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The Developmental Origins of Health and Disease

Implications for Paleopathology

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Abstract

The Developmental Origins of Health and Disease (DOHaD) hypothesis evolved from earlier research by Barker and colleagues in the 1980s, which demonstrated a link between early life adversity and increased risk of cardiovascular disease (CVD) in adulthood. Since then, a growing body of work has emphasized the significance of the first 1,000 days of life (from conception) for disease risk in later life, including stroke, diabetes, CVD, osteoporosis, and mental health. This period is conceptualized as a particularly sensitive window of developmental plasticity, with exposure to environmental stimuli during this time resulting in potentially adverse adjustments to an individual's phenotypic trajectory. The integration of DOHaD within bioarchaeological and paleopathological analysis has heralded a conceptual shift away from an exclusive emphasis on proximate causes of disease and toward a greater consideration of life histories and intergenerational factors. This chapter summarizes some of the key features and applications of DOHaD for bioarchaeology, including theoretical debates, and implications of this approach for our understanding of body/society interactions in the past.

Introduction

Seminal epidemiological research by Barker and colleagues in the 1980s provided evidence linking low birth weight with chronic disease risk in adulthood, including cardiovascular disease (CVD), type 2 diabetes, stroke, and mental health. These results indicated that adverse factors relating to the intrauterine environment were having life-long impacts on morbidity and mortality. Since then, an overwhelming body of evidence has supported these findings, leading to what has now become known as the Developmental Origins of Health and Disease (DOHaD) hypothesis. This work characterizes the first 1,000 days of life (from conception) as a particularly sensitive window of developmental plasticity, in which exposure to environmental stimuli can result in adjustments to phenotypic trajectories that increase disease risk (Barker et al., 2002; Gluckman & Hanson, 2006; Barker, 2007).

The plasticity of the human skeleton and phenotypic modifications in response to environmental exposures have long been a central concern for evolutionary anthropologists and bioarchaeologists (Temple, 2019, McPherson, 2021). Research in evolutionary anthropology has focused on plasticity as an adaptive response to social and ecological circumstances to improve biological and reproductive fitness. Within evolutionary anthropology, there is an emphasis on life history trade-offs, referring to the reallocation of energy during periods of stress between the key functions of growth, maintenance (e.g., immune activity), and reproduction (McDade, 2003). Any disruption to homeostasis via disease or malnutrition will result in shifts in energy from one function to another, such as from growth to immune activity (Bogin et al., 2007). Such trade-offs are energetically costly and can result in longer term disease risk; for example, longitudinal studies of growth have demonstrated a relationship between growth disruption and reduced life expectancy, even in those who had experienced catch-up growth (Barker, 2012). DOHaD has strong synergies with life history theory but places a focus on the pathological consequences of plastic responses to adversity (see McKerracher et al., 2020). Both approaches are concerned with the entangled and reactive nature of bodies and their spatial, temporal, and socio-ecological niches.

The emphasis on life history and the life course within paleopathology and bioarchaeology is important because there has long been a tendency to interpret disease in terms of immediate casualties alone. For example, the presence of enamel defects or delayed growth in the skeleton of a young child is often interpreted as direct evidence of weaning-related hazards, with little or no consideration of maternal health. In his seminal paper, “Prisoners of the Proximate”, the epidemiologist McMichael (1999) described such a focus as a constraining approach within his own discipline. The integration of DOHaD within paleopathological analysis has heralded a conceptual shift away from proximate factors alone and toward a life course perspective (Gowland, 2015; Agarwal, 2016). Because DOHaD is

concerned with intrauterine development, a time when one body is entwined with another, it is also necessary to extend the temporal scale of risk intergenerationally. DOHaD has highlighted the hitherto unexplored potential for direct intergenerational impacts of socio-ecological adversity from parents to grandchildren: a female fetus will produce all the gametes she will have in her lifetime whilst in utero; therefore, stress affecting a pregnant woman could directly impact three generations (Barker, 2012). This has implications for the way in which paleopathologists consider, for example, the intergenerational impact of catastrophic events such as famine in the past.

There are a variety of mechanisms underpinning developmental plasticity in response to adversity, but one garnering much of the attention in recent years is epigenetic change (affecting gene expression rather than gene sequence). What is often overlooked within the DOHaD paradigm are the structural, cultural, and behavioral determinants that perpetuate over generations and their contribution to epigenetic regulation within populations. Environmental cues may trigger epigenetic alterations, which can affect developmental trajectories and have direct intergenerational impacts (Kuzawa, 2005). Normal temporal regulators may become hyper- or hypo-regulated due to these environmental triggers. Epigenetic research reveals how a single genotype can be expressed in phenotypically diverse ways in response to stimuli during development. Adverse environments, including poor diet, exposure to toxins, and stress (trauma), can cause epigenetic changes that alter vulnerabilities to disease in later life and between generations. Subsequently, DOHaD requires paleopathologists and bioarchaeologists to consider the effects of longer term intergenerational adversity as a source of hidden heterogeneity in frailty (McPherson, 2021). DOHaD therefore speaks to well-established debates within bioarchaeology regarding the "osteological paradox" (Wood et al., 1992; DeWitte & Stojanowski, 2015). The inter-weaving of social and biological biographies across generations also requires a theoretical shift in our conceptualization of the life course, and individualized, bounded biologies (Gowland, 2015; Gowland & Newman, 2018). If socio-ecological adversity affecting our grandmother (and mother) has impacts for our own metabolic regulation and disease risk, when does our biography begin and hers end?

Bioarchaeologists are perennially concerned with the genes, environment, and culture triad (Lewontin, 2000); the inter-relationship between these, and how they manifest in the hard tissues of the body. DOHaD likewise emphasizes the centrality of environment and culture in epidemiological research, providing a more integrated paradigm that challenges fundamental disciplinary divides regarding the body and society. Bioarchaeologists have always worked at the interface between culture and biology; therefore, transcending disciplinary divides is comfortable ground. One method to study the socio-ecological effects of our ancestors' past and present health

outcomes is by using the model of "Ethnogenetic Layering". This is a non-traditional race model that observes the ancestral, genomic, environmental, cultural, geo-spatial, and behavioral implications of a population. By localizing populations and creating a holistic view of human variation, the explicit details contributing to a population's health outcomes can be observed and effectively treated. The efforts of studying human variation in a localized fashion will advance epigenomic research over time (Jackson, 2008). Contextualized, "local biologies" (referring to the material embedding of bodies geographically, ecologically, temporally and culturally, Lock, 1993) have long been important for the interpretations of past skeletal remains (Appleby, 2019). Such a nuanced approach is also essential for interpreting evidence within a DOHaD framework – there never has been, nor can be, a "one size fits all". This is because history is becoming increasingly important, and a consideration of different temporal scales – evolutionary, developmental, generational, and biographical – are essential to our analysis of disease and what Krieger (2013) has referred to as the emergent "embodied phenotype". The more recent sociological turn within paleopathology and an increasing focus on biographical narratives, means that DOHaD aligns well with existing research approaches and imperatives (Agarwal, 2016). This chapter will explore and summarize some of the key features and applications of DOHaD for paleopathology and bioarchaeology, including theoretical considerations regarding the life course, and the inter-relationship between bodies and societies in the past.

DOHaD: Origins of a Hypothesis

Barker and colleagues' research initially aimed to understand the geographical pattern in CVD within the UK (Barker & Osmond, 1986; Barker et al., 1989). CVD prevalence increased during the 20th century in tandem with increasing national prosperity. Paradoxically, however, the highest rates were amongst individuals living in the most deprived locations. Barker and colleagues' research identified a geographic correlation between the frequency of CVD and areas with high infant mortality six decades previously (Barker & Osmond, 1986; Barker et al., 1989). Other relevant risk factors (e.g., cigarette smoking, or diets high in saturated fats) presented no similar correlation, leading to the novel explanation that factors affecting intrauterine development were pre-disposing people to heart disease in later life (Barker & Osmond, 1986). These findings built on previous research in other countries that had found associations between risk of CVD and childhood poverty (Forsdahl, 1977; Buck & Simpson, 1982).

Since these pioneering studies, the link between low birth weight and coronary heart disease has been established around the world (Gluckman & Hanson, 2006; Heindel & Vandenberg, 2015). Further work by Barker and colleagues' (1989) also highlighted connections between low birth weight and life expectancy, leading to the conclusion that factors affecting intrauterine growth and development, rather than the postnatal environment, were key to life-long health (Barker, 2007). This work has had its detractors; one of the key arguments being that association is not causation, and the range of confounding risk factors that cannot be adequately controlled for in epidemiological studies such as these (Schulz, 2010). Since this early research, however, a wealth of other evidence has demonstrated similar links between intrauterine adversity and chronic disease, including, for example, insulin resistance, obesity, and high blood pressure (Gluckman & Hanson, 2006; Wadhwa et al., 2009). This work then became known as the *Fetal Origins of Adult Disease* hypothesis (Barker, 1995), otherwise referred to as the "Barker hypothesis". Sensitivity to adverse conditions is particularly heightened during embryogenesis, such that under-nutrition or environmental toxins could impact on cell differentiation and influence the epigenome (Heindel & Vandenberg, 2015). These adverse effects do not necessarily manifest in any visible birth defect, but rather create subtle alterations in the function of affected tissues that accumulate in significance over the course of a person's lifetime. The window of developmental sensitivity was subsequently extended into the postnatal period, to recognize infancy and early childhood as a period of continuing developmental plasticity, becoming known as the *Developmental Origins of Health and Disease hypothesis* (Gluckman & Hanson, 2006; Gluckman et al., 2007). The focus of this hypothesis is the first 1,000 days of life; plasticity does occur after this period, but during early development, environmental impacts will have a more profound effect on phenotypic trajectories (McPherson, 2021).

Many DOHaD-related studies focused initially on the impact of maternal nutrition for later life health outcomes. One of the best and most discussed illustrative examples of the impact of nutritional deficits on fetal development is the Dutch Famine, also known as the Dutch Hunger Winter, during World War II. This was a well-documented famine event of clearly delineated, five-month duration, in which food-intake dropped to approximately 400–900 kilocalories for all inhabitants, irrespective of social class. After this period, food intake quickly returned to normal levels, creating an exceptional and distinct period of deprivation (Roseboom et al., 2001, 2006). The availability of detailed records for both the duration of the event and since, has allowed a series of longitudinal studies to assess the repercussions for women who were pregnant, and/or conceived during this period, and their offspring (and

grandchildren). These studies demonstrated a range of life-long and intergenerational impacts, which varied depending on the gestational age at which individuals were affected. For example, while birth weight was not affected in those exposed during early gestation, these individuals had a greater likelihood of CVD and obesity in adulthood. By contrast, those who were exposed in late gestation tended to have a low birth weight and were small throughout their lives, but with lower rates of obesity (Roseboom et al., 2006). Those affected in late gestation, however, would also have continued to be impacted by the famine for a short period postnatally, limiting the capacity for catch-up growth in the months after birth. The famine did not necessarily affect linear growth but resulted in disturbed metabolic regulation, resulting in increases in diabetes, cardiovascular disease, hypertension, and schizophrenia (for further details see Ravelli et al., 1999; Roseboom et al., 2001, 2006; Lumey et al., 2011). Further longitudinal studies have provided unequivocal evidence that three generations were *directly* affected by the famine – the expectant mother, her child, and her grandchild; the latter because the ova develop in the fetus during gestation.

As Landecker (2011:177) discusses in relation to the Dutch example, "this is a model in which food enters the body and, in a sense *never leaves it*, because food transforms the organism's being as much as the organism transforms it". It has been argued that one of the reasons for the increase in metabolic disease amongst Dutch famine victims was the mismatch between the intrauterine signaling and the environment into which the child subsequently grew up (Godfrey et al., 2007). Other longitudinal studies of famine events, such as the Great Famine in China from 1959 to 1961, have likewise demonstrated a range of long-term health problems for those who were born during this time, including cognitive issues and stroke (Kim et al., 2017; Li et al., 2020). Such studies should inspire paleopathologists to take a longer term, intergenerational approach to the study of morbidity and mortality in relation to similar catastrophic events in the past, rather than conceptualizing them (as has tended to happen) as a moment in time.

Additional research has explored environmental cues other than nutrition; for example, the impact of exposure to chemical toxins during early life for risk of asthma and immunological problems, psycho-social stress, and social status (Wadhwa et al., 2009; Heindel & Vandenberg, 2015). Factors such as maternal stress have also been shown to be significant for mental as well as physiological well-being in later life (Wadhwa et al., 2009; Hertzman, 2012). Studies have demonstrated that stress during pregnancy can even affect the stress reactivity of offspring after their birth. Differences in maternal care in early infancy have also been shown to have potential life-long consequences,

via epigenetic alterations, for the regulation of adult stress reactivity (Weaver et al., 2004). New techniques in paleopathology and bioarchaeology are now allowing us to explore maternal stress in the past via intrauterine isotopic values of carbon and nitrogen in infants, thus opening up new avenues for investigating the mother/infant nexus (e.g., Beaumont et al. 2015).

Much of the original focus of DOHaD was undoubtedly chronic disease risk, and this may be one of the reasons that it was slow to be adopted by bioarchaeologists: much of our work is focused on populations living prior to the epidemiological transition, when infectious disease rather than chronic disease was a far more prevalent threat to mortality. Recent work, however, has shown that early life adversity also has implications for susceptibility to infectious diseases. For example, a series of studies on health in rural Gambia has demonstrated that children born shortly after the "hungry season" suffer from an increased risk of mortality from infectious disease in early adulthood compared to other times of the year. The authors argue that immune function and disease susceptibility is programmed in early life and affected by intrauterine growth retardation (Moore et al., 1999, 2004). Life history trade-offs are an important consideration here: when resources are scarce, growth disruption may occur as they are directed toward supporting the immune response to bolster short-term survival prospects (Temple, 2019, McPherson, 2021). As McDade et al. (2016:7) note "developmental plasticity and ecological sensitivity are defining features of the human immune system". When observing consistent growth delay in non-adults excavated from archaeological cemeteries, paleopathologists could reflect on this as a barometer of immunological stress within the broader populations, with repercussions for adult longevity in the survivors (e.g., Watts, 2015).

The idea that vulnerabilities to chronic disease are programmed into a person's biology prior to birth, via environmentally induced processes, rather than just genetics, represented a profound shift in our understanding of public health, with repercussions for government policies and medical interventions (Müller et al., 2017). In the UK, it shifted the foci of medical policies from adult behaviors/risks, onto mothers, infants, and early childhood, with the instigation of government health initiatives that provided greater social and medical welfare for pregnant women and young children (e.g., the Marmot Review, 2010). Timely and targeted interventions were seen as a cost-effective investment in the overall and longer term health of the population. It has been argued that within a DOHaD paradigm, obesity, diabetes, osteoporosis, cardiovascular morbidity, and neurodegenerative diseases can *all* be considered pediatric diseases: not because they occur in children but because they originate during development (Heindel & Vandenberg, 2015). Early interventions at the time when tissues are forming and biological systems are

most sensitive to environmental insults, have the potential to lead to improved lifelong health, although as the sections below illustrate, longer term strategies are needed.

Plastic Fantastic: What is Epigenetic Change

Modifications to the epigenome are a mechanism underpinning developmental plasticity and the alterations in disease risk identified in DOHaD research. Not all DOHaD research presumes an epigenetic origin to phenotypic phenomena; nevertheless, epigenetic processes are frequently conceptualized as a key component. Epigenetics can be broadly defined as "those genetic mechanisms that create phenotypic variations without altering the base-pair nucleotide sequence of the genes" (Gilbert & Epel, 2008:12). Epigenetic factors are those which cause changes in the regulation of gene expression (see, Haig, 2012, for more detail). Epigenetic modifications include DNA methylation, histone modification, and non-coding RNAs. The most heavily researched in terms of maternal exposures is DNA methylation, which refers to the addition of a methyl group to cytosine nucleotides, which then alters gene expression (usually "silencing" it), with subsequent impacts for phenotypic trajectories (Landecker & Panofsky, 2013:338). Epigenetic changes have been identified in response to a range of social and environmental stressors. The analogy of "memory" is often invoked in reference to epigenetic changes: studies often refer to the molecular embedding of social and environmental exposures during the period of development into the "memory" of an organism (e.g., Thayer & Kuzawa, 2011; Meloni, 2014; Kuzawa, 2020).

As the Dutch famine example (discussed above) has demonstrated, the direct effects of a particularly profound episode of adversity can be passed on to three generations, described using the notation F0 (mother) to F1 (daughter) and F2 (grandchild). Any effects beyond this (F3) are classed as transgenerational rather than intergenerational and are much more open to debate (Susser et al., 2012; Heindel & Vandenberg, 2015). Epigenetic information is generally not thought to survive across the germ line, due to post-fertilization re-programming (although see Ryan and Kuzawa, 2020). If the social and environmental circumstances that initiated the epigenetic changes in the F0 generation still exist in F3 then this implies transmission beyond the initial exposure and transgenerationally. However, presumably similar epigenetic markers can be triggered in F3 if the original socio-ecological conditions persist (Susser et al., 2012; Heindel & Vandenberg, 2015). Epigenetic changes have been identified in infants conceived during the hungry season in rural Gambia, and these infants have a greater risk of low birth weight and

mortality (Waterland et al., 2010; Dominguez-Salas et al., 2014). Landecker (2011:277) and Landecker and Panofsky (2013) discuss in more detail the potential triggering of an epigenetic response due to sub-optimal nutritional conditions. Research on those affected by the Dutch Famine has also shown that epigenetic effects are strongly influenced by the gestational age of exposure, although further empirical studies are required (Lumey et al., 2011). These early life exposures can invoke phenotypic change which can persist via mitosis throughout an individual's life course, although in some circumstances these may be reversible (Meloni, 2014).

Epigenetics provides a process in which an organism can rapidly alter in response to ecological/social stimuli, without more fundamental genetic changes (Wells, 2010). As Wells (2010:3) states: "Plasticity allows genes to 'stay in the game' through modification of the relationship between genotype and phenotype". While the impact of social and environmental factors for triggering, for example, different patterns of methylation, has been explored intensively, it is important to highlight the nascent status of epigenetic research in terms of broader implications for health and disease in humans (Heijmans & Mill, 2012). Current experiments are mostly focused on rodent species and seek to explore epigenetic responses to different environmental variables (e.g., maternal nutrition, psycho-social stressors) (Hertzman, 2012). The translation of results from rodent species, which have high litter numbers and short life spans, to humans is not straightforward. Further research is expanding to longer lived species, including primates. The majority of epigenetic research has also tended to focus on the triggering of responses rather than potential reversibility (Meloni, 2014).

Bridging the Gap Between the Biological and Social Sciences

Despite some of the limitations, epigenetic research has been regarded as revolutionary; the immutability of DNA has been challenged and the extent of its responsive and reactive nature is now being discovered (Niewöhner & Lock, 2018). Consequently, epigenetic research has been immersed in a considerable amount of hype and excitement (Pickersgill, 2021). Epigenetics explicitly breaks down the barriers between the body and society in understanding human health as never before (Meloni, 2014). The embedding of social factors directly into the epigenome challenges traditionally dichotomized views of the body and society (Niewohner, 2011; Müller et al., 2017). As part of the post-genomic landscape, epigenetics represents a move away from the reductionist turn characterized by genomic research in the 1990s, and instead bridges research in human biology and society (Meloni, 2014; Müller et al., 2017). Even on a biomolecular level, our bodies are malleable and influenced by social

environment. It has been argued by some medical anthropologists that there is still a danger that health will be viewed via a "molecular optics", with individuals reduced to their epigenome, potentially contributing to a molecularization of social processes (Lock, 2013). For many though, epigenetics heralds a new and exciting, post-dichotomous, post-genomic era in which human biology has become more fully reconciled with the social (Meloni, 2014; Richardson, 2015; Pickersgill, 2021). Meloni (2014:732) has argued that epigenetics has helped to constitute "a more pluralistic and contingent vision of 'the biological'" (2014:742).

While the epigenetic impact of the Dutch Famine (Heijmans et. al., 2008) is widely accepted, the catastrophic multi-generational impact of the Trans-Atlantic Slave Trade (TAST), enslavement, Jim Crow era, Segregation, and the Prison Industrial Complex seems to be a less acceptable argument for the epigenetic effects of chronic disease and trauma in Legacy African American (LAA) communities. LAAs are the descendants of chattel slavery forcibly brought to the United States for the economic advancement of the country. They are referred to as LAAs because of their ancestry but also to capture the contemporary diversity of African North American populations which includes LAAs and recent, first-, and second-generation African and Caribbean immigrants who significantly contribute to the Black American population (Caldwell & Jackson, 2021).

While LAAs are genetically closely related to the highly diverse ethnic groups in Africa, it is ironic that the population is less well represented in genomic databases, which leads to under-investing in complex disease mapping and epigenetic regulation of disease (Tishkoff et al., 2009; Landry et al., 2018). LAAs are disproportionately affected by chronic disease, major health disparities, and adverse risk factors for disease. To put this into context, 56% of the overall African North American population lives in the Stroke Belt. The Stroke Belt is home to the largest pre-Middle Passage slave port in Charleston, South Carolina, and is called the Stroke Belt due to the high prevalence of stroke and CVD phenotypes that plague populations who live there of all ethnic backgrounds. This flux in CVD and other chronic diseases phenotypes could be the result of intergenerational biological adaptations to social and economic disparities (Sinha et al., 2021). When LAA women were enslaved, they were still responsible for tedious agricultural duties, many breast-fed slave owner's children and their own, and were forced to complete these tasks while experiencing malnourishment and traumatic living conditions. If the Dutch Famine impacted the next generation, the epigenetic damage done during 400 years of enslavement and prejudice experienced by Black mothers is unquantifiable.

Because of their evolutionary history and arrival into the Americas, African Americans contribute greatly to the genomic and thus epigenetic health outcomes exhibited today. Ancestral proportions and degrees of population homogeneity and heterogeneity mirror recent levels of admixture within and across populations. For example, African Americans were born of a large bottle neck migration created by the TAST (Lachance et al., 2018). While great allelic diversity was present in Africa, the TAST forced African Americans to become more genetically homogenous over time. One form of evolutionary effect can be found in the Gullah Geechee, LAA sub-population found in the Lowcountry (<30 miles inland) of South Carolina, North Carolina, Georgia, and Florida coastal areas. Gullah Geechee are an amalgamation of West, West Central, and Windward Coastal Africans. They retained language and customs found in their homelands, and due to their relative isolation in the Lowcountry coast and islands, they usually retain >90% African genomic information with modest gene flow from surrounding populations (Ely et al., 2006). The Gullah Geechee are also a progenitor population for modern African Americans (Caldwell & Jackson, 2021). While geo-spatial restrictions during colonial periods deeply impacted reproductive patterns, the internal Second Middle Passage to the Deep South (1790–1865), and the Great Migrations from the south to northern states (1865–1970s) created genomic re-shuffling that, alongside institutionalized racism, led to clear health disparities between US populations in the past and which are evident today (Baharian et al., 2016). Decades of research shows that approximately 300,000 Africans were brought to the United States. One-third were women, yielding approximately 70,000 women of childbearing years to "mother" the contemporary LAA populations. This is essential to view through the lens of epigenetic repercussions. During enslavement, African American women carried weighty burdens as field and house workers, "breeders", and objects of sexual and medical exploitation. Pregnancy gave them no reprieve. As medical "subjects" LAAs were characterized as primitive and "animalistic" and were argued to have higher pain thresholds than whites (Booker, 2014); prejudices that continue today. This has led to acute distrust of the medical community and, consequently, discourages genomic testing and research that may improve our understanding of the epigenetic bases of health disparities and assist us ameliorating them.

The repercussions of racial disparities, past and present, are evident. Disparities in environmental, geographical, educational, and socio-economic experiences affect epigenetic mechanisms that alter DNA expression. For example, LAAs infants have a 50% increased risk in being Low Birth Weight and CVD and CVD comorbidities, such as hypertension, obesity, and heart disease, are more common within this population. From the cradle to the grave, and

from generation to generation, external and internal stressors have perpetuated health disparities for African Americans (Mohottige et al., 2022).

African Americans today are a young and genetically rich population. Pew Research observed that over 1:3 of the African American population was under 22 years old in 2019, and Millennials constituted an additional 23% of the total population, rendering around 60% of the African American population less than or equal to 38 years old (Tamir, 2022). The diversity in African American sub-populations, many migrations, systemic prejudices, and subsequent intergenerational experiences, contribute to an epigenetic imprint of trauma and resilience. African Americans are thus superb populations to study in order to understand the development and prevalence of human disease, mechanisms that catalyze health disparities, and genetic and environmental factors that contribute to human development, diseases, and mortality.

Hence, the imprinting of social exposures on skeletal biology must be a paradigm that is adopted by paleopathologists, especially since this field operates within the blurred space between the traditional disciplinary divides of science and social theory (Gowland & Thompson, 2021). Research that highlights the impact of environmental cues on phenotype and disease risk fits well within paleopathology's existing remit. For bioarchaeologists and paleopathologists, however, epigenetic research, developmental plasticity, and DOHaD provides a new model for understanding disease aetiology and risk, one in which the parameters have expanded to encompass biographical and intergenerational exposures.

Generations of Risk: Back to the Future

One of the key features of DOHaD is that it has altered our perception of timescales of risk and exposure to environmental adversity in early life. Life histories, and in particular the early developmental periods, are taking center stage. For disciplines such as paleopathology and bioarchaeology that have long marginalized the significance of fetal and infant remains, and almost entirely overlooked maternal bodies, this is particularly significant (Han et al. 2017; Gowland & Halcrow, 2020; Halcrow et al., 2020; Hodson, 2021). Infant remains at archaeological sites now take on a new source of significance as windows into overall population health and intergenerational conduits (Gowland, 2018).

DOHaD has also placed a spotlight on maternal health as a key source of vulnerability for the life-long well-being of the developing fetus. Unfortunately, however, within this paradigm, mothers have become conceptualized as a potential source of harm to their fetus, which represents a marked shift away from the previous perception of the maternal body as selfless/nurturing/buffering (Richardson et al., 2014). One consequence of this is that pregnancy within a clinical setting is now regarded as a productive period for medical intervention (Pickersgill et al., 2013). Richardson (2015) argues that DOHaD has essentially produced a deficit model, by presenting ways in which mothers can harm their offspring (Richardson, 2015). There is a danger that pregnant women will be subjected to increasing censure and surveillance from the medical profession because they are viewed as a source of epigenetic triggering that will adversely impact the phenotypic trajectory of their child. The maternal body within DOHaD has been partially re-conceptualized: from protector to "epigenetic vector" (Richardson, 2015:211). Postnatal care is also under scrutiny. For example, well-cited research has revealed that rat pups who were less intensively groomed by their mothers showed epigenetic changes and heightened stress (Weaver et al. 2005). When hastily translated to humans, expectations of maternity become intensified: women must optimize their pre-conception fitness through a regimen of nutrition and exercise, their natal health by adopting a specific lifestyle, and then follow an idealized model of optimum infant care. If she does not then she will pre-dispose her child (and potentially grandchild) to a life of enhanced biological and social disadvantage, including life-long mental health issues. One outcome of DOHaD and cognate research is an increased pressure on pregnant women to be "good reproductive citizens" (Longhurst, 2008), and the privileging of fetal over maternal wellbeing (Richardson, 2015).

Given that DOHaD research has shown that stressors during pregnancy can impact phenotype, it is logical to suppose that interventions during this period, such as nutritional supplementation, will result in more successful birth outcomes and a reduced risk of chronic disease for offspring. Whilst optimal maternal health is clearly desirable, targeting the intrauterine period, however, has not necessarily proven to be the most effective method of securing the future good health of the developing fetus (Richardson et al., 2014). A growing body of research has demonstrated relatively modest increases in birth weight for the offspring of women provided with nutritional supplements during pregnancy, except perhaps in very marginal environments (Kuzawa, 2005, Chung & Kuzawa, 2014). Birth weight is of course only a very crude indicator of fetal adversity, and very small improvements can result in positive reproductive outcomes (Gluckman & Hanson, 2006). Studies indicate that programs of nutritional intervention may well have a positive outcome on growth and health, but this may happen over intergenerational

rather than immediate timeframes (Chung & Kuzawa, 2014). For example, a large-scale randomized nutritional intervention was undertaken in Guatemala between 1969 and 1977, and results showed that the infants of women who were the beneficiaries of nutritional supplements during their own fetal development were significantly larger than those who had received no supplementation (Behrman et al., 2009). This study is significant because it demonstrates the heightened importance of the mother's own birth weight and childhood nutritional experience for her offspring. Sletner et al. (2014), also demonstrated that birth weight of infants was more closely related to the mother's own developmental history than current socio-economic status and living conditions.

The maternal body can, in fact, provide considerable buffering against immediate nutritional deficits through the deployment of glycogen stores, but as Wells (2010) observes, the efficacy of this is dependent upon "maternal somatic capital", which will vary greatly in relation to social, structural, and ecological factors. Wells (2010) and Kuzawa and Thayer (2011) argue that maternal cues to the fetus are constrained by epigenetic "memories", passed via the nutritional experiences of the mother and recent matrilineal ancestors. Within this model, the mother's liabilities are reduced in the face of nutritional deprivation, and conversely, pregnant women have a limited potential to actively improve the wellbeing of their developing fetus through nutritional regimes. This mechanism limits any plastic response to short-term ecological fluctuations, which is prudent from an evolutionary perspective in a long-lived species such as humans, who are exposed to seasonality and other perturbations in resource availability (Wells, 2010).

Research indicates that growth patterns in infancy and childhood, therefore, track the maternal phenotype closely: the mother is essentially a conduit of past generational experiences (Chung & Kuzawa, 2014). Of course, if the infant is born into an environment that is markedly different from ancestral circumstances then the ancestrally derived constraints can potentially result in maladaption. The theoretical model provided by Kuzawa and colleagues is one in which plasticity is not "predictive" of the future as Gluckman and Hanson (2006) have argued, nor reflective of the present, but instead is predicated on past generational experiences (Kuzawa, 2005). Within this model, bodies are backward rather than forward looking and plasticity is constrained rather than facilitated by the "memories" of ancestral experiences (Richardson, 2015). As Han and colleagues note, the fetus "is both materially and metaphorically a product of the past, a marker of the present, and an embodiment of the future" (Han et al. 2017:1). This new body of research also highlights the mechanism by which differing birth outcomes may occur

within similar environments: it is because they are contingent upon the diverse life histories of the mothers rather than reflecting current social and ecological settings.

Kuzawa and Thayer (2011) and Thayer et al. (2020) argue that different biological processes are sensitive to different timescales. While nutritional perspectives would more fruitfully consider life history and generational timescales, as outlined above, severe psycho-social stress during pregnancy can have more acute impacts. Kuzawa and Thayer (2011) highlight events such as natural disasters which have had well-documented, detrimental impacts on birth weight and infant mortality, irrespective of nutrition. A well-cited example being the terrorist attack of September 11, 2001 in the United States, which resulted in adverse birth outcomes for a significant proportion of female residents with Arabic names (Kuzawa & Sweet, 2009). Some studies of the longer term effects of disasters, including Hurricane Katrina and September 11th, have indicated continuing impacts on reproductive health (Harville et al., 2015). Other studies have likewise highlighted the significance of psycho-social stress, including post-traumatic stress disorder for the developing fetus, although results are sometimes inconclusive (Harville et al., 2010; de Oliveira et al., 2021). Kuzawa and Thayer argue that the biological response to acute stressors is directly transmitted to the fetus and therefore work on a more proximate timescale than nutritional stress. Within DOHaD, therefore, we need to consider the impact of both immediate and ancestral cues and how these might work to both initiate and constrain developmental plasticity (McPherson, 2021). This research provides additional nuance and complexity to our understanding of the effects of intrauterine stress in response to environmental adversity.

As discussed above, current DOHaD-related intervention programs tend to focus on the behaviors, lifestyle, and nutrition of mothers. While the potential of mothers to elicit a developmental response, via intrauterine environment and breastfeeding, is greater than for fathers, it is important for research to also consider paternal influences (Richardson et al., 2014). Sharp et al. (2018) analyzed articles published in the *Journal of Developmental Origins of Health and Disease*, demonstrating that 84% were focused on maternal exposures, while only 4% discussed paternal influences on disease risk. New DOHaD research has started to focus on the importance of patrilineal experiences, with factors such as diet also impacting epigenetically on sperm (Richardson et al., 2014). Recent research is also exploring the impact of epigenetic signaling from the paternal line and is re-evaluating just how complete the epigenetic erasure of the germ-line actually is (Ryan & Kuzawa, 2020). Sharp et al. (2019) and Richardson (2015) also caution against the rushing in of DOHaD findings into public and clinical policy in the absence of a more holistic understanding, which includes paternal factors.

Research shows that routing DOHaD within the context of individualized risks and behaviors will have a minimal impact, compared to wider structural inequities within societies, in which individuals are exposed to adversity over generations. There is now significant evidence that we need to consider health in terms of cumulative, intergenerational biographies. This research creates a new imperative to understand the more insidious effects of deeply entrenched structural inequalities that serve to marginalize the very poorest in society as well as racially marginalized groups. If the social adversity experienced by grandparents continues to impact subsequent generations, it can reinforce the poverty trap and become self-fulfilling. Wells (2010) refers to this as a "metabolic ghetto" stating: "If pregnancy is a niche occupied by the fetus…, then economic marginalization over generations can transform that niche into a physiological ghetto where the phenotypic consequences are long-term and liable to reproduction in future generations" (Wells, 2010:11). The social past literally becomes embodied, and shapes future developmental trajectories (Kuzawa & Sweet, 2009:11).

The Body, Society, and DOHaD in Paleopathology and Bioarchaeology

In paleopathology and bioarchaeology, interpretations of skeletal remains are predicated on the fact that past societies and ecologies become embedded within the chemical and morphological fabric of the hard tissues of the body. It is the role of the paleopathologist to tease these out via a suite of analytical techniques and interpret them in relation to a range of contextual evidence. For bioarchaeologists, embodiment is literal rather than figurative, as the biology of past people yields unique insights into their lives. The plasticity of the human skeleton and the lesions caused by various stressors have long formed an important basis of paleopathological studies. DOHaD provides an extended temporal and life course perspective for our interpretation of skeletal variation and pathology.

One of the implications of DOHaD for paleopathology and bioarchaeology is the new emphasis on mothers and infants. Maternal health and infancy have largely been overlooked in archaeology and very few studies of infants have interpreted their remains with reference to the infant/mother nexus (Gowland, 2018; Gowland & Halcrow, 2020, Riccomi et al., 2021, and Chapter 23, this volume). The varied socio-cultural practices and beliefs surrounding conception and pregnancy have likewise been under-explored. There is a rich ethnographic and sociological evidence that points to a range of culturally specific, spatial, and dietary constraints/taboos that control maternal bodies and by extension affect the developing fetus (e.g., see chapters in Han et al., 2017 and Gowland & Halcrow,

2020). New theoretical developments (including DOHaD), alongside methodological innovations, are now leading to a resurgence of interest.

One such innovation is high-resolution isotopic data from dentine, which can reveal longitudinal dietary changes for the duration of tooth formation. Nitrogen and carbon isotope values can be plotted at intervals of approximately nine months, from just before birth to 15 years of age, depending on the tooth being sampled (Beaumont et al., 2013; Montgomery et al., 2013). Deciduous dentition and the first permanent molar are particularly valuable for comparing pre- and postnatal exposures to adversity. This method also allows, for the first time, a means of making direct comparisons between survivors and non-survivors and has considerable potential for exploring DOHaD within the bioarchaeological record, particularly when integrated with skeletal data (Gowland, 2015; Beaumont et al., 2015, 2018; Kendall et al., 2020).

Incremental stable isotope analysis of deciduous teeth can provide a window into maternal stress during the intrauterine period during which the tooth crowns were developing. Opposing covariance in δ^{15}Nitrogen values and δ^{13}Carbon isotope values potentially indicates physiological stress (Beaumont & Montgomery, 2016). The association between high δ^{15}Nitrogen values and starvation has also been recorded in the clinical literature in studies of hair samples obtained from individuals attending clinics for eating disorders (Mekota & Grupe, 2006). Beaumont et al. (2015) have noted a disparity between maternal δ^{15}Nitrogen values and perinatal offspring. The perinatal values reflect the period of development in utero, whilst maternal values represent pooled data relating to the last five to ten years of the woman's life (depending on the bone sampled). Elevated δ^{15}Nitrogen values in archaeological infants have previously been interpreted exclusively in terms of breastfeeding; instead, Beaumont and colleagues (2015) argue that in some cases, these may reflect the recycling of proteins in the mother in response to environmental adversity. The perinate, therefore, provides high-resolution maternal isotope values, in the absence of the mother herself (Gowland, 2018).

Kendall et al.'s (2020) high-resolution isotope analysis of individuals from a site of putative malaria endemicity (Littleport, Ely, UK) demonstrated a much more erratic pattern of values than the contemporaneous and nearby (but non-malarial) site of Edix Hill. In particular, opposing covariance in δ^{15}Nitrogen and δ^{13}Carbon values in several Littleport individuals indicates maternal malnutrition late in pregnancy. Interestingly, for two of these individuals, a divergence in carbon and nitrogen values continues postnatally alongside skeletal indicators of metabolic stress (Kendall et al., 2020:118). Pregnancy is associated with greater susceptibility to malaria, with one of the associated

pathological changes being anemia (Gowland & Western, 2012). Such studies have great potential for exploring reasons underpinning the osteological paradox and hidden heterogeneity in mortality risks.

Preliminary research by Leskovar et al. (2019) indicates that isotope analysis of collagen from ear ossicles also has the potential to provide a signal of maternal health. Formation occurs prior to dental development and therefore provides isotopic information for a hitherto invisible stage of fetal development. This method is still nascent but has enormous potential to improve our understanding of early infant development and maternal stress in the past. The archaeological study of cortisol values from teeth also has the potential to examine aspects of early life adversity (Quade et al., 2021). One application would be to compare cortisol levels in perinatal teeth, with high values potentially related to maternal stress. Comparisons can also be made between cortisol concentrations and other dental indicators of stress. As Kuzawa and Thayer (2011) have noted, acute maternal stress is a risk factor for low birth weight and infant mortality. Should techniques of cortisol analysis become more sensitive, perhaps it would be possible to sample teeth incrementally in a similar way to isotope data to investigate any trends or anomalies in intrauterine values.

A number of studies within paleopathology have provided evidence in support of DOHaD from archaeological contexts, noting correlations between indicators of childhood health stress such as linear enamel hypoplasia (LEH), vertebral neural canal dimensions, cribra orbitalia, growth stunting, and reduced adult longevity (e.g., Armelagos et al., 2009; Watts, 2011, 2013, 2015; Roberts & Steckel, 2018; Temple, 2019; Garland, 2020). Paleopathological analysis of infant remains is often controversial due to the difficulties of differentiating between pathological new bone formation and normal growth (Lewis, 2017; Hodson, 2021). Some studies, however, have provided unequivocal evidence for pathological processes on perinatal remains (e.g., Lewis, 2010; Hodson, 2017). For example, the high proportion of infants from the Roman site of Piddington, Northamptonshire, UK, showed a range of pathological lesions, indicating adverse maternal health that likely reflects a much broader population disease burden (Hodson, 2017). Studies of DOHaD are not limited to the study of infants and young children, and indeed it is the longer terms effects of adversity that are of interest. McPherson (2021) summarizes a series of skeletal indicators that may indicate adversity during the sensitive window of plasticity, and which may be potentially useful for exploring DOHaD.

Both Temple (2014) and Lorentz et al. (2019) demonstrated that the timing and frequency of microscopic dental defects were significant predictors of age-at-death in archaeological samples from Japan and Iran, respectively.

Temple (2019) also noted that individuals with dental defects at an earlier age had a higher mortality risk, lending further support to the DOHaD hypothesis. Lawrence et al (2021) analyzed LEH in individuals of known genetic relatedness, finding a correlation that may relate either genetic or epigenetic frailty, suggesting the intergenerational transmission of heterogenous frailty. Brickley et al. (2020) adopted a novel approach for examining vitamin D deficiency in early life. They undertook a histological analysis of inter-globular dentine (diagnostic of vitamin D deficiency), prior to, and after the neonatal line, which forms at birth. They provided an example of a child who died aged three years with evidence of healed rickets at the time of death, and pre-natal evidence of vitamin D deficiency. The paleopathological evidence, however, does not always straightforwardly map onto DOHaD. For example, Amoroso and Garcia's (2018) study of a 19th–20th-century Portuguese identified skeletal collection, examined the relationship between vertebral neural canal dimensions, indicative or childhood stress, and age-at-death but found no correlation. They argued that cultural or behavioral strategies ameliorated the impact of this developmental response to stress on mortality risk, and also suggest that results align with Gluckman and Hanson's (2006) predictive adaptive response model. It is important, however, to be cognizant of the arguments by Kuzawa (2005) and Wells (2010) against the ability of environmentally induced intrauterine signals to predict postnatal environments. Holder et al. (2021) integrated a DOHaD and life history theory approach to examine variability in body mass and stature of a sample of Napoleonic soldiers. They found no clear relationship between LEH and final adult stature; however, catch-up growth is a possibility. As discussed in relation to life history theory and the trade-offs between growth, immunity, and reproduction, catch-up growth is energetically costly and growth disruption during childhood can increase morbidity and mortality risks in later life, leading to reduced life expectancy (Barker, 2012; Temple, 2019). LEH may result from acute stressors, whereas reduced stature tends to indicate an extended period of stress (Holder et al., 2021). Studies that focus on permanent teeth, most of which are formed postnatally, are not likely to provide such strong associations within a DOHaD framework, which is constrained to the first 1,000 days of life. Nevertheless, it is clear that there are sometimes "discrepancies" in terms of what might be expected with regard to early life stressors and adult mortality that requires a nuanced, contextualized analysis, and interpretation. Bioarchaeological studies utilizing the DOHaD concept have also now started to consider pathology in intergenerational terms. For example, Godde and colleagues (2020) argue that the series of famines that preceded the Black Death in 14th-century England created an environment of chronic stress that contributed, via epigenetic mechanisms, to patterns of mortality observed in a Black Death cemetery assemblage. Yaussy et al. (2016) also

compared stress indicators and mortality amongst famine victims versus an attritional skeletal sample in medieval London and observed an association between early life stressors and mortality. Work by these authors on 14th-century London have highlighted the intergenerational impacts of famine as a source of heterogeneity in frailty. Well's (2010) "metabolic ghetto" is also evident in intergenerational indicators of stress observed in post-medieval sites in Northern England (Gowland et al., 2018). Severe growth stunting and dental enamel defects on deciduous and permanent teeth can be attributed in this context to low social status and associated health inequality due to a lack of "maternal somatic capital". Early life adversity included chronic, intergenerational under-nutrition, and exposure to environmental pollutants. Life history trade-offs between growth and immunity, compounded by continuing poor living and working conditions for the children, attenuated any likelihood of "catch-up" growth and resulted in a high frequency of adolescent deaths (Gowland et al., 2018).

As discussed above, structural violence in the form of slavery also has long-term, intergenerational consequences that increases disease susceptibility and mortality risks. Continuing structural inequalities today through the racialization of individuals and groups creates adverse social and ecological systems that reproduce and perpetuate vulnerabilities to a wide range of disease risks (Gravlee, 2009). This has been exemplified by the higher rates of mortality experienced by many Black and ethnic minority groups in the UK and United States during the COVID-19 pandemic. For many African Americans, living a healthy lifestyle free of complex disease is rare. Racial bias and systemic racism play a pivotal role in the health outcomes for all Americans but access to education and health care, as well as having higher income do not unequivocally lead to better health outcomes for African Americans in comparison to other ethnic minorities. Historical racial beliefs that are infused within modern medical prejudices and practices continue to influence health care dynamics today. CVD and maternal and fetal health are complex health issues with historical relevance to contemporary issues in African American communities. It is important that paleopathological and bioarchaeological research, which seeks to address structural inequalities, avoid narratives of biological disadvantage that creates further stigmatization (Müller et al., 2017) and diminishes the role of individual and collective agency to shield against, and transcend, social adversity. Studying the African Diaspora and LAAs is pivotal in this process and for unveiling biological processes that further our understanding of all human-kind (Clinton & Jackson, 2021).

Conclusions

As always in paleopathology and bioarchaeology, context is everything. Human bodies are constituted within a complex entanglement of molecular, social, ecological, evolutionary, intergenerational, and biographical factors, such that it is no longer adequate to use "interactionist vocabulary" such as biology-culture, nature-nurture (Niewöhner & Lock, 2018). Current research is increasingly recognizing the constraints of the boundaries we have constructed between disciplines and the ways in which these have shaped a reductionist view of human biology (Meloni, 2014). Sociological, evolutionary, and epigenetic research is also challenging the indivisibility of bodily boundaries and individual biographies in terms of environmental exposures and the accumulation of disease risk across a life course and intergenerationally (Gowland, 2015, 2020). The reactivity and plasticity of the human body in relation to socio-ecological niches has long been considered an important component of human adaptation. For bioarchaeologists, it is crucial to consider the long-term pathological outcomes of early life phenotypic adjustments that are initiated to secure short-term survival advantages.

Paleopathology and bioarchaeology over the last decade have taken a more explicit theoretical turn, embracing sociological understandings of the body and a more integrative approach for interpreting "embodied phenotypes" (Krieger, 2013). Bioarchaeologists have started to utilize detailed, individualized, osteobiographical narratives, and life histories (Agarwal, 2016). A life course approach needs to consider the range of socio-cultural and environmental conditions that could both ameliorate or exacerbate early life adversity in terms of disease risk and mortality in later life. Adopting a life history and life course approach to interpreting socio-ecological entanglements is crucial for our understanding of past disease. DOHaD and epigenetic research expands the temporal framework of our interpretations to encompass intergenerational evidence. For paleopathology and bioarchaeology, embracing the concepts of DOHaD and life histories, also means that the human body is becoming increasingly "particularized" (Niewöhner & Lock, 2018:687). The potential for heterogeneity of individual responses to similar socio-ecological circumstances is governed, in part, by the experiences of our predecessors (Sletner et al., 2014:448). As Krieger (2013:25) writes: "history matters—deeply, at multiple levels and time scales—to claims about disease etiology and causes of health inequities". The integration of DOHaD within paleopathological and bioarchaeological interpretations, and, in particular, the intergenerational dimension, represents a considerable conceptual shift for our interpretations of skeletal growth and disease in the past.

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