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DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Evidence, proposed mechanisms, and ideas for future applications

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Introduction

The idea that early life experience, including conditions *in utero*, can influence the well-being of individuals is shared across many cultures. Such ideas motivate many of the practices, treatments, taboos, and rules followed by pregnant women and their partners before, during, and after pregnancy (Selin and Stone 2009). In the last 30 years, this general idea that early environments can affect the developing child has been codified into a scientific research program known as Developmental Origins of Health and Disease (DOHaD). Growing out of the fetal origins hypothesis described by David Barker (1994), DOHaD explores how early environments influence the development of non-communicable diseases—including cardiovascular, immune, neurological, and reproductive disorders—from infancy and early childhood to adulthood.

The central assumption of DOHaD is that conditions encountered during key developmental periods, including exposure to psychosocial, nutritional, and toxicological insults, have disproportionate impacts on an individual relative to similar exposures in adulthood (Suk et al. 2016). Certain developmental windows appear to be more sensitive than others, especially during very early development. For instance, research conducted in Chile following the 2005 Tarapaca earthquake found the rate of low birth weight, which predicts increased short- and long-term morbidity risk, increased after the quake, particularly among mothers who had been in their first trimester (Torche 2011).

This early sensitivity is thought to reflect an evolved capacity for developmental plasticity, which allows organisms to modify their development in order for their physiology to be better matched to their environment (Kuzawa 2007). While initially focused on the importance of fetal development for later life health, researchers now believe that environmental exposures across the preconceptional, prenatal, and/or early postnatal periods can all have substantial health effects (Hanson and Gluckman 2016). For example, in a large study in New Zealand, prenatal and postnatal adversity, as indexed by a composite measure of familial and neighborhood-level variables (e.g., maternal depression and neighborhood deprivation), were independently found to predict elevated body mass index (BMI), an indicator of cardiometabolic disease risk, in 4.5-year-old children (Farewell et al. 2018a, 2018b). However, children who experienced

adversity across both prenatal and postnatal development had the highest BMI, indicating a dose-response effect.

The principles of DOHaD have been readily incorporated by anthropologists interested in questions of developmental plasticity and life-history theory (Kuzawa and Quinn 2009; Temple 2019; Wells 2018). There is also an interest in applying this research to advocate for financial and social resources to support families across pregnancy and postpartum (Goodman et al. 2018; Thayer et al. 2020; Novilla et al. 2019), as well as using DOHaD principles as a framework for promoting health nutrition in pregnancy (McKerracher et al. 2019). Understanding how the timing and duration of adversity affect offspring has important implications for the appropriate timing of public health interventions aimed at improving maternal and child health (Farewell et al. 2018a).

This chapter provides an overview of the DOHaD concept, beginning with its history. We describe examples of developmental responses to stressors that impact health and disease risk, including discrimination, poor nutrition, war, and violence. We address some of the proposed biological mechanisms for DOHaD effects, focusing on the epigenome and microbiome. These systems are of interest since it is possible they can be modified in response to intervention, potentially allowing a reversal of developmentally-induced health effects. Next, we discuss some of the challenges within DOHaD, including an overemphasis on mothers that can result in blaming women and the issues associated with describing developmental responses as “programmed.” We close with a brief discussion of understudied areas in DOHaD of potential interest in the anthropology of reproduction.

Background

Brief history of DOHaD concept

Living in a gene-centric era, it is easy to forget that current principles of heredity did not exist before the twentieth century. Lamarck is one of the most famous theorists to propose what he called the “inheritance of acquired characters,” which posited that traits changed over the life course of parents (in response to lived experiences) and were passed onto offspring. Writing half a century later, Darwin not only accepted these ideas, but he also created his own description of heredity (pangenesis) to account for it (Amundson 2005). However, August Weissman later asserted that the environment only affected the soma (cells that cannot pass genetic information, like most comprising the human body), which he differentiated from the germline (cells that pass genetic information, like ova and sperm). Thus, according to this view, developmental experience and environmental conditions did not affect offspring (Mayr 1985).

Yet, the idea that individual biology is predetermined was later challenged. Several mid-twentieth-century studies evaluating the intergenerational impacts of nutritional shortage and stress associated with WWII provided the basis for what would become DOHaD. The Dutch winter famine studies, which demonstrated the impact of famine exposure during pregnancy on birth weight and later life health (Lumey 1992; Roseboom et al. 2001), became the best known of these, but similar cohorts were studied in Leningrad (Stanner and Yudkin 2001) and Germany (Dörner 1973).

Building on this work, Barker demonstrated geographic associations between a high prevalence of infant mortality from 1921 to 1925 and mortality from ischemic heart disease from 1968 to 1978 (Barker and Osmond 1986). The places which were characterized by adverse outcomes at the start of life, as indexed by high infant mortality, also exhibited high rates of heart disease in adulthood. Later, Barker demonstrated associations between low birth weight

and later risk of death from heart disease, cardiovascular disease, and type 2 diabetes (Barker et al. 1989, 1993a, 1993b). Many of these early studies focused on birth weight as a proxy of intrauterine experience. While birth weight may be a useful indicator of early adversity in some cases, developmental insults can also occur without affecting it, making size at birth inappropriate for capturing the full range of early life factors that can influence later disease risk. An interest in the impact of prenatal conditions on later health therefore led to studies assessing the impacts of environmental exposures in the postnatal period.

DOHaD, developmental plasticity, and mismatch

Developmental changes to individual biology and behavior are hypothesized to improve life-long health through calibrating biological responses to environmental conditions. Sometimes called predictive adaptive responses (PAR), these changes are thought to prepare the individual for future conditions (Bateson 2001; Nettle and Bateson 2015). These changes are expected to be beneficial if the environmental cues experienced during key developmental periods reliably signal future conditions (Nettle and Bateson 2015). Yet, developmentally induced changes may have the opposite effect. They may contribute to poor health because humans have relatively long lifespans and environmental conditions may change dramatically between early life and adulthood, leading to a potential “mismatch” between expected and experienced conditions.

Mismatches can have important consequences for disease risk, perhaps due in part to changes in the epigenome or microbiome, described below, which impact individual biological responses (e.g., metabolism and stress reactivity). While developmental mismatches can be caused by a range of circumstances, nutritional transitions are a common example (Gluckman et al. 2019). Limited nutritional availability (e.g., due to living in low-income or war-torn areas) during key development periods is thought to shape physiological development, with the expectation of continued poor nutrition favoring an enhanced ability to store fat whenever possible. Yet if the individual gains access to reliable sources of excess high-calorie food (e.g., due to national economic development and the introduction of affordable processed foods, migration to a different country, or the end of prolonged war), those early life signals prove inaccurate. In these instances, laying down fat, which may have been beneficial in a nutrient-poor environment, may instead lead to an increased risk of cardiovascular and metabolic disease (Barker et al. 2001).

Human technological innovations, coupled with an increasing ability to manipulate our surroundings, have resulted in environmental conditions that would be unrecognizable to human ancestors. These evolutionarily novel environments may alter early life experiences in ways that affect underlying physiological processes, with consequences for later health. For instance, replacing human breast milk with formula derived from cow’s milk alters infant nutrient supply, impacting the transfer of immunological compounds and the establishment of gut bacteria important for digestion (Gluckman et al. 2019; Li et al. 2012; also see Tomori, Quinn, and Palmquist in this volume). Formula feeding during critical developmental windows has consequently been linked with altered immune responses and increased obesity risk (Owen et al. 2005). Developmental mismatches and evolutionarily novel environments therefore have important implications for lifelong health.

Evidence for DOHaD

The influence of early life factors on later disease risk has been an increasing area of focus for researchers interested in optimizing public health interventions. Here we explore some examples.

Stress and discrimination

Innovative studies have highlighted how the experience of stress and discrimination among socially disadvantaged women can negatively impact birth outcomes, specifically low birth weight (LBW; < 2,500 g/5.5 lbs at birth), a risk factor for infant mortality and the later development of chronic disease (Barker 2012). The birth weights of infants born to White and Arab American mothers in California did not significantly differ prior to the terrorist attacks of September 11, 2001; notably, Black, Asian, or Hispanic mothers had higher odds of giving birth to LBW infants (Lauderdale 2006). However, following 9/11, Arab American women exhibited a 34% increased risk of giving birth to LBW infants. This effect was greatest among infants given “ethnically distinct” names—a proxy for strong ethnic identity—with LBW risk more than doubling. Although these women lived far from the sites of the attacks, the changes in birth outcomes were attributed to their increased experience of discrimination in the year following 9/11.

Similar patterns were also documented in the effects of government-conducted immigrant raids on Latinx workers living in Postville, Iowa (Novak et al. 2017). In May 2008, approximately 4,000 Latinx meat-processing plant workers were arrested in a surprise ICE raid, resulting in the deportation of 297 people. Novak and colleagues examined birth weights in the time immediately preceding the raid and the 37 weeks following it. White and Latina mothers exhibited comparable LBW rates before the raid, but following the raid, LBW rates increased by 24% in Latina mothers only. This pattern held regardless of whether the women were born in the US or a different country, indicating the effect was likely dependent on ethnicity alone, not immigration status. The effects were strongest among mothers who experienced the raid during their first trimester (Novak et al. 2017), consistent with other research suggesting first-trimester stress may especially impact fetal development.

Indigenous communities also exhibit higher rates of poor birth outcomes, again likely due to experiences of discrimination. In New Zealand, reported ethnic discrimination was linked with lower birth weights and shorter gestation length among Indigenous Māori women (Thayer et al. 2019). Likewise, minority and immigrant women reporting experiences of ethnic discrimination were significantly more likely to give birth to infants with higher cortisol reactivity—an indicator of stress physiology functioning—independent of ethnicity or maternal resource access (Thayer and Kuzawa 2015). These studies cumulatively indicate discrimination negatively impacts intergenerational health as evidenced by an increased risk of poor birth outcomes and altered stress reactivity in children.

Nutritional factors

Insufficient or excessive nutrition during development has been associated with the later development of non-communicable diseases. For instance, a focus of recent DOHaD studies relates to vitamin D (Folami et al. 2019). Vitamin D is derived from both the diet and from UV exposure; however, nutritional supplementation is often necessary. In the US, 80% of pregnant women were vitamin D deficient (McAree et al. 2013). Even individuals living in areas with high UV exposure may exhibit vitamin D deficiency; for example, one study found that 90% of pregnant women in Malaysia were vitamin D deficient (Bukhary et al. 2016). Vitamin D deficiency in pregnancy is associated with giving birth to LBW infants, but with higher weight at nine months postnatal, indicating catch-up growth, itself a risk factor for later chronic disease (Santamaria et al. 2018).

Major nutrient deficiencies appear to impact prenatal development in ways that shape future health. While animal models have been used in experiments to study these processes,

historical instances of famine have been examined to understand the effects of early nutrition restriction on later health among humans (Patrycja and Deborah 2019). A study of the health effects of the 1925–1961 Chinese famine found that prenatal exposure to famine was linked with increased odds of hyperglycemia and type 2 diabetes in adulthood (Li et al. 2017). The famine's effects were also apparent in subsequent generations. Compared with the offspring of non-exposed parents, children born to parents who had been prenatally exposed to famine also had increased hyperglycemia risk in adulthood, especially when both parents had been exposed.

War and violence

Retrospective studies examining birth weights document the negative intergenerational health effects of prolonged war (Clarkin 2017). During World War I, birth weights in Vienna, Austria decreased appreciably, likely due to parental elevated stress levels, lack of food, and disease spread (Steckel 1998). Likewise, birth weights in the Netherlands decreased during World War II, a pattern attributed to an extreme reduction in nutrient and calorie consumption (Smith 1947).

Reductions in birth weight are also observed when the mother is exposed to unpredictable social or interpersonal violence, especially during the first trimester of pregnancy, even if maternal bodily injury does not occur (Clarkin 2017). Examples include LBW infants born to women living in areas impacted by escalating drug wars in Mexico (Brown 2018); terrorist attacks in Pakistan (Grossman et al. 2019); high local crime rates in Scotland (Clemens and Dibben 2017); and homicides in Brazil (Koppensteiner and Manacorda 2016). Intimate partner violence, physical and/or sexual, has also been associated with lower birth weight and preterm birth (Hill et al. 2016).

Summary

There are many examples of sensitivity to environmental exposures in early life. Some of these exposures may reflect pathological, negative development effects. Others may induce developmental adjustments meant to maximize survival and adaptive calibration to the anticipated environment. Determining whether developmental responses reflect pathology or adaptation is often unclear, but should always be considered (Ellison and Jasienska 2007). Below we discuss some of the intermediate pathways through which these environmental exposures may impact biology and health.

Proposed pathways

Epigenetics

DOHAD is focused on understanding how early environments impact biology. Epigenetic modifications are environmentally sensitive DNA modifications that impact gene expression. Epigenetic marks include chemical modifications to DNA and DNA-associated proteins (histones) that do not change the underlying DNA sequence (Aristizabal et al. 2019). These modifications are functionally important because they influence which genes get expressed, or turned on. Epigenetic modifications are what allow cells that are genetically identical to take on different roles, such as cells that make up your heart, your skin, and your hair. While there are many types of epigenetic modification, DNA methylation, which refers to the attachment of a methyl group to a cytosine DNA base, is the most commonly studied.

Unlike DNA bases, which are generally stable across an individual's life course, epigenetic modifications are sensitive to environmental exposures, including nutrition, psychosocial stress, and toxicants. This is particularly true during early development, with extensive DNA methylation establishment occurring during pregnancy. Maternal restriction of macro- and micro-nutrients during pregnancy has been associated with epigenetic changes in offspring (Ideraabduallah and Zeisel 2018). Patterns of parental care have also been associated with differences in DNA methylation. For example, increased licking and grooming behavior in mother rats (Weaver et al. 2004) and maternal stroking of a human newborn's head (Murgatroyd et al. 2015) have been associated with differences in offspring methylation at the glucocorticoid gene that helps regulate stress physiology functioning. Environmental experience of prior generations may also impact patterns of DNA methylation in descendants (Perez and Lehner 2019), which provides a biological basis for constructs such as historical trauma (Conching and Thayer 2019).

Interest in epigenetic mechanisms mediating DOHaD effects has resulted in the investigation of these marks in a growing number of longitudinal, population-based studies (Felix and Cecil 2019). Epigenetic-wide association studies (EWAS) are being increasingly used to prospectively assess associations between prenatal and/or early life environmental exposures with epigenetic modifications at birth or in childhood, and/or between such modifications with subsequent measures of offspring phenotype. A consistent finding validated in a meta-analysis is that prenatal stress is associated with a difference in methylation at the glucocorticoid receptor gene (Palma-Gudiel et al. 2015). A recent study reported changes in methylation associated with breastfeeding (Odintsova et al. 2019), which could help explain its long-term health effects such as slower cellular aging (as indexed by telomere length) in childhood (Elwan et al. 2016) and lower obesity risk across the life course (Owen et al. 2005).

There have been intriguing findings about the impacts of prenatal and early life stressors on epigenetic age, a measure of biological aging (Jylhävä et al. 2017; Ryan 2020). While biological age is correlated with chronological age, it can accelerate or decelerate in response to environmental experience. Epigenetic age is measured through the creation of epigenetic clocks, which evaluate methylation across multiple sites of the genome associated with chronological age (Bell et al. 2019). This measure has been prospectively associated with increased morbidity and mortality risk (Marioni et al. 2016), with accelerated epigenetic age predicting more asthma symptoms in children (Peng et al. 2019) and increased risk of cardiovascular disease among adults (Perna et al. 2016). Exposure to adversity (Marini et al. 2019) and family conflict (Gettler et al. 2019) have been associated with differences in epigenetic age among children.

The potential reversibility of epigenetic marks makes them compelling from an intervention perspective. A recent experiment in a rat model found that the administration of a pharmacological agent known to alter DNA methylation, zebularine, was able to reverse the effects of early adversity on maternal behavior (Keller et al. 2019). Specifically, a low resource environment during development (e.g., limited food and nesting materials) was associated with subsequent maltreatment (e.g., rough handling, stepping on, dropping, dragging, or actively ignoring) of offspring. Administration of low-resource-raised dams (mothers) with zebularine caused those dams to not mistreat their own offspring. This work suggests environmental exposures that impact the epigenome and subsequent phenotype can be reversed at both the epigenetic and phenotypic levels.

Among humans, adolescents belonging to families that exhibited harsh parenting, but participated in an intervention to reduce those behaviors had lower epigenetic aging relative to similar peers whose families did not participate (Brody et al. 2016). These results suggest that DNA methylation marks are reversible in humans as well, and that reversal can occur through behavioral (not only pharmacological) interventions.

Microbiome

The influence of the microbiome—the genetic material of the 100 trillion bacteria and other microbes residing in the human intestinal tract—on human health is firmly established, including the role that gut bacteria play in calibrating the immune system, defending against pathogens, and supporting key digestive processes like vitamin synthesis and fiber break-down (Stiemsma and Michels 2018; Stinson 2019). However, the influence of the early life microbiome on long-term health has only been recognized recently (Stiemsma and Michels 2018; Shreiner et al. 2008). Microbiome establishment follows a predictable trajectory in the first two years of life, from a highly dynamic composition at birth to a transitional period at approximately one year, and reaching a stable and mature phase at two to three years (Stinson 2019). Thus, lifestyle factors in these first years are thought to be critical to long-term microbiome-associated health outcomes.

The infant microbiome is influenced by a range of factors. Bacterial colonization of the microbiome begins at birth, with infant exposure to maternal vaginal and fecal microbiotas (Stiemsma and Michels 2018; Stinson 2019; Dominguez-Bello et al. 2010). Babies delivered by cesarean section exhibit microbiotas populated by bacteria found on the mother's skin, leading to very different microbiome compositions and a potentially increased risk of poor health outcomes (e.g., asthma, allergy, obesity, leukemia) (Tamburini et al. 2016). Breastfeeding seeds the infant's gut microbiome and supports the stabilization of its healthy composition (Pannaraj et al. 2017). Antibiotic exposure also appears to be an important determinant. A recent prospective study of antibiotic use in eight countries found the average child receives 4.9 courses of antibiotics per year in the first two years of life (Rogawski et al. 2017). However, prenatal maternal or early life antibiotic treatment has been associated with changes in infant microbiome development and possible microbiome-linked diseases later in life (Bokulich et al. 2016; Keski-Nisula et al. 2013; Tormo-Badia et al. 2014; Corvaglia et al. 2016).

These findings suggest that the microbiome mediates the relationship between early lifestyle factors and later health outcomes. Shifts in microbiome composition may direct immune system development, sometimes leading to hypersensitivity and/or hyperinflammation (Stiemsma and Michels 2018; Shreiner et al. 2008). However, cesarean sections, formula feeding, and antibiotic use are at times unavoidable, and these findings highlight how a DOHaD perspective can be applied to improve infant health. For instance, preliminary evidence suggests that swabbing infants delivered by cesarean section with maternal vaginal fluids immediately following birth leads to the partial recovery of the microbiome composition observed in vaginally delivered infants, although further testing is needed to determine long-term health effects (Stiemsma and Michels 2018; Dominguez-Bello et al. 2016; Dietert 2017). Breastfeeding (or use of donor milk) plays a critical role in seeding the microbiome, supporting the colonization and maturation of the infant gut microbiome (Mueller et al. 2015; Yasmin et al. 2017). It also appears to facilitate mother-infant microbial exchange postnatally (Mueller et al. 2015). Sustained breastfeeding—coupled with the avoidance of unnecessary antibiotics—may therefore represent another strategy to promote a healthy infant microbiome following cesarean section (Cunnington et al. 2016; Yasmin et al. 2017).

Challenges in DOHaD

Too much focus on moms

Most DOHaD research has focused on how maternal experiences negatively impact infant health, with few studies considering paternal experiences (Pentecost et al. 2018; Soubry 2018;

Sharp et al. 2018, 2019). Yet, evidence indicates that environmental insults may trigger both genetic and epigenetic changes which impact sperm development, with implications for offspring health (Soubry et al. 2014; Cordier 2008; Hur et al. 2017). Thus, the transfer of paternal environmental information may play a role in shaping later disease risks. For example, older paternal age has been linked with increased odds of child morbidity, likely due to a higher risk of epigenetic damage in sperm during aging (Soubry et al. 2014; Rando and Chang 2012; Jenkins et al. 2014). Paternal under- and over-nutrition have also been linked with poor metabolic health in offspring, attributed to the sperm-based inheritance of epigenetic factors influencing metabolism (Hur et al. 2017).

Experienced trauma also appears to be transmitted along paternal lines. For example, American Indian boarding school attendance has been linked with high rates of physical and sexual abuse, especially among men (Brave Heart 1999). Two studies found that the children of men who attended boarding school have an elevated risk of chronic poor health (e.g., tuberculosis, diabetes, arthritis, high blood pressure, heart disease, stroke, high cholesterol, etc.) in adulthood (Brave Heart 1999; Running Bear et al. 2019). Men should thus be considered in future DOHaD paradigms to construct a more complete picture of how environmental exposures shape both genetic and epigenetic processes in both sexes, with consequences for long-term offspring health (e.g., Pentecost et al. 2018; Sharp et al. 2018, 2019; also see Gray, Staffis, and Anderson in this volume). Increased research focus on paternal contributions to DOHaD will also help clarify the exact mechanisms behind paternal germ transmission to offspring (Soubry 2018). The inclusion of paternal data in DOHaD studies will allow for the better application of evidence-based medical interventions to support infant health; for example, by educating men about the potential consequences of smoking and toxin exposure to their offspring.

Dangers of focus on developmental “programming”

Despite the central role of developmental plasticity in DOHaD, many of the study results are interpreted within the framework of developmental “programming” (Waggoner and Uller 2015). This means that DOHaD studies that explore health inequalities may be misinterpreted to reify notions of inherent biological difference, inadvertently leading the public to mistakenly conclude that poor and racialized people are destined to have poor health. Reviewing the way that DOHaD studies are talked about in popular contexts demonstrates this point. Yehuda et al. (2018) described the public perception of transgenerational trauma studies. Despite the fact that responsible scientists discuss their findings within the broader context of limitations and call for replication, science journalists often simplify these messages for public consumption, leading to an assumption of predetermined poor health among those with a personal or familial history of trauma. To avoid these inappropriate interpretations, DOHaD researchers must be careful to emphasize plasticity over programming. More fundamentally, future work may require a shift in the research questions that are asked in the first place. Studies that place more emphasis on intervention, resilience, or positive aspects of the environment can help shift the dialogue from faulty preconceptions that disadvantaged people are doomed to suffer.

While exposures during early development are incredibly important, focusing only on this period can have problematic impacts. For example, improving nutrition in the perinatal period, but not providing nutritional support across the life course could inadvertently result in a developmental mismatch, with expectations based on early life experience not matching those conditions experienced in later life (Bateson et al. 2014). In fact, dietary macronutrient interventions in pregnancy have had minimal effects on improving offspring birth weight. The Maternal Nutritional Buffering Model proposes the reason why is that placental mammals, such as humans,

have evolved mechanisms to buffer the developing fetus from transient nutritional changes that are not necessarily reflective of long-term environmental experience (Thayer et al. 2020).

Offspring biology is affected not only by periconceptual factors, but also by long-term trends in parental environmental experience. In order to substantially increase birth weight, it is therefore necessary to have more sustained interventions. A study in Guatemala, which provided supplementation across multiple pregnancies and into childhood, provides preliminary support for this hypothesis (Martorell 1995). Specifically, supplementation across two pregnancies and the intervening lactation period resulted in the birth of infants that were 301 grams heavier (Villar and Rivera 1988). Daughters whose mothers were provided nutritious supplements as children gave birth to offspring who were 116 grams heavier than mothers provided with less nutritious supplements (Behrman et al. 2009). In contrast, a systematic Cochrane Review summarizing the impacts of macronutrient supplementation trials during pregnancy reported only a modest 41-gram increase in birth weight (Ota et al. 2015). These results suggest the best outcomes will be achieved by improving longer-term environmental experiences and conditions across the life course.

Conclusions

This chapter provided a review of the DOHaD concept, highlighting recent examples of research and the potential for environmentally induced epigenetic and microbiome changes

Table 2.1 List of underexplored DOHaD applications of potential interest to anthropologists

<i>Broad area</i>	<i>Potential research questions</i>	<i>Background reading</i>
Assisted reproductive technologies	How does infertility stress and/or stress associated with ART affect fetal development?	(Thayer 2020)
Incarceration/detention	How does stress associated with incarceration or forced detention affect fetal development?	(Testa et al. 2019)
Climate change	What is the impact of increased climate change-related natural disasters, such as fires, on prenatal stress and fetal development?	(O'Donnell and Behie 2013)
	What are the impacts of thermal stress and air pollutants on fetal development and later life health?	(Wang et al. 2019)
Paternal psychosocial stress	How do paternal depression, stress, and anxiety affect offspring development?	(Liu et al. 2016)
	How does this vary according to species-specific or cross-cultural expectations for paternal involvement in childcare?	(Feldman et al. 2019)
Protective early life experiences	What protective factors buffer the impact of early life stress on development?	(Werner 2000)
	What are the appropriate timescales for intervention?	(Thayer et al. 2020)
Historical trauma	What are the biological, behavioral, and cultural pathways through which historical trauma can influence health?	(Conching and Thayer 2019)
COVID-19 pandemic	How has the COVID-19 pandemic impacted maternal stress during pregnancy and the postpartum period, and what impacts has that had on offspring development?	(Gildner and Thayer 2020)

to mediate the impacts of early environments on biology and health. While work in this field has historically focused on maternal effects, there is an increased interest in the impacts of paternal environmental experiences on offspring development. Future studies must also move away from the idea that early life experiences “program” individuals, predestining their health.

There are a number of topics in the anthropology of reproduction within DOHaD, that point to future research directions (see Table 2.1). The nature of these questions promote collaboration among anthropologists from a range of sub-fields. To take one example, a robust sociocultural literature documents the social and psychological impacts of infertility and the different cultural expectations of reproduction shaping individual experiences of infertility for both men and women, as well as the uses of assisted reproductive technologies (Inhorn and Patrizio 2015). However, infertility-related stress has only been recently considered in DOHaD research (Thayer 2020), and the few studies that have applied DOHaD to assisted reproductive technologies have been chiefly interested in understanding the biological impacts of the procedures themselves (Roseboom 2018).

A DOHaD perspective has important health policy implications, although its utility has yet to be fully recognized. Long-term interventions should be implemented whenever possible, lasting and ideally extending beyond the duration of critical developmental periods. These targeted interventions, while challenging to fund, could include creative approaches to altering environmental signals, such as supplementing pregnant or breastfeeding mothers to enhance offspring developmental and health outcomes in populations where nutritional deficiencies are prevalent, but not triggering a developmental mismatch. Additional work is needed to determine the efficacy of these interventions and the duration required to exert beneficial developmental effects.

References

- Amundson, Ron. 2005. *The Changing Role of the Embryo in Evolutionary Thought: Roots of Evo-Devo. Cambridge Studies in Philosophy and Biology*. Cambridge: Cambridge University Press. <https://doi.org/10.1017/CBO9781139164856>.
- Aristizabal, Maria J, Ina Anreiter, Thorhildur Halldorsdottir, Candice L Odgers, Thomas W McDade, Anna Goldenberg, Sara Mostafavi, Michael S Kobor, Elisabeth B. Binder, Marla B. Sokolowski, and Kieran J. O'Donnell. 2019. “Biological Embedding of Experience: A Primer on Epigenetics.” *Proceedings of the National Academy of Sciences*, 201820838. <https://doi.org/10.1073/pnas.1820838116>.
- Barker, DJP. 1994. “The Fetal Origins of Adult Disease.” *Fetal and Maternal Medicine Review* 6 (2) : 71–80. Cambridge University Press. <https://doi.org/10.1017/S0965539500001005>.
- Barker, DJP. 2012. “Developmental Origins of Chronic Disease.” *Public Health* 126 (3): 185–189. <https://doi.org/10.1016/j.puhe.2011.11.014>.
- Barker, D J P, C Osmond, P D Winter, B Margetts, and S J Simmonds. 1989. “Weight in Infancy and Death from Ischaemic Heart Disease.” *The Lancet* 334 (8663): 577–80. [https://doi.org/10.1016/s0140-6736\(89\)90710-1](https://doi.org/10.1016/s0140-6736(89)90710-1). PMID: 2570282.
- Barker, David J P, Tom Forsén, Antti Uutela, Clive Osmond, and Johan G Eriksson. 2001. “Size at Birth and Resilience to Effects of Poor Living Conditions in Adult Life: Longitudinal Study.” *BMJ* 323 (7324): 1273.
- Barker, David J P, Keith M Godfrey, Peter D Gluckman, Jane E Harding, Julie A Owens, and Jeffrey S Robinson. 1993a. “Fetal Nutrition and Cardiovascular Disease in Adult Life.” *The Lancet* 341 (8850): 938–41.
- Barker, David J P, C Nicholas Hales, C H D Fall, Clive Osmond, K Phipps, and P M S Clark. 1993b. “Type 2 (Non-Insulin-Dependent) Diabetes Mellitus, Hypertension and Hyperlipidaemia (Syndrome X): Relation to Reduced Fetal Growth.” *Diabetologia* 36 (1): 62–67.
- Barker, David J P, and Clive Osmond. 1986. “Infant Mortality, Childhood Nutrition, and Ischaemic Heart Disease in England and Wales.” *The Lancet* 327 (8489): 1077–81.
- Bateson, Patrick. 2001. “Fetal Experience and Good Adult Design.” *International Journal of Epidemiology* 30 (5): 928–34.

- Bateson, Patrick, Peter Gluckman, and Mark Hanson. 2014. "The Biology of Developmental Plasticity and the Predictive Adaptive Response Hypothesis." *The Journal of Physiology* 592 (11): 2357–68.
- Behrman, Jere R, Maria C Calderon, Samuel H Preston, John Hoddinott, Reynaldo Martorell, and Aryeh D Stein. 2009. "Nutritional Supplementation in Girls Influences the Growth of Their Children: Prospective Study in Guatemala." *American Journal of Clinical Nutrition* 90 (5): 1372–79.
- Bell, Christopher G, Robert Lowe, Peter D Adams, Andrea A Baccarelli, Stephan Beck, Jordana T Bell, Brock C Christensen, et al. 2019. "DNA Methylation Aging Clocks: Challenges and Recommendations." *Genome Biology* 20 (1): 249. <https://doi.org/10.1186/s13059-019-1824-y>.
- Bokulich, Nicholas A, Jennifer Chung, Thomas Battaglia, Nora Henderson, Melanie Jay, Huilin Li, Arnon D Lieber, Fen Wu, Guillermo I Perez-Perez, and Yu Chen. 2016. "Antibiotics, Birth Mode, and Diet Shape Microbiome Maturation during Early Life." *Science Translational Medicine* 8 (343): 343ra82–343ra82.
- Brave, Heart, Maria Yellow Horse. 1999. "Gender Differences in the Historical Trauma Response among the Lakota." *Journal of Health & Social Policy* 10 (4): 1–21.
- Brody, Gene H, Gregory E Miller, Tianyi Yu, Steven R H Beach, and Edith Chen. 2016. "Supportive Family Environments Ameliorate the Link Between Racial Discrimination and Epigenetic Aging: A Replication Across Two Longitudinal Cohorts." *Psychological Science* 27 (4): 530–41. <https://doi.org/10.1177/0956797615626703>.
- Brown, Ryan. 2018. "The Mexican Drug War and Early-Life Health: The Impact of Violent Crime on Birth Outcomes." *Demography* 55 (1): 319–40.
- Bukhary, Noriklil Bukhary Ismail, Zaleha Md Isa, Khadijah Shamsuddin, Khor Geok Lin, Zaleha Abdullah Mahdy, Haslinda Hassan, and Noor Sharifatul Hana Yeop. 2016. "Risk Factors for Antenatal Hypovitaminosis D in an Urban District in Malaysia." *BMC Pregnancy and Childbirth* 16 (1): 156. <https://doi.org/10.1186/s12884-016-0939-3>.
- Clarkin, P. 2017. "Prenatal 'Shocks' and Birth Outcomes." <https://kevishere.com/2017/09/15/prenatal-shocks-and-birth-outcomes/>.
- Clemens, Tom, and Chris Dibben. 2017. "Living in Stressful Neighbourhoods during Pregnancy: An Observational Study of Crime Rates and Birth Outcomes." *European Journal of Public Health* 27 (2): 197–202.
- Conching, Andie Kealohi Sato, and Zaneta Thayer. 2019. "Biological Pathways for Historical Trauma to Affect Health: A Conceptual Model Focusing on Epigenetic Modifications." *Social Science and Medicine* 230: 74–82. <https://doi.org/10.1016/j.socscimed.2019.04.001>.
- Cordier, Sylvaine. 2008. "Evidence for a Role of Paternal Exposures in Developmental Toxicity." *Basic & Clinical Pharmacology & Toxicology* 102 (2): 176–81.
- Corvaglia, Luigi, Giacomo Tonti, Silvia Martini, Arianna Aceti, Giuseppe Mazzola, Irene Aloisio, Diana Di Gioia, and Giacomo Faldella. 2016. "Influence of Intrapartum Antibiotic Prophylaxis for Group B Streptococcus on Gut Microbiota in the First Month of Life." *Journal of Pediatric Gastroenterology and Nutrition* 62 (2): 304–8.
- Cunnington, Aubrey J, Kathleen Sim, Aniko Deierl, J Simon Kroll, Eimear Brannigan, and Jonathan Darby. 2016. *British Medical Journal* 352: i227. doi:10.1136/bmj.i227.
- Dietert, Rodney R. 2017. "The Microbiome-Immune-Host Defense Barrier Complex (Microimmunosome) and Developmental Programming of Noncommunicable Diseases." *Reproductive Toxicology* 68: 49–58. <https://doi.org/10.1016/j.reprotox.2016.04.026>.
- Dominguez-Bello, Maria G, Elizabeth K Costello, Monica Contreras, Magda Magris, Glida Hidalgo, Noah Fierer, and Rob Knight. 2010. "Delivery Mode Shapes the Acquisition and Structure of the Initial Microbiota across Multiple Body Habitats in Newborns." *Proceedings of the National Academy of Sciences* 107 (26): 11971–75.
- Dominguez-Bello, Maria G, Cassandra M De Jesus-Laboy, Nan Shen, Laura M Cox, Amnon Amir, Antonio Gonzalez, Nicholas A Bokulich, Se Jin Song, Marina Hoashi, and Juana I Rivera-Vinas. 2016. "Partial Restoration of the Microbiota of Cesarean-Born Infants via Vaginal Microbial Transfer." *Nature Medicine* 22 (3): 250.
- Dörner, G. 1973. "Possible Significance of Prenatal And-or Perinatal Nutrition for the Pathogenesis of Obesity." *Acta Biologica et Medica Germanica* 30 (5): K19.
- Ellison, P T, and G Jasienska. 2007. "Constraint, Pathology, and Adaptation: How Can We Tell Them Apart?" *American Journal of Human Biology* 19 (5): 622–30. <https://doi.org/10.1002/ajhb.20662>.
- Elwan, Deena, Melvin B Heyman, Janet M Wojcicki, Elizabeth Blackburn, Jue Lin, and Elissa Epel. 2016. "Early Exclusive Breastfeeding Is Associated with Longer Telomeres in Latino Preschool Children." *The American Journal of Clinical Nutrition* 104 (2): 397–405. <https://doi.org/10.3945/ajcn.115.115428>.

- Farewell, C V, Z M Thayer, J E Puma, and S Morton. 2018a. "Exploring the Timing and Duration of Maternal Stress Exposure: Impacts on Early Childhood BMI." *Early Human Development* 117. <https://doi.org/10.1016/j.earlhumdev.2017.12.001>.
- Farewell, CV, Z M Thayer, D P Tracer, and S Morton. 2018b. "Prenatal Stress Exposure and Early Childhood BMI: Exploring Associations in a New Zealand Context." *American Journal of Human Biology*. <https://doi.org/10.1002/ajhb.23116>.
- Feldman, Ruth, Katharina Braun, and Frances A Champagne. 2019. "The Neural Mechanisms and Consequences of Paternal Caregiving." *Nature Reviews Neuroscience* 1 (20) : 205–224.
- Felix, J F and Charlotte A M Cecil. 2019. "Population DNA Methylation Studies in the Developmental Origins of Health and Disease (DOHaD) Framework." *Journal of Developmental Origins of Health and Disease* 10 (3): 306–13.
- Folami, Y Ideraabdullah, M Belenchia Anthony, S Rosenfeld Cheryl, W Kullman Seth, Knuth Megan, Mahapatra Debabrata, Bereman Michael, D Levin Edward, and A Peterson Catherine. 2019. "Maternal Vitamin D Deficiency and Developmental Origins of Health and Disease (DOHaD)." *Journal of Endocrinology* 241 (2): R65–80. <https://doi.org/10.1530/JOE-18-0541>.
- Gettler, Lee T, David T S Lin, Valchy Miegakanda, Sheina Lew-Levy, Geeta N Eick, J Josh Snodgrass, Julia L MacIsaac, Katia E Ramadori, Michael S Kobor, and Adam H Boyette. 2019. "Epigenetic Aging in Children from a Small-Scale Farming Society in The Congo Basin: Associations with Child Growth and Family Conflict." *Developmental Psychobiology* 0 (0): 1–16. <https://doi.org/10.1002/dev.21935>.
- Gildner, T, and Z Thayer. 2020. "Maternal and Child Health during the COVID-19 Pandemic: Contributions in the Field of Human Biology." *American Journal of Human Biology*, e23494. <https://doi.org/10.1002/ajhb.23494>.
- Gluckman, Peter D, Mark A Hanson, and Felicia M Low. 2019. "Evolutionary and Developmental Mismatches Are Consequences of Adaptive Developmental Plasticity in Humans and Have Implications for Later Disease Risk." *Philosophical Transactions of the Royal Society B: Biological Sciences* 374 (1770): 20180109. <https://doi.org/10.1098/rstb.2018.0109>.
- Goodman, Julia, Janne Boone-Heinonen, Dawn Richardson, Sarah Andrea, and Lynne Messer. 2018. "Analyzing Policies Through a DOHaD Lens: What Can We Learn?" *International Journal of Environmental Research and Public Health* 15 (12): 2906. <https://doi.org/10.3390/ijerph15122906>.
- Grossman, Daniel, Umair Khalil, and Arijit Ray. 2019. "Terrorism and Early Childhood Health Outcomes: Evidence from Pakistan." *Social Science and Medicine* 237: 112453.
- Hanson, Mark, and Peter Gluckman. 2016. "Commentary: Developing the Future: Life Course Epidemiology, DOHaD and Evolutionary Medicine." *International Journal of Epidemiology* 45 (4): 993–96. <https://doi.org/10.1093/ije/dyw105>.
- Hill, Amber, Christina Pallitto, Jennifer McCleary-Sills, and Claudia Garcia-Moreno. 2016. "A Systematic Review and Meta-Analysis of Intimate Partner Violence during Pregnancy and Selected Birth Outcomes." *International Journal of Gynecology & Obstetrics* 133 (3): 269–76.
- Hur, Suzy S J, Jennifer E Cropley, and Catherine M Suter. 2017. "Paternal Epigenetic Programming: Evolving Metabolic Disease Risk." *Journal of Molecular Endocrinology* 58 (3): R159–68. <https://doi.org/10.1530/JME-16-0236>.
- Ideraabdullah, F Y, and S H Zeisel. 2018. "Dietary Modulation of the Epigenome." *Physiological Reviews* 98: 667–95. <https://doi.org/10.1152/physrev.00010.2017>.
- Inhorn, Marcia C, and Pasquale Patrizio. 2015. "Infertility around the Globe: New Thinking on Gender, Reproductive Technologies and Global Movements in the 21st Century." *Human Reproduction Update* 21 (4): 411–26.
- Jenkins, Timothy G, Kenneth I Aston, Christian Pflueger, Bradley R Cairns, and Douglas T Carrell. 2014. "Age-Associated Sperm DNA Methylation Alterations: Possible Implications in Offspring Disease Susceptibility." *Plos Genetics* 10 (7): e1004458.
- Jylhävä, Juulia, Nancy L Pedersen, and Sara Hägg. 2017. "Biological Age Predictors." *EBioMedicine* 21: 29–36. <https://doi.org/10.1016/j.ebiom.2017.03.046>.
- Keller, Samantha M, Tiffany S Doherty, and Tania L Roth. 2019. "Pharmacological Manipulation of DNA Methylation Normalizes Maternal Behavior, DNA Methylation, and Gene Expression in Dams with a History of Maltreatment." *Scientific Reports* 9 (1): 10253. <https://doi.org/10.1038/s41598-019-46539-4>.
- Keski-Nisula, Leea, Hanna-Reetta Kyyräinen, Ulla Kärkkäinen, Jari Karhukorpi, Seppo Heinonen, and Juha Pekkanen. 2013. "Maternal Intrapartum Antibiotics and Decreased Vertical Transmission of *L. Actobacillus* to Neonates during Birth." *Acta Paediatrica* 102 (5): 480–85.

- Koppensteiner, Martin Foureaux, and Marco Manacorda. 2016. "Violence and Birth Outcomes: Evidence from Homicides in Brazil." *Journal of Development Economics* 119: 16–33.
- Kuzawa, C W. 2007. "Developmental Origins of Life History: Growth, Productivity, and Reproduction." *American Journal of Human Biology* 19 (5): 654–61. <https://doi.org/10.1002/ajhb.20659>.
- Kuzawa, Christopher W, and Elizabeth A Quinn. 2009. "Developmental Origins of Adult Function and Health: Evolutionary Hypotheses." *Annual Review Of Anthropology* 38: 131–47.
- Lauderdale, Diane S. 2006. "Birth Outcomes for Arabic-Named Women in California Before and After September 11." *Demography* 43 (1): 185–201. <https://doi.org/10.1353/dem.2006.0008>.
- Li, Jie, Simin Liu, Songtao Li, Rennan Feng, Lixin Na, Xia Chu, Xiaoyan Wu, et al. 2017. "Prenatal Exposure to Famine and the Development of Hyperglycemia and Type 2 Diabetes in Adulthood across Consecutive Generations: A Population-Based Cohort Study of Families in Suihua, China." *The American Journal of Clinical Nutrition* 105 (1): 221–27. <https://doi.org/10.3945/ajcn.116.138792>.
- Li, Ruowei, Joselito Magadia, Sara B Fein, and Laurence M Grummer-Strawn. 2012. "Risk of Bottle-Feeding for Rapid Weight Gain During the First Year of Life." *Archives of Pediatrics & Adolescent Medicine* 166 (5): 431–36. <https://doi.org/10.1001/archpediatrics.2011.1665>.
- Liu, Can, S Cnattingius, Malin Bergström, Viveca Östberg, and Anders Hjern. 2016. "Prenatal Parental Depression and Preterm Birth: A National Cohort Study." *BJOG: An International Journal of Obstetrics and Gynaecology* 123 (12): 1973–82.
- Lumey, Lambert H. 1992. "Decreased Birthweights in Infants after Maternal in Utero Exposure to the Dutch Famine of 1944–1945." *Paediatric and Perinatal Epidemiology* 6 (2): 240–53.
- Marini, Sandro, Kathryn A Davis, Thomas W Soare, Yiwen Zhu, Matthew J Suderman, Andrew J Simpkin, Andrew D A C Smith, Erika J Wolf, Caroline L Relton, and Erin C Dunn. 2019. "Adversity Exposure during Sensitive Periods Predicts Accelerated Epigenetic Aging in Children." *Psychoneuroendocrinology*, 104484. <https://doi.org/10.1016/j.psyneuen.2019.104484>.
- Marioni, Riccardo E, Sarah E Harris, Sonia Shah, Allan F McRae, Thomas von Zglinicki, Carmen Martin-Ruiz, Naomi R Wray, Peter M Visscher, and Ian J Deary. 2016. "The Epigenetic Clock and Telomere Length Are Independently Associated with Chronological Age and Mortality." *International Journal of Epidemiology* 45 (2): 424–32.
- Martorell, Reynaldo. 1995. "Results and Implications of the INCAP Follow-up Study." *Journal of Nutrition* 125 (4 Suppl): 1127S–1138S.
- Mayr, Ernst. 1985. "Weismann and Evolution." *Journal of the History of Biology* 18 (3): 295–329.
- McAree, T, B Jacobs, T Manickavasagar, S Sivalokanathan, L Brennan, P Bassett, S Rainbow, and M Blair. 2013. "Vitamin D Deficiency in Pregnancy – Still a Public Health Issue." *Maternal and Child Nutrition* 9: 23–30. <https://doi.org/10.1111/mcn.12014>.
- McKerracher, L, T Moffat, M Barker, D Williams, and D M Sloboda. 2019. "Translating the Developmental Origins of Health and Disease Concept to Improve the Nutritional Environment for Our next Generations: A Call for a Reflexive, Positive, Multi-Level Approach." *Journal of Developmental Origins of Health and Disease* 10 (4): 420–28. <https://doi.org/10.1017/S2040174418001034>.
- Mueller, Noel T, Elizabeth Bakacs, Joan Combellick, Zoya Grigoryan, and Maria G Dominguez-Bello. 2015. "The Infant Microbiome Development: Mom Matters." *Trends in Molecular Medicine* 21 (2): 109–17.
- Murgatroyd, C, J P Quinn, H M Sharp, A Pickles, and J Hill. 2015. "Effects of Prenatal and Postnatal Depression, and Maternal Stroking, at the Glucocorticoid Receptor Gene." *Transl Psychiatry* 5: e560. <https://doi.org/10.1038/tp.2014.140>.
- Nettle, Daniel, and Melissa Bateson. 2015. "Adaptive Developmental Plasticity: What Is It, How Can We Recognize It and When Can It Evolve?" *Proceedings of the Royal Society B: Biological Sciences* 282 (1812): 20151005.
- Novak, Nicole L, Arline T Geronimus, and Aresha M Martinez-Cardoso. 2017. "Change in Birth Outcomes among Infants Born to Latina Mothers after a Major Immigration Raid." *International Journal of Epidemiology* 46 (3): 839–49. <https://doi.org/10.1093/ije/dyw346>.
- Novilla, M, B Lelinneth, Michael C Goates, Michael D Barnes, and Justin M Packer. 2019. "Public Health and Social Policy Perspectives on DOHaD." In *Early Life Origins of Ageing and Longevity*, edited by Alexander Vaiserman, 285–302. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-24958-8_15.
- O'Donnell, M H, and A M Behie. 2013. "Effects of Bushfire Stress on Birth Outcomes: A Cohort Study of the 2009 Victorian Black Saturday Bushfires." *International Journal of Disaster Risk Reduction* 5: 98–106. <https://doi.org/10.1016/j.ijdrr.2013.08.002>.

- Odentsova, Veronika V, Fiona A Hagenbeek, Matthew Suderman, Doretta Caramaschi, Catharina E M van Beijsterveldt, Noah A Kallsen, Erik A Ehli, et al. 2019. "DNA Methylation Signatures of Breastfeeding in Buccal Cells Collected in Mid-Childhood." *Nutrients* 11 (11): 2804. <https://doi.org/10.3390/nu11112804>.
- Ota, Erika, Hiroyuki Hori, Rintaro Mori, Ruoyan Tobe-Gai, and Diane Farrar. 2015. "Antenatal Dietary Education and Supplementation to Increase Energy and Protein Intake." *Cochrane Database of Systematic Reviews* 2015 (6): CD000032. <https://doi.org/10.1002/14651858.CD000032.pub3>. PMID: 26031211.
- Owen, Christopher G, Richard M Martin, Peter H Whincup, George Davey Smith, and Derek G Cook. 2005. "Effect of Infant Feeding on the Risk of Obesity Across the Life Course: A Quantitative Review of Published Evidence." *Pediatrics* 115 (5): 1367–77. <https://doi.org/10.1542/peds.2004-1176>.
- Palma-Gudiel, H, A Córdova-Palomera, E Eixarch, M Deuschle, and L Fañanás. 2015. "Maternal Psychosocial Stress during Pregnancy Alters the Epigenetic Signature of the Glucocorticoid Receptor Gene Promoter in Their Offspring: A Meta-Analysis." *Epigenetics* 10 (10): 893–902. <https://doi.org/10.1080/15592294.2015.1088630>.
- Pannaraj, Pia S, Fan Li, Chiara Cerini, Jeffrey M Bender, Shangxin Yang, Adrienne Rollie, Hely Adisetyo, Sara Zabih, Pamela J Lincez, and Kyle Bittinger. 2017. "Association between Breast Milk Bacterial Communities and Establishment and Development of the Infant Gut Microbiome." *JAMA Pediatrics* 171 (7): 647–54.
- Patrycja, A Jazwicz, and M Sloboda Deborah. 2019. "Nutritional Adversity, Sex and Reproduction: 30 Years of DOHaD and What Have We Learned?" *Journal of Endocrinology* 242 (1): T51–68. <https://doi.org/10.1530/JOE-19-0048>.
- Peng, Cheng, Andres Cardenas, Sheryl L Rifas-Shiman, Marie-France Hivert, Diane R Gold, Thomas A Platts-Mills, Xihong Lin, et al. 2019. "Epigenetic Age Acceleration Is Associated with Allergy and Asthma in Children in Project Viva." *Journal of Allergy and Clinical Immunology* 143 (6): 2263–2270.e14. <https://doi.org/10.1016/j.jaci.2019.01.034>.
- Pentecost, M, F C Ross, and A Macnab. 2018. "Beyond the Dyad: Making Developmental Origins of Health and Disease (DOHaD) Interventions More Inclusive." *Journal of Developmental Origins of Health and Disease* 9 (1): 10–14. <https://doi.org/10.1017/S2040174417000629>.
- Perez, Marcos Francisco, and Ben Lehner. 2019. "Intergenerational and Transgenerational Epigenetic Inheritance in Animals." *Nature Cell Biology* 21 (1): 143–151. <https://doi.org/10.1038/s41556-018-0242-9>.
- Perna, Laura, Yan Zhang, Ute Mons, Bernd Holleczeck, Kai-Uwe Saum, and Hermann Brenner. 2016. "Epigenetic Age Acceleration Predicts Cancer, Cardiovascular, and All-Cause Mortality in a German Case Cohort." *Clinical Epigenetics* 8 (1): 64. <https://doi.org/10.1186/s13148-016-0228-z>.
- Rando, Thomas A, and Howard Y Chang. 2012. "Aging, Rejuvenation, and Epigenetic Reprogramming: Resetting the Aging Clock." *Cell* 148 (1–2): 46–57.
- Rogawski, Elizabeth T, James A Platts-Mills, Jessica C Seidman, Sushil John, Mustafa Mahfuz, Manjeswori Ulak, Sanjaya K Shrestha, Sajid Bashir Soofi, Pablo Penataro Yori, and Estomih Mduma. 2017. "Use of Antibiotics in Children Younger than Two Years in Eight Countries: A Prospective Cohort Study." *Bulletin of the World Health Organization* 95 (1): 49.
- Roseboom, Tessa J. 2018. "Developmental Plasticity and Its Relevance to Assisted Human Reproduction." *Human Reproduction* 33 (4): 546–52. <https://doi.org/10.1093/humrep/dey034>.
- Roseboom, Tessa J, Jan H P Van Der Meulen, Anita C J Ravelli, Clive Osmond, David J P Barker, and Otto P Bleker. 2001. "Effects of Prenatal Exposure to the Dutch Famine on Adult Disease in Later Life: An Overview." *Molecular and Cellular Endocrinology* 185 (1): 93–98.
- Running Bear, Ursula, Zaneta M Thayer, Calvin D Croy, Carol E Kaufman, and Spero M Manson. 2019. "The Impact of Individual and Parental American Indian Boarding School Attendance on Chronic Physical Health of Northern Plains Tribes." *Family and Community Health* 42 (1): 1–7. <https://doi.org/10.1097/FCH.0000000000000205>.
- Ryan, Calen P. 2020. "'Epigenetic Clocks': Theory and Applications in Human Biology." *American Journal of Human Biology*: e23488. <https://doi.org/10.1002/ajhb.23488>.
- Santamaria, Christina, Wei Guang Bi, Line Leduc, Negar Tabatabaei, Prévost Jantchou, Zhong-Cheng Luo, François Audibert, Anne Monique Nuyt, and Shu Qin Wei. 2018. "Prenatal Vitamin D Status and Offspring's Growth, Adiposity and Metabolic Health: A Systematic Review and Meta-Analysis." *British Journal of Nutrition* 119 (3): 310–19. <https://doi.org/10.1017/S0007114517003646>.

- Selin, Helaine, and Pamela Kendall Stone, eds. 2009. *Childbirth across Cultures: Ideas and Practices of Pregnancy, Childbirth and the Postpartum*. Dordrecht: Springer Science.
- Sharp, G C, L Schellhas, S S Richardson, and D A Lawlor. 2019. "Time to Cut the Cord: Recognizing and Addressing the Imbalance of DOHaD Research towards the Study of Maternal Pregnancy Exposures." *Journal of Developmental Origins of Health and Disease* 10 (05): 509–12. <https://doi.org/10.1017/S2040174419000072>.
- Sharp, Gemma C, Deborah A Lawlor, and Sarah S Richardson. 2018. "It's the Mother!: How Assumptions about the Causal Primacy of Maternal Effects Influence Research on the Developmental Origins of Health and Disease." *Social Science and Medicine* 213: 20–27. <https://doi.org/10.1016/j.socscimed.2018.07.035>.
- Shreiner, Andrew, Gary B Huffnagle, and Mairi C Noverr. 2008. "The 'Microflora Hypothesis' of Allergic Disease." In *GI Microbiota and Regulation of the Immune System*, edited by Gary Huffnagle and Mairi Noverr, 113–34. New York: Springer.
- Smith, Clement A. 1947. "Effects of Maternal Undernutrition upon the Newborn Infant in Holland (1944–1945)." *Journal of Pediatrics* 30: 229–43.
- Soubry, Adelheid. 2018. "Epigenetics as a Driver of Developmental Origins of Health and Disease: Did We Forget the Fathers?" *Bioessays* 40 (1): 1700113. <https://doi.org/10.1002/bies.201700113>.
- Soubry, Adelheid, Cathrine Hoyo, Randy L Jirtle, and Susan K Murphy. 2014. "A Paternal Environmental Legacy: Evidence for Epigenetic Inheritance through the Male Germ Line." *Bioessays*, n/a–n/a. <https://doi.org/10.1002/bies.201300113>.
- Stanner, Sara A, and John S Yudkin. 2001. "Fetal Programming and the Leningrad Siege Study." *Twin Research and Human Genetics* 4 (5): 287–92.
- Steckel, Richard H. 1998. "Birth Weights and Stillbirths in Historical Perspective." *European Journal of Clinical Nutrition* 52 (Supplement 1): S16–20.
- Stiemsma, Leah T, and Karin B Michels. 2018. "The Role of the Microbiome in the Developmental Origins of Health and Disease." *Pediatrics* 141 (4): e20172437. <https://doi.org/10.1542/peds.2017-2437>.
- Stinson, Lisa F. 2019. "Establishment of the Early-Life Microbiome: A DOHaD Perspective." *Journal of Developmental Origins of Health and Disease*, 1–10. <https://doi.org/10.1017/S2040174419000588>.
- Suk, William A, Hamid Ahanchian, Kwadwo Ansong Asante, David O Carpenter, Fernando Diaz-Barriga, Eun-Hee Ha, Xia Huo, et al. 2016. "Environmental Pollution: An Under-Recognized Threat to Children's Health, Especially in Low- and Middle-Income Countries." *Environmental Health Perspectives* 124 (3): A41–45. <https://doi.org/10.1289/ehp.1510517>.
- Tamburini, Sabrina, Nan Shen, Han Chih Wu, and Jose C Clemente. 2016. "The Microbiome in Early Life: Implications for Health Outcomes." *Nature Medicine* 22 (7): 713.
- Temple, Daniel H. 2019. "Bioarchaeological Evidence for Adaptive Plasticity and Constraint: Exploring Life-History Trade-Offs in the Human Past." *Evolutionary Anthropology: Issues, News, and Reviews* 28 (1): 34–46. <https://doi.org/10.1002/evan.21754>.
- Testa, Alexander, Dylan B Jackson, Michael G Vaughn, and Jennifer K Bello. 2019. "Incarceration as a Unique Social Stressor during Pregnancy: Implications for Maternal and Newborn Health." *Social Science and Medicine* 246: 112777. <https://doi.org/10.1016/j.socscimed.2019.112777>.
- Thayer, Z M, and C W Kuzawa. 2015. "Ethnic Discrimination Predicts Poor Self-Rated Health and Cortisol in Pregnancy: Insights from New Zealand." *Social Science and Medicine* 128. <https://doi.org/10.1016/j.socscimed.2015.01.003>.
- Thayer, Z. 2020. "Assisted Reproductive Technologies and Low Birth Weight: The Potential Role of Developmental Sensitivity to Stress." *Evolution, Medicine, and Public Health* 1: 82–83. <https://doi.org/10.1093/emph/eoaa008>.
- Thayer, Z, Julieanne N Rutherford, and C Kuzawa. 2020. "The Maternal Nutritional Buffering Model: An Evolutionary Framework for Pregnancy Nutritional Intervention." *Evolution, Medicine, and Public Health* 1: 14–27. <https://doi.org/10.1093/emph/eoz037>.
- Thayer, Zaneta, Laia Bécares, and Polly Atatoa Carr. 2019. "Maternal Experiences of Ethnic Discrimination and Subsequent Birth Outcomes in Aotearoa New Zealand." *BMC Public Health* 19 (1): 1271. <https://doi.org/10.1186/s12889-019-7598-z>.
- Torche, Florencia. 2011. "The Effect of Maternal Stress on Birth Outcomes: Exploiting a Natural Experiment." *Demography* 48 (4): 1473–91. <https://doi.org/10.1007/s13524-011-0054-z>.

- Tormo-Badia, Neivis, Å Håkansson, K Vasudevan, G Molin, S Ahrné, and C M Cilio. 2014. "Antibiotic Treatment of Pregnant Non-obese Diabetic Mice Leads to Altered Gut Microbiota and Intestinal Immunological Changes in the Offspring." *Scandinavian Journal of Immunology* 80 (4): 250–60.
- Villar, José, and Juan Rivera. 1988. "Nutritional Supplementation during Two Consecutive Pregnancies and the Interim Lactation Period: Effect on Birth Weight." *Pediatrics* 81 (1): 51–57.
- Waggoner, Miranda R, and Tobias Uller. 2015. "Epigenetic Determinism in Science and Society." *New Genetics and Society* 34 (2): 177–95. <https://doi.org/10.1080/14636778.2015.1033052>.
- Wang, Qiong, Qianhong Liang, Changchang Li, Meng Ren, Shao Lin, Luke D Knibbs, Huanhuan Zhang, Wei Gong, Junzhe Bao, and Suhan Wang. 2019. "Interaction of Air Pollutants and Meteorological Factors on Birth Weight in Shenzhen, China." *Epidemiology* 30 (Supplement 1): S57–66.
- Weaver, Ian C G, Nadia Cervoni, Frances A Champagne, Ana C D'Alessio, Shakti Sharma, Jonathan R Seckl, Sergiy Dymov, Moshe Szyf, and Michael J Meaney. 2004. "Epigenetic Programming by Maternal Behavior." *Nature Neuroscience* 7 (8): 847–54. https://doi.org/http://www.nature.com/neuro/journal/v7/n8/supinfo/n1276_S1.html.
- Wells, Jonathan C K. 2018. "Life History Trade-Offs and the Partitioning of Maternal Investment: Implications for Health of Mothers and Offspring." *Evolution, Medicine, and Public Health* 2018 (1): 153–66.
- Werner, Emmy E. 2000. "Protective Factors and Individual Resilience." *Handbook of Early Childhood Intervention* 2: 115–32.
- Yasmin, Farzana, Hein Min Tun, Theodore Brian Konya, David S Guttman, Radha S Chari, Catherine J Field, Allan B Becker, Piush J Mandhane, Stuart E Turvey, and Padmaja Subbarao. 2017. "Cesarean Section, Formula Feeding, and Infant Antibiotic Exposure: Separate and Combined Impacts on Gut Microbial Changes in Later Infancy." *Frontiers in Pediatrics* 5: 200.
- Yehuda, Rachel, Amy Lehrner, and Linda M Bierer. 2018. "The Public Reception of Putative Epigenetic Mechanisms in the Transgenerational Effects of Trauma." *Environmental Epigenetics* 4 (2): dvy018. <https://doi.org/10.1093/eep/dvy018>.