetime. Once routinely collected by hospitals in the US and UK, Guthrie cards contain dried blood spots from newborns taken shortly after birth which were originally used to screen for preventable diseases, and remain kept in storage in many hospitals today (Pollitt, 2009). According to a study conducted by McEwen and Reilly (1994), at least eight states in the US have a policy of storing Guthrie cards for over 10 years, three states between 20 and 25 years, and, based on the results of their research, 17 out of 50 US states would potentially grant access to researchers, provided IRB approval and informed consent are obtained. Although there are many potential challenges with using Guthrie cards for retrospective epigenetic research (e.g., controlling for differences in collection methods and storage conditions, as well as informed consent issues, etc.) this remains a potentially viable research method strategy and data source. Assuming proper informed consent can be obtained, Guthrie cards, like other biological materials that may have been saved and stored since birth (e.g., cord blood, dried blood spots, and encapsulated placenta by women engaging in the practice of placentophagy [Selander et al., 2013]) may offer new possibilities to DOHaD researchers despite having been originally collected and stored with a different purposes in mind (Benyshek, 2010).

Finally, although biomarkers offer a potentially rich source of information on some aspects of the early life environment, they stand weak on their own. Because of this, there exists a need for retrospective information from adult subjects on experiences and habits over the course of their (and possibly their parents' and grandparents') lifetimes. One of the most important (and surprisingly least-studied) types of data in this category is retrospective dietary information—particularly during and around the time of pregnancy. Even though a handful of studies have addressed the reliability of remote recall of diet ($>$ 10 years) and found correlation coefficients to be at least as good as recall of diet from the recent past ($<$10 years) in some cases (see Friedenreich et al., 1992 for a review), very few studies have specifically addressed the ability of women to recall diet from a past pregnancy (Bunin et al., 2001; Bosco et al., 2010). While more validation studies are required, the potential value of a reliable means to retrospectively assess individual diets (rather than relying on population based diet data, such as historical crop yield records) is undeniable. Work in this area has predominantly been limited to nutritional scientists conducting studies with general mixed-ethnicity populations in the US and UK, with little input from DOHaD-oriented anthropologists working in small-scale communities, many of which are the very populations currently in the midst of the nutrition transition suffering the most staggering increases in obesity and cardiometabolic disorders. Future interventions, capable of breaking the intergenerational transmission cycle of cardiometabolic traits associated with the global obesity pandemic will likely only materialize as new methods and sources of data in DOHaD research are developed in service of this goal.

SUMMARY AND CONCLUDING REMARKS

Recent research in the field of the DOHaD has revealed that there is much more to the global obesity/

cardiometabolic syndrome pandemic than "thrifty genes," western diets, and sedentary lifestyles. We now know that environmental cues acting during critical windows of development can program physiology in ways that predispose to cardiometabolic disease in the context of the global nutrition transition. In addition, we are now learning that some of these programmed effects can be transmitted (non-genomically) to future generations of offspring. Ultimately, devising and implementing successful interventions to combat the growing health crisis of cardiometabolic disease will require a better understanding of the role early life events and environments play in the current pandemic. But it will also require a more complete understanding of how the past experiences and conditions of paternal and maternal ancestors also shape—and even help perpetuate—the crisis through "epigenetic memory." Ironically, it may be that the basis of the transgenerational developmental processes that help shape the current cardiometabolic health crisis may also provide the means by which it can be effectively prevented.

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