Environmental influences on health and development: nutrition, substance exposure, and adverse childhood experiences

MAURA B GENTNER[1] | MARY L O'CONNOR LEPPERT[1,2]

1 Department of Neurodevelopmental Medicine, Kennedy Krieger Institute, Baltimore, MD; **2** Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Correspondence to Mary L O'Connor Leppert, Kennedy Krieger Institute, 801 North Broadway, Room 552, Baltimore, MD 21205, USA. E-mail: leppert@kennedykrieger.org

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ABBREVIATIONS

ACE	Adverse childhood experiences
HBCS	Helsinki Birth Cohort Studies
HPA	Hypothalamic–pituitary–adrenal

Scientific advances over the last century have generated compelling evidence of the primary and secondary effects of gestational, infant, and childhood conditions. These early environmental influences have the potential not only to impact an individual's health outcomes, such as heart disease, type 2 diabetes, and cancer, but also to confer various protections and risks to that individual's descendants. The immediate and extended ramifications of early environmental exposure bring an understanding of epidemiological impact on disease states and a hope for prevention. This review highlights the contributions of several key population studies and briefly explores specific environmental influences, including nutritional deficiencies, exposure to substances and infections, and adverse childhood experiences. Mechanisms of these influences (e.g. stress and epigenetics) are discussed, as well as possible means of mitigating their negative consequences.

Carefully collected observations from the last century have borne out the importance of environmental influences during critical developmental periods, with significant health consequences not only in childhood but also into adulthood and extending even to the lives of subsequent generations. These findings underpin the concept known as fetal origins of adult disease (FOAD) or developmental origins of health and disease (DOHaD), which holds that the foundations of some adult diseases may be programmed in early life. This epidemiological trend was explored in population studies linking societal well-being with infant and adult health outcomes. Many early contributions to the literature surround undernutrition or poor nutrition during fetal, infant, and early childhood development. This research was followed by examinations of the individual and intergenerational influences of the environment on the fetus and young child. Complementing these earlier observations, the advances of the last half century have provided an understanding of genetic and epigenetic mechanisms, which may begin to explain the environmental-biological dynamic.

THE CONTRIBUTION OF POPULATION STUDIES

In 1934, Kermack et al.[1] investigated the relative mortality rates of 10-year birth cohorts from England, Scotland, Wales, and Sweden and found that each cohort's relative mortality rate remained constant across the cohort's collective lifespan. Vital statistics records demonstrated a clear drop in the relative mortality rate with each successive cohort, which Kermack et al. attributed to incremental societal advances (e.g. industrial legislation and medical advances to reduce infectious disease), this in turn helped improve conditions of childhood. This line of investigation led Kermack et al. to the following conclusion:

> The figures behave as if the expectation of life was determined by the conditions which existed during the child's earlier years. For instance, we may postulate that, the health of the child is determined by the environmental conditions existing during the years 0-15, and that the health of the man is determined preponderantly by the physical constitution with which the child was built up.[1]

Observations by Barker and colleagues have complemented and expanded upon Kermack et al.'s conclusions. Barker and Osmond[2] studied the 1968 to 1978 death rates from ischemic heart disease in adults from different geographical areas of England and Wales, and observed a correlation with infant mortality rates in the same areas decades earlier. They found the highest rates of infant mortality and ischemic heart disease in the least affluent of the geographic areas, suggesting that poor nutrition in infancy and early childhood was associated with ischemic heart disease later in life.

This suggestion was subsequently strengthened by Barker et al.[3] in their review of 5654 males born over a 20-year period in Hertfordshire, England. Death rates from ischemic heart disease were high among all social strata of males who were of low birthweight or had low weight at 1 year of age, and those who had low weight both at birth and at 1 year of age fared worst. Subsequently, Godfrey and Barker proffered the Barker's hypothesis, which holds that changes in nutrition, endocrine function, and other physiological processes in the

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fetal and early life environment cause long-lasting alterations in the function of organ systems during development, which preprogram an individual for disease risk as they age.[4]

The Helsinki Birth Cohort Studies (HBCS) I (births in 1924–1933) and II (births in 1934–1944) expanded upon Barker's work, looking not only at low birthweights but also leanness at birth using the ponderal index. The HBCS II study assessed mitigators of adult health outcomes infants with low ponderal indices.[5] Children with low ponderal indices were found to have higher rates of adult heart disease as well as stroke, hypertension, and type 2 diabetes. The HBCS II also showed that children with low ponderal index and poor catch-up growth at 1 to 2 years of age had additional risk of non-communicable diseases in adulthood. Further, those with low ponderal index at birth who demonstrated rapid and excessive catch-up growth after infancy showed increased risk for heart disease. Low socioeconomic status compounded the risk for heart disease in children with low ponderal indices.

Maternal obesity, a condition associated with greater risk of congenital defects in newborn infants, was also associated with higher risks of cardiovascular disease, cancer, and type 2 diabetes in the offspring followed in the HBCS II. These risks were not related to the socio-economic status of the offspring.[5] The idea that infants who are either undernourished in utero or are born to overweight mothers are at increased risk for non-communicable adult diseases was further supported by the observation that the birthweight of infants of egg donors of surrogate mothers is more influenced by the surrogate mother's weight than the biological mother's.[6]

The circumscribed duration and geography of the Dutch famine of 1944 and 1945 yielded powerful observational data about the effects of nutritional deficiencies during pregnancy, adding to the understanding of the scope of Barker's hypothesis. The famine effected a 6-month period during which war and harsh winter deprived the population of access to basic nutritional needs. Adult mortality rates and stillbirths in the first trimester during famine exposure rose while placental weight, birth length, and head circumference of exposed offspring fell. There was a dramatic effect on birthweight, particularly during the third trimester of pregnancy.[7] Susser and Stein also reported on data collected from military induction records in Dutch soldiers 19 years after the famine.[8] These records showed that soldiers who were exposed to famine during early pregnancy had higher rates of obesity, whereas those with exposure later in gestation did not. Further, the offspring of females exposed in utero to the famine during their first two trimesters went on to have their own children, who had lower birthweights than the children of unexposed females. The offspring of females who were exposed in utero to famine in the third trimester did not have offspring with lower birthweights.[8] This remarkable finding introduces the possibility that an adverse environment during early fetal or childhood development may have intergenerational consequences.

What this paper adds

- Substance exposures in utero are associated with epigenetic changes and negative outcomes.
- Adverse childhood experiences in early childhood can induce HPA and epigenetic changes.

The findings of these cohort studies, reproduced in many human and animal population studies, provide clear evidence that adverse conditions in utero or early childhood influence early and later health outcomes of the individuals as well as subsequent generations. The questions then turn to what (besides nutritional deficiencies) constitutes adverse conditions in utero or early childhood that may extend their influences, what the mechanisms of the influence are, and how those influences might be mitigated (Fig. 1).

INFLUENCES, MECHANISMS, AND MITIGATORS

The underlying principle of the DOHaD is programming – the adaptive response to an insult/change that occurs during a critical time in development and may potentially have lifelong effects, including an increased risk of adult disease. There are several proposed mechanisms for the downstream effect of intrauterine adversity. Interestingly, each of the proposed mechanisms results in phenotypic changes in individuals without changing the genotype. Intrauterine stress from paucity of requirements such as nutrients, oxygen, and hormones may have direct effects on the growth and capacity of developing organs. Perhaps in an effort to optimize delivery of requirements to some organs during critical phases of development, other organ systems are deprived, thereby compromising their size and function.[5,9] This theory is of particular interest in the case of low-birthweight and nutritionally deprived infants, where nutrients are preferentially allocated to brain and heart tissue and diverted from the developing liver, kidney, and pancreas, resulting in smaller organs with fewer cells and lesser functional capacity. Ultimately, the diminished capacity of these vital organs contributes to poor postprandial triglyceride and insulin regulation, higher rates of dyslipidaemia, and thus the higher rates of type 2 diabetes, heart disease, and hypertension seen in the HBCS II[5] and other studies.

Excess glucocorticoids may offer another mechanism for DOHaD. The nutritionally deprived fetus or the fetus exposed to elevated glucocorticoids from maternal stress may be a second mechanism of fetal programming through alterations in the hypothalamic–pituitary–adrenal (HPA) axis. Defects in maternal nutrition and increased maternal stress are believed to affect the growth of fetal organs through an increase in fetal cortisol levels or fetal glucocorticoid receptor expression.[10] Altered regulation of the HPA axis during fetal development has been linked to the development of hypertension, cardiovascular disease, and type 2 diabetes in adulthood.[5]

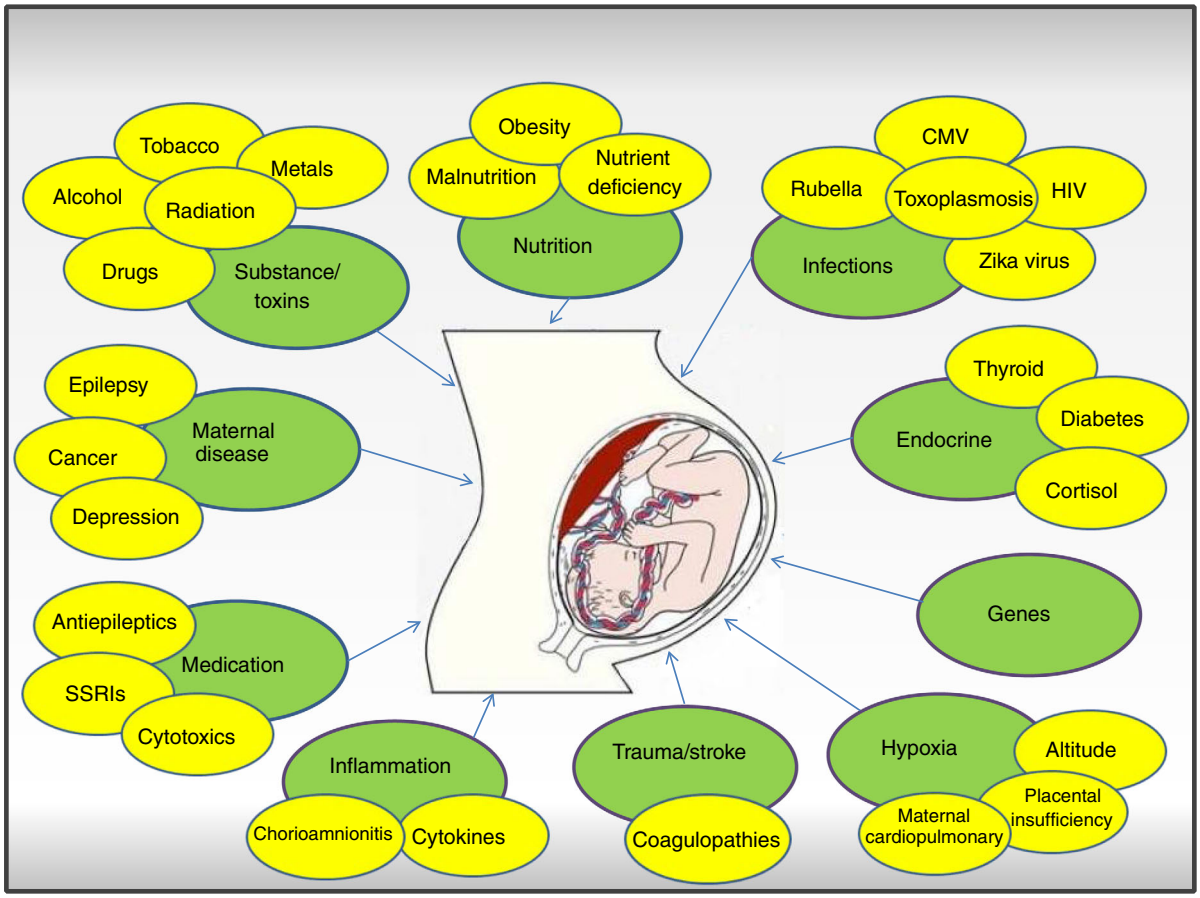

Figure 1: Influences on fetal environment. CMV, cytomegalovirus; HIV, human immunodeficiency virus; SSRIs, selective serotonin reuptake inhibitors. [Colour figure can be viewed at wileyonlinelibrary.com].

In his 1953 article, Waddington reported several revolutionary findings.[11] Environmental stimuli could change the phenotype of a progeny of drosophila and the same stimuli present in the development of subsequent generations replicated the changed phenotype until the phenotypic changes occurred in the absence of the stimuli; he called this phenomena 'genetic assimilation'.[11] We have since come to understand this phenomenon as epigenetic change; a change in gene expression without a change in genotype.

Gene expression can be regulated through epigenetic mechanisms that cause the gene activation (able to be transcribed) or gene silencing (unable to be transcribed). Chromatin can be made active or inactive through the use of several epigenetic mechanisms, such as the modification (acetylation/methylation) of histones and the methylation/demethylation of promoter regions of DNA.[10] A chromatin containing acetylated histones and promoters free of methyl groups allows transcription factors to bind and thereby to undergo transcription. An additional post-transcriptional modification can be found in the regulation of microRNAs; a messenger RNA strand that is bound by a microRNA will be rendered inactive and unable to be translated.[10] Maternal factors, such as age, diet, alcohol consumption, genetic conditions, and metabolic conditions, such as obesity and diabetes, can affect epigenetic pathways in the fetus/offspring through the aforementioned mechanisms.

Advances in our understanding of epigenetic mechanisms have revealed that epigenetic alterations may be common to teratogens such as substance and infection exposures in utero as well as alterations in maternal metabolic and hormonal and hormonal state. Tobacco exposure in utero has well established health consequences for the fetus, including higher rates of stillborn or preterm birth, metabolic and cardiovascular effects, and neurodevelopmental sequelae such as learning disability and attention-deficit/hyperactivity disorder. Tobacco crosses the placental and blood brain barriers and is associated with atypical cytosine-phosphate-guanine methylation of a large number of genes, some of which have implications for neurodevelopmental outcomes. Alcohol, a known teratogen with accompanying growth, cognitive, neurodevelopmental, and physical consequences, has been noted to influence the HPA axis and insulin/glucose intolerance in animal models.[12] A large Canadian study of a fetal alcohol spectrum disorder cohort found hundreds of methylation site alterations, several of which are associated with neurodevelopmental disorders.[13]

Thus both hormonal and epigenetic mechanisms may be at play in the consequences of intrauterine alcohol exposure.

Recent understanding of the influence of in utero exposure to infection also supports the idea that infection may induce phenotypic changes in the fetus in several ways: through direct effect of the pathogen, through the inflammatory cascade associated with infection, or through epigenetic alterations. Intrauterine exposure to rubella, cytomegalovirus, varicella, toxoplasmosis, and now the Zika virus can all have devastating physical and neurodevelopmental costs. Zika virus, for example, exerts a change in the infant RNA through methylation changes.[14] Infants exposed to maternal infection and febrile illness have more copy number variants and higher rates of autism spectrum disorder.[15–17]

Maternal hormonal and metabolic variations exert modifications in fetal development through a number of mechanisms. Hyperglycemia of maternal gestational diabetes is a known teratogen, causing neural tube defects and neurodevelopmental disorders. Some proposed mechanisms for the programming effects of hyperglycemia include increased oxidative stress and accumulation of reactive oxidative species, which alter DNA methylation. Neural stem cell histone acetylation alterations and changes in microRNA are also seen in fetal exposure to hyperglycemia.[17] Maternal obesity is associated with HPA axis changes and increased inflammatory markers. Decreased DNA methylation is seen in pregnancies of females with high body mass indices.[17] In addition to hormonal influences of the HPA axis, the effect of hypothyroidism on the developing fetus has long been documented. Uncorrected maternal hypothyroidism has serious and lasting physical and developmental consequences for the newborn infant, which are again suggestive of epigenetic origin.

There is an emerging body of evidence that environmentally induced epigenetic alterations are also paternally contributed. This evidence includes the observation that paternal nutritional deficits during the preconceptional or periconceptional period impact the metabolic state of children and even grandchildren.[18] Alcohol use in biological fathers is associated with lower cognitive scores and higher rates of attention-deficit/hyperactivity disorder in their children. Recent animal studies also suggest that paternal substance use (e.g. opiates, cocaine) also affects the behavior and development of offspring. Finally, paternal age seems to mitigate health conditions of their progeny, as is seen in the higher incidence of autism spectrum disorder in advanced paternal age.[19,20]

EARLY CHILDHOOD

The influence of the environment on later health and disease does not seem to be limited to the fetal environment but also includes influences in the early years of life. The HBCS[4] and the Hertfordshire[3] studies show that children of low birthweight who remain lean at 1 year of age have higher rates of adult non-communicable disease, as do infants who demonstrate robust rebound weight gain in the first year of life.

In addition to the observations that food scarcity, or dietary limitations in the first years of life, are associated with higher rates of disease in later life, it is becoming clear that the gut microbiome in the first years of life also confers risk for later medical disorders through epigenetic effects. The gut flora is influenced in the first years of life by the method of delivery (vaginal delivery associated with more diverse gut flora in the infant), the child's diet (breast-fed infants have more uniform gut microbiota than formula-fed infants), and the use of antibiotics in early years. Healthy gut microorganisms affect the cellular environment and the balance of enzymes, minerals, and low molecular weight substances (e.g. folate, biotin, butyrate) which are involved in epigenetic processes. Dysbiosis, or microbial imbalance of the gut, alters the cellular environment and therefore the balance of substances required for epigenetic modifications. Gut dysbiosis and consequent epigenetic alterations are implicated in the observed higher rates of irritable bowel disease and celiac disease in children born by Cesarean section, and with colon cancer in diets with high fat and red meat content.[21,22]

More recently, evidence shows that trauma or adverse childhood experiences (ACEs) in infancy and early childhood can also induce HPA and epigenetic changes with consequent increases in adult disease. Stressors that are considered emotionally traumatic or ACEs include but are not limited to exposure to physical, psychological, and sexual abuse; neglect; violence in the home or community; parent mental illness or substance abuse; natural disaster; war; death or separation of caregivers; serious illness or injury; and bullying. Toxic stress – extreme, prolonged, or multiple stress exposures in childhood – is clearly associated with higher rates of adult disease, including ischemic heart disease, stroke, diabetes, and depression. Further, the risk of adult disease increases with each added adverse childhood experience.[23] Similar to fetal exposures, the proposed mechanisms of this increased risk for disease include the neuroendocrine and immune response to alterations, cytokines, and HPA axis dysregulation, as well as their downstream epigenetic responses brought about by continual exposure to stress.[24] There is also significant evidence that epigenetic alterations are a consequence of early childhood environment through DNA methylation/demethylation.[25]

It is also apparent that there is an environmental contribution to language use in early childhood, which confers a lasting influence on a child's linguistic and academic success. There appears to be an inherent genetic endowment which affects the efficiency with which children learn language, and there is evidence that the environment (largely due to parent or caregiver traits) can shape, remediate, or limit language ability. There also appears to be an impact of environmental influences on genetic expression, as there is growing evidence of neurobiological consequences of

environmental exposures that may further change the way we approach language development.

Language studies on the effects of 'environment' largely focus on family characteristics, socio-economic status, parental education, childcare settings, ACEs, and quantitative and qualitative exposure to language. Firstborn children, those in high quality childcare settings, those with higher parental education attainment, and those raised in bilingual environments appear to have better linguistic and academic outcomes. Poorer linguistic outcomes are seen in various at-risk groups, including children in larger families, lower quality childcare settings, and single caregiver homes, as well as those exposed to toxic substances (tobacco, lead) and those whose caregivers suffer from depression or substance abuse or were raised in impoverished, neglectful, or abusive environments. The disparity of language exposure by socio-economic status and parental education was well illustrated by Hart and Risley,[26] who assiduously measured word exposure among children in three different groups: higher socio-economic status professional families, working class families, and welfare families. Over a span of 100 hours, the children of higher socio-economic status professional families were exposed to an average of 215 000 words, whereas their lower socio-economic status welfare counterparts were exposed to 62 000 words. This equates to a 32-million word difference by age 4 years. Additionally, the sophistication of the words to which the children were exposed was much higher in the professional families. The quality of caregiver language use with children also predicts later language development and ultimately academic success. Quality variables include the number of word types, syntax, word sophistication (use of rare words), decontextualized language use, and conversational turns that children are exposed to in early childhood.[27] Though much of the literature on the influences on language development in early childhood focuses on either genetic variations or environmental influences, there is a growing interest in the middle ground – the epigenetic effects of environment on linguistic competency and phenotype.[28]

INTERGENERATIONAL EFFECTS

The observation that fetal environmental deficiencies or excesses have an effect on the next generation should not come as a surprise. Females are born with all of the eggs that they will ever have, are subject to the health of their grandmother's pregnancy, and may carry programmed effects to the next generation. This pattern of inheritance is known as intergenerational inheritance and affects the individual fetus (child) and the germline of that fetus (grandchildren).

The effects of the Dutch famine on the children and grandchildren of females pregnant during the famine demonstrate intergenerational inheritance. Fetal development during the food shortage of the famine was associated with an increase in cardiovascular disease and type 2 diabetes later in life. Unexpectedly, the grandchildren of females pregnant during the famine were more likely to be heavy or obese if they were born to males conceived and carried during the famine than if they were born to females conceived and carried during that same period.[29]

The childhood environment that extends its influences to future generations is, however, somewhat unforeseen. The evaluation of food availability during the slow growth period (8–10y for females and 9–12y for males) and health outcomes of three birth cohorts (birth in 1890, 1905, and 1920) suggests that intergenerational programming effects may extend beyond early childhood. In these cohorts, males who were raised during periods of low food availability had children with lower rates of cardiovascular causes of death and grandchildren with lower rates of diabetes. Males who had sufficient food supply during their slow growth period conferred greatly increased risk for type 2 diabetes to their grandchildren.[18]

Changes in phenotype (rather than genotype) induced by the mechanisms of fetal programming bring the hope that risks for some non-communicable diseases of adults may be diminished by correction of adverse uterine environments. A study on the effects of in utero nutritional deficiency found 30% to 40% lower birthweights in rats that consistently received protein-deficient nutrition in utero. Subsequent cohorts of progeny of these undernourished rats were fed adequate protein beginning in utero, immediately after birth, or 4 weeks after birth. The first generation of rats fed adequate protein in utero were larger than controls, but their birthweight normalized by the third generation. Those fed adequate protein at birth showed improved weight in the first generation and catch-up growth by the third generation, while the cohort whose adequate protein intake began at 4 weeks of life showed no improvement in growth in the first generation but near normal weights by the third generation.[30]

There is also a small but growing literature on the intergenerational consequences of adverse experiences in early childhood. It appears that the offspring of females with four or more ACEs in early childhood have much higher rates of biomedical and psychosocial adversity in early childhood.[31] In a study of homeless parent-child dyads, the number of parent ACE exposures in early childhood predicted higher ACEs in their offspring.[32]

The phenotypical changes seen in the intergenerational effects of epigenetic change from environment exposure are largely thought to 'reset' in generations without direct, intrauterine, or germline exposure. Some phenotypic modifications appear to persist in subsequent generations in the absence of the environmental stimuli that initially induced them. This persistence of a phenotype may represent encoding of a characteristic that contributes evolutionary advantage in an environment of continuing change.[18]

THE HOPE OF PREVENTION

The investigation of the origin of health and disease brings understanding of some of the underlying mechanisms, an opportunity to optimize fetal and early childhood

environments on both individual and societal levels, and hope for prevention, or at least mitigation, of the consequences of adverse environments. Optimizing maternal nutrition and maternal health insofar as possible is the first and clearest goal. Equally important is optimizing the child's nutrition in the first years of life by promoting favorable gut microbiota and ensuring that low-birthweight infants are not subjected to overfeeding.

Understanding mechanisms of disease may also provide opportunities to mitigate disease. Folic acid, for example, has tremendously reduced the number of children born with neural tube defects. Folate is a methyl group donor; deficiency of folate alters the methylation of DNA and microRNA, as well as mutation of the methionine synthase/reductase gene. The mechanistic effect of folate sufficiency may have a tremendous protective effect on epigenetic mechanisms. Ongoing studies of the mechanism of epigenetics, including methylation and histone modifications, may someday lead to improvements in medical treatment.

In early childhood, there is a protective effect of the presence of a nurturing adult caregiver, as the HPA axis response to stress is better regulated than in children who lack a nurturing caregiver.[24] Children whose parents are less nurturing but were themselves raised by more nurturing caregivers still enjoy the benefit of better HPA regulation and more appropriate responses to stress and perhaps decreased frequency of some adult diseases.[24,33] Further, language rich environments appear to enhance linguistic abilities, which optimize academic outcomes. Optimizing children's physical, psychological, and academic health through good nutrition, nurturing caregiving, and high-volume exposure to quality language seems a modest ambition with potentially tremendous individual and societal benefit.

The nature-nurture argument regarding the origin of health and disease (including physical health, psychological well-being, and linguistic, academic, and cognitive proclivities) seems to be coming to a neutral closure. Nature provides the underpinnings of genetic endowment. However, it is very likely that risks and protections for health, disease, and developmental constitution are mitigated through mechanisms of organogenesis, neuroendocrine alterations, and epigenetics.[34] Moreover, it is becoming clear that nurture, understood as environmental influences, includes the prenatal, fetal, early childhood, and previous generation environments, all of which may influence the nature of the individual child, entire generations, and subsequent generations. The ramifications of improved understanding of the nature-nurture, environmental-biological intersection on disease prevention are imponderable at the present, but this type of knowledge brings with it the promise of reducing poor outcomes through optimal environments.

CONFLICT OF INTEREST

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

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RESUMEN

INFLUENCIAS AMBIENTALES EN LA SALUD Y EL DESARROLLO: NUTRICIÓN, EXPOSICIÓN A SUSTANCIAS Y EXPERIENCIAS ADVERSAS EN LA INFANCIA

Los avances científicos en el último siglo han generado pruebas convincentes de los efectos primarios y secundarios de las condiciones de la gestación, el infante y la infancia. Estas influencias ambientales tempranas tienen el potencial no solo de afectar los resultados de salud de una persona, como la enfermedad cardíaca, la diabetes tipo 2 y el cáncer, sino también para conferir diversas protecciones y riesgos a los descendientes de esa persona. Las ramificaciones inmediatas y prolongadas de la exposición ambiental temprana permiten comprender el impacto epidemiológico en los estados de enfermedad y una esperanza de prevención. Esta revisión destaca las contribuciones de varios estudios de población clave y explora brevemente las influencias ambientales específicas, incluidas las deficiencias nutricionales, la exposición a sustancias e infecciones y las experiencias adversas en la infancia. Se discuten los mecanismos de estas influencias (por ejemplo, estrés y epigenética), así como los posibles medios para mitigar sus consecuencias negativas.

RESUMO

INFLUÊNCIAS AMBIENTAIS NA SAÚDE E DESENVOLVIMENTO: NUTRIÇÃO, EXPOSIÇÃO A SUBSTÂNCIAS, E EXPERIÊNCIAS ADVERSAS NA INFÂNCIA

Avanços científicos no ultimo século geraram evidência convincente de efeitos primários e secundários de condições gestacionais e da infância. Estas influências ambientais precoces tem potencial não apenas de impactar os resultados de saúde de um indivíduos, como doença cardíaca, diabetes tipo 2 e câncer, mas também conferem várias proteções e riscos para os descendentes deste indivíduo. As ramificações imediatas e extendidas da exposição ambiental precoce trazem uma compreensão do impacto epidemiológico nos estados de doença, e uma esperança de prevenção. Esta revisão destaca as contribuições de vários estudos populacionais importantes, e explora brevemente infuências ambientais específicas, incluindo deficiências nutricionais, exposição a substâncias e infecções, e experiências adversas na infância. Os mecanismos destas influências (ex: estresse e epigenética) são discutidos, assim como possíveis formas de mitigar suas consequências negativas.