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Unpacking developmental programming: a conceptual and historical analysis in the context of DOHaD

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Review

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Abstract

The Developmental Origins of Health and Disease (DOHaD) paradigm posits that early environmental factors may influence a child's development and long-term health outcomes. Developmental programming (DP) is central to this paradigm, whereby specific early life exposures during critical periods of development are associated with changes to physiological and metabolic pathways, potentially predisposing individuals to disease. However, no standard definition of DP exists, and various terms have been used to describe similar processes. This analysis aimed to develop a conceptual definition for DP to inform interdisciplinary research, education, and practice. Walker and Avant's eight-step method was employed to analyze the literature, incorporating elements of Rogers' evolutionary approach to present the temporal and contextual evolution of the concept. A systematic search of MEDLINE with the EBSCOhost database was performed using the search term "developmental programming," resulting in 95 titles included in this review. Defining attributes associated with DP include epigenetics, ontogeny, critical periods, and plasticity. Antecedents for DP may include maternal and infant nutrition, maternal disease and medication, lifestyle choices, environmental exposures, and stress. The potential consequences include cardiovascular disease, metabolic disorders, diabetes, neurodevelopmental disorders, endocrine disruption, reproductive issues, and mental health conditions. Effective healthcare provider education, knowledge dissemination, and addressing the social determinants of health through a population health approach are essential to translate DP theory and empirical evidence into practice. A common language and understanding of DP can improve the interdisciplinary advancement of DOHaD research to inform practice and education.

The genetics, genomics, and epigenetics literature frequently references the Developmental Origins of Health and Disease (DOHaD) paradigm. The DOHaD framework adopts a life-course perspective, proposing that environmental and lifestyle exposures during critical developmental periods (e.g., *in utero*, the first 1000 days after conception, and adolescence) may influence long-term health trajectories. These exposures may exert lasting effects through biological mechanisms such as the epigenetic regulation of gene expression, alterations in tissue structure and composition, and perturbations of the intestinal microbiota, increasing susceptibility to preventable noncommunicable diseases later in life.[1–3] Central to this paradigm is the concept of *developmental programming* (DP), a proposed biological mechanism underlying the DOHaD approach. A DOHaD approach is highly relevant to healthcare education, practice, and research, as it provides evidence of the importance of early-life environments on lifelong health trajectories and informs interventions spanning preconception counseling, perinatal care, and community-based health promotion and prevention.

Diverse disciplines study DP, including biology, health sciences, sociology, and psychology. However, a standardized definition of DP is lacking. Furthermore, various terms are used, sometimes interchangeably, to describe similar phenomena, such as biological embedding, biological programming,[4–6] metabolic imprinting,[7] priming, induction, and conditioning.[8] Disciplinary perspectives influence minor differences in the meaning of these terms despite the same theoretical foundations. Therefore, this review aims to analyze the concept of DP, synthesizing theoretical and empirical evidence to develop a unified conceptual definition. A common understanding of this concept can inform interdisciplinary research, healthcare provider education, and practice.

Background

Historical uses of the concept of developmental programming

Developmental origins of health and disease

The DOHaD approach has its empirical origins in epidemiological research by Barker and colleagues in the 1980s. The evidence from this research provided the foundation for what Barker referred to as the *fetal origins of adult disease hypothesis*, sometimes called *Barker's hypothesis of fetal origins*.[9,10] Barker's research challenged the notion that coronary heart disease (CHD) could be solely attributed to lifestyle factors and genetic predisposition, as these explanations did not sufficiently account for changing incidence patterns. For example, while CHD incidence fluctuated between the mid-1980s and early 2000s, adult lifestyle behaviors remained stable.[10] Additionally, risk factors of smoking, high blood pressure, and cholesterol levels were correlated with CHD, yet even men with minimal risk factors experienced high mortality rates from the disease.[10] Therefore, Barker hypothesized that additional predisposing factors must contribute to the development of CHD beyond lifestyle choices and genetics.[10]

Through geographical epidemiological studies using early 20th-century data from midwife postnatal visits, Barker's team examined 23 common causes of death in adults.[9] The authors used historical infant mortality rates, closely associated with poor social conditions such as low socioeconomic status, food insecurity, and limited healthcare access, as a proxy for adverse environmental influences during early life. They found that adult mortality from bronchitis, rheumatic heart disease, stomach cancer, and CHD exhibited similar geographic distributions to historical infant mortality rates.[10] However, the temporal trends diverged. Over the prior century, infant mortality, bronchitis, rheumatic heart disease, and stomach cancer declined in prevalence, while the rates of CHD increased. The authors ruled out poor social conditions as a precursor to adult lifestyle choices by looking at the rates of lung cancer (as a proxy for smoking) and dietary fat consumption (a contributor to CHD), neither of which aligned with past infant mortality patterns. They concluded that poor social conditions leading to health-damaging lifestyle choices could not be the sole explanation linking infant mortality and heart disease. The authors hypothesized that prenatal and early postnatal environmental factors, such as nutritional deficiencies, could permanently alter physiology and metabolism through DP, predisposing individuals to CHD and stroke later in life.[10] Subsequent studies by Barker and colleagues revealed associations between low birth weight and increased risk of cardiovascular disease, metabolic syndrome, and type 2 diabetes.[9,11] In the years that followed, additional research, particularly in large cohorts exposed to famine, built upon this foundational evidence, with findings that reinforced Barker's hypothesis.[12–17]

In 1999, the International Council on the Fetal Origins of Adult Disease was formed, and in 2001, it was renamed the Society for the Fetal Origins of Adult Disease (the Society). In 2003, following discussions among the scientific community at two consecutive meetings of the World Congress on Fetal Origins of Adult Disease, the DOHaD was adopted in place of *the Fetal Origins of Adult Disease* to reflect the evolving understanding of the impacts of environmental exposures during and beyond the in-utero period.[18] In 2020, the Society became the International DOHaD Society, and they continue to support collaborative interdisciplinary research and knowledge translation about DOHaD.[19]

In 2022, Barker's original observations[10] were validated and extended by Baker et al.[20] using data from over 370,000 participants in the UK Biobank. The authors replicated Barker's finding that the relationship between infant mortality rates and ischemic heart disease persisted after accounting for geographic variation, supporting the robustness of this relationship. In addition, elevated infant mortality rates were strongly associated with lower socioeconomic status, indicating that early-life conditions linked to social disadvantage contribute to later cardiovascular disease risk through pathways extending beyond prenatal undernutrition.[20]

The authors further argue that infant mortality rates may act as a proxy for unobserved characteristics of socioeconomic status and environmental factors that vary between families, such as household income, food security, exposure to environmental pollutants, parental genetics and health status, and effects of individual home environments or family infrastructure. Additionally, Baker et al.[20] incorporated polygenic risk scores for ischemic heart disease and demonstrated effect-modification by early-life environment. Among individuals with high genetic risk, higher infant mortality rates were associated with a significantly greater risk of ischemic heart disease. Conversely, where infant mortality rates were lower, genetic risk was not statistically significant. These findings provide empirical evidence that adverse early-life environments may amplify genetic susceptibility, while more favorable early-life conditions may attenuate the expression of genetic risk. Collectively, this work strengthens the evidence for gene-environment interplay in the developmental origins of cardiovascular disease.

The evolution of developmental programming as a concept

DOHaD is the overarching paradigm, of which *programming* is a tenet. Programming describes the physiological and biological mechanisms by which lasting changes to an organism's structure, function, and metabolism occur due to exposures during specific periods.[9,21] The earliest work that laid the foundations for developmental theory is that of Douglas Alexander Spalding in the 1870s (see Figure 1). Spalding examined animal behaviors and transferred attachment, and hypothesized that critical periods can influence development.[22] Subsequent animal studies building on this foundation led to the work of Konrad Lorenz in the 1930s, who described a phenomenon where birds immediately imprint upon or firmly attach to objects they were exposed to upon hatching.[23] Lorenz's theory purported that this behavioral programming, or *imprinting* as he called it, was influenced by early exposures experienced during a specific period, and the resulting changes persisted through adulthood.[7]

Dörner was the first to introduce the term *programming*. In 1974, his work examined the impact of neurotransmitters, hormones, and metabolites during critical periods of early development on neurodevelopment and disease onset in adulthood.[24] Dörner also proposed the potential for gene-environment interactions. Barker's research in the 1980s connected programming to the fetal origins of health and disease as the mechanistic underpinning.

In the 1990s, Hertzman and Wiens examined the impacts of early experience on health and disease development from an epidemiological and public health lens.[4,25,26] The authors referred to the *biological embedding* of early experiences of social gradients in health status, although their theory was founded on the same animal models as programming theory.[26] Like programming, embedding describes a mechanistic process,[6] emphasizing the social determinants of health and the influence of psychosocial conditions on child development. The key contribution of this theory was the link between human

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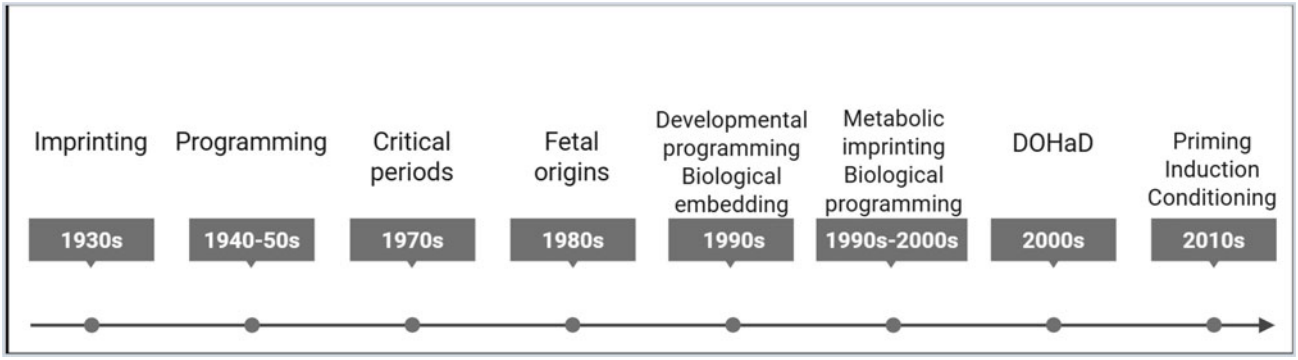

Figure 1. The evolution of developmental programming as a concept. The term developmental programming has evolved over the last eighty years. It is intricately linked with the developmental origins of health and disease. Currently, various terms describe similar phenomena, primarily influenced by disciplinary perspectives. Created in https://BioRender.com.

development and population health, and the consideration of the environment to include factors outside the womb. In addition to recognizing critical periods, Hertzman proposed that health behaviors that contribute to long-term health outcomes and cumulative effects further compound health impacts.[27] This term became commonly used in health equity research.[28] In 1991, the programming concept was further refined by Lucas, who coined the term "*developmental programming.*"[29] However, this term faced criticism for implying a fixed set of instructions, which did not accurately capture the dynamic nature of developmental processes.[8]

Toward the end of the decade (1999), Waterland and Garza[7] suggested *metabolic imprinting* was a more appropriate term to refer to the specific relationship between early nutritional exposures and the onset of disease later in life. It was intended to refer specifically to the biological mechanisms occurring,[7] and it appears to be more commonly used in developmental biology. The term *biological programming* gained popularity in the late 1990s and into the 2000s. A concept analysis to distinguish between biological programming and biological embedding identified that the former is less frequently used and has a high degree of variation in how it is interpreted and applied.[27]Biological programming tends to be used more broadly, without restriction to development. Biological embedding has a more consistently used definition and is more commonly used in sociology, psychology, and developmental medicine.[27] However, there is significant overlap between the two terms, and they are often used interchangeably.[27,28]

In 2014, Hanson and Gluckman expressed a preference for *priming*, *induction*, or *conditioning*, believing these terms were less deterministic than programming.[8] Their conceptual framing was rooted in developmental physiology, developmental biology, and evolutionary biology. Priming refers to the presence of an environmental stimulus that elicits a phenotypic response, whereas conditioning similarly denotes a stimulus-response relationship, further implying the adaptive modification of biological systems which may become more efficient or reliable with repeated exposure.[8] Despite this proposed shift in terminology, the articles included in this review suggest that DP remains frequently utilized in DOHaD research.

This review revealed an expansive body of literature on DP, including numerous recent publications. However, no universally accepted definition was found. To enhance clarity, it would be beneficial to have a shared conceptual definition so that researchers, regardless of their discipline, can collaborate in advancing the science of DOHaD.

Methods

A concept analysis is a systematic process of reviewing the literature to examine the meaning of a concept, clarify ambiguous terms, and distinguish it from related concepts to contribute to theory development and knowledge translation.[30] The concept of DP was analyzed by synthesizing the findings from this review according to the eight-step method proposed by Walker and Avant:[30] (1) selecting a concept, (2) determining the aim of the analysis, (3) identifying all uses of the concept, (4) determining the defining attributes, (5) constructing a model case, (6) constructing borderline and contrary cases, (7) identifying antecedents and consequences, and (8) defining empirical referents. Recognizing the limitations of a linear approach, this analysis also draws on Rodgers'[31] evolutionary perspective, which acknowledges that concepts are dynamic and context-dependent and evolve over time and across disciplinary boundaries. Therefore, the sequence of steps was adapted: antecedents and consequences were examined before case construction to better reflect the temporal trajectory and contextual shifts in the usage of the concept of DP. This allowed for the development of empirically grounded cases.

Data sources

A systematic search of MEDLINE(EBSCOhost) was performed using the exact phrase "developmental programming." Searches were limited to peer-reviewed articles published in English with full text available. No start date restrictions were applied, and the search was conducted through December 30th, 2024. At the time of the original search, this strategy yielded 194 records. The Google Scholar database was subsequently searched using the same keywords to identify potentially relevant records not captured in database searches. The first several pages of results were screened, yielding 57 additional titles for review (see Figure 2). Additionally, the online Cambridge Dictionary and Merriam-Webster dictionaries were consulted for the term "developmental programming." MEDLINE and Google Scholar were further searched for (1) "developmental programming" AND definition, and (2) "developmental programming" AND "concept analysis."

All retrieved articles were imported into Rayyan,[32] a web tool for literature review article screening. Articles were included if the population included human maternal-offspring dyads, the exposures were environmental factors in the prenatal or perinatal periods, and the outcomes described were associated physiological

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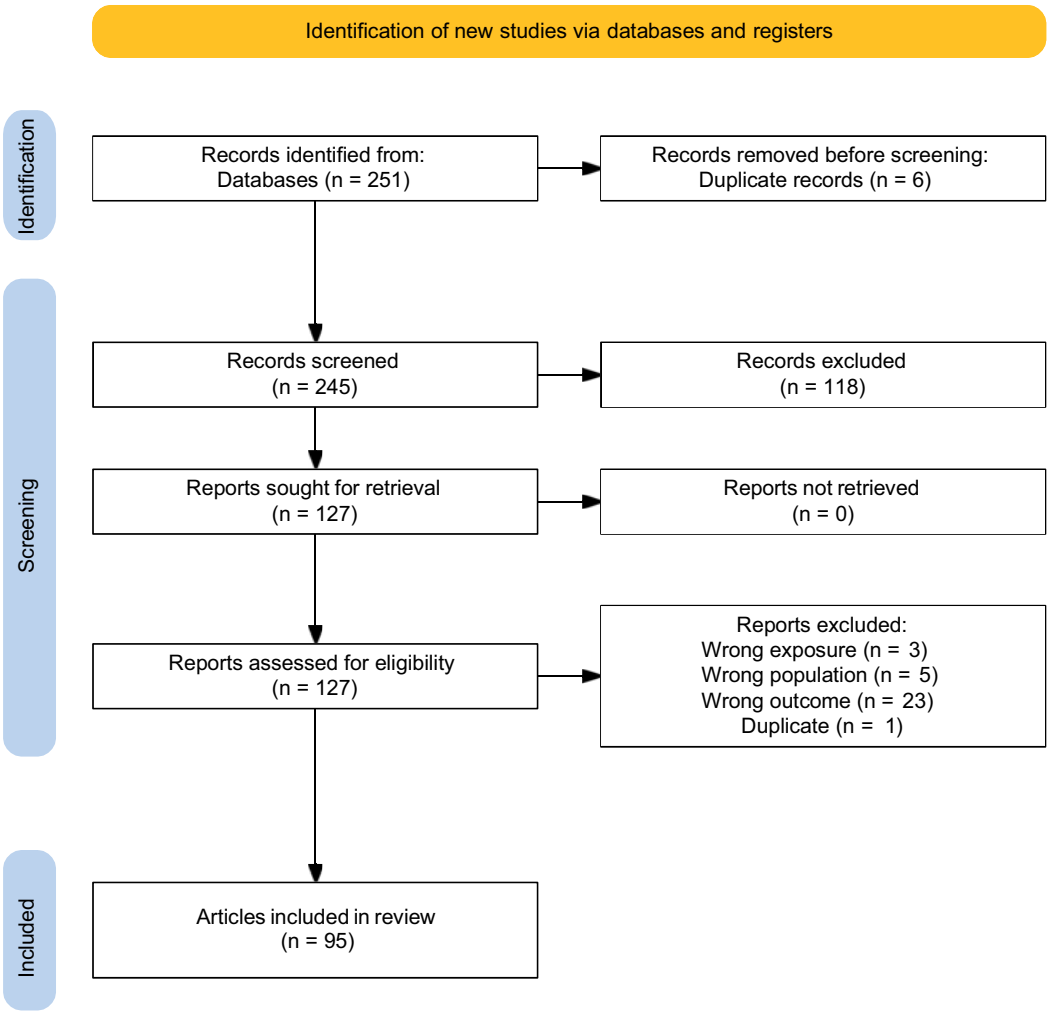

Figure 2. PRISMA flow diagram of article selection for the concept of developmental programming.

consequences the maternal exposures on offspring. After removing the six duplicates, 245 articles were screened by titles and abstracts. Of these, 127 full-text articles were further screened, resulting in 95 included in this review. Articles were then analyzed for themes related to attributes, antecedents, consequences, and empirical referents. No definitions for DP were located, nor was there any prior published concept analysis. One concept analysis on biological embedding was located.

Re-execution of the original search on January 7th, 2026, retrieved a larger number of records due to changes in the MEDLINE (EBSCOhost) search platform and ongoing database updating processes. Further limiting the dates to articles published between December 30th, 2024, and January 7th, 2025, yielded 4 records, none of which met the inclusion criteria for this review.

Findings

Defining attributes of developmental programming

Defining attributes are the characteristics of a concept that appear repeatedly and help shape the definition of a concept.[30] They are the qualities associated with a specific concept that allow it to be recognized and distinguished from related concepts. This review identified four defining attributes that emerged as central to DP: (1) epigenetics, (2) ontogeny, (3) critical or sensitive periods, and (4) plasticity.

Epigenetics

Epigenetics is the scientific study of how the environment influences the expression of an individual's genes.[33] It was previously thought that genes were deterministic; one's DNA sequence was fixed, and one's genetic code determined phenotypes and health outcomes. It is now known that epigenetic mechanisms can regulate gene expression, impacting protein production and potentially altering an organism's phenotype or disease state.[11] Barouki et al.[34] aptly described this by stating, "each individual has one genome but will hold multiple epigenomes."

DNA methylation is the most frequently studied epigenetic mechanism, and in humans, it commonly involves transferring a methyl group to the cytosine-guanine (CpG) dinucleotide by DNA methyltransferase.[35,36] Hypermethylation is often present in promoter regions, and for many years, it has been thought to contribute to gene suppression.[36,37] However, it is now more appropriately considered repression. Conversely, hypomethylation can occur, activating gene expression.[36] Hence, DNA methylation functions like a dimmer switch that can up- or down-regulate expression to various degrees.[38] Advancing technology has allowed the realization of other consequences of DNA methylation,

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including splicing, transcription factor recruitment, and the positioning of nucleosomes.[36] As a result, DNA methylation can alter the phenotype (within the limitations of the genotype). As such, DNA methylation is a dynamic process that begins *in utero* and continues after birth.[21] For example, alterations in DNA methylation patterns in offspring have been linked to lower maternal prenatal intake of methyl-group donors, such as folate, betaine, methionine, and choline, and associated with phenotypic outcomes, including congenital heart and neural tube defects, and cleft lip and palate.[39] In the *Agouti* mouse model, supplements containing methyl donors provided to pregnant dams increased offspring DNA methylation at the *Agouti* allele. These offspring were born with a different coat color.[40] Animal studies have shown that early adversity, such as poor or neglectful maternal care, can lead to epigenetic changes in infants that persist into adulthood.[41] Human studies have also shown that child maltreatment is associated with altered epigenetic regulation in genes that impact physiological and psychological outcomes related to stress, such as *NR3C1*.[41] Although much of the research in humans is associative, methodologies such as Mendelian randomization (MR) offer greater strength in making causal inferences about associations between DNA methylation and health outcomes. A recent study employed a two-sample MR to examine DNA methylation loci across multiple developmental stages.[42]The authors identified potentially causal associations between DNA methylation at sites associated with adversity and physical and mental health outcomes, including attention deficit hyperactivity disorder, depression, and asthma.[42]

Although DNA methylation is the most frequently studied, histone modification and chromatin remodeling are other epigenetic mechanisms. Histones are proteins that help condense the large volume of DNA to fit inside the nucleus. They provide structural support for chromosomes and are involved in gene expression.[38,43] Enzymes can modify histones, altering gene expression without changing the DNA sequence. Gene expression can be regulated through variant histones or modification of histone tails post-translation.[44] There are also epigenetic mechanisms specific to RNA, such as microRNA (miRNA) and long noncoding RNA, which may be implicated in DP. However, the role of noncoding RNA is still being fully explored. MicroRNAs are also noncoding but are only 21–25 nucleotides long.[44] They can modify gene expression post-transcriptionally by pairing with messenger RNAs and targeting the 3' untranslated region, suppressing translation.[44] Gene expression can be repressed or activated by controlling the miRNA produced.[44] Therefore, epigenetics is a multimodal molecular mechanism of DP, which can act as an intermediary between environmental influences and phenotypic expression.

Transgenerational epigenetic inheritance. Contrary to the vertical transmission from mother to fetus, transgenerational epigenetic inheritance is the heritable transmission of environmentally induced phenotypes[45] through alteration of the epigenome of fetal germ cells.[21] Genetic information in germ cells is passed along in the DNA of the haploid gametes (i.e., oocytes, spermatozoa).[44] Environmental exposures that produce epigenetic changes may modify the sperm in males, or alter the germ cells of the fetus in pregnant females, creating nongenetic inheritance in the third generation. In other words, transgenerational inheritance refers to the transmission of genetic information from grandparents to grandchildren.[46] As a result, altered gene expression patterns predisposing to disease can be passed on for multiple generations.[33,47,48]

For example, the male germline can be negatively impacted by undernutrition; this is heritable through the sperm to the fetus, and when the fetus reproduces, these changes are conveyed to its offspring.[10] In animal models, mice exposed to a low-calorie diet during gestation produced offspring with an increased propensity for developing diabetes.[46]Notably, male offspring from this F_1 generation sired progeny with an elevated risk of developing diabetes despite normal caloric intake, suggesting intergenerational transmission of metabolic vulnerability.[46] Complementary evidence from ovine models indicates that dietary manipulation in the form of methionine supplementation resulted in heritable epigenetic modifications and phenotypic alterations transmitted across five generations, extending prior assumptions regarding the temporal limits of transgenerational epigenetic inheritance.[48] A growing body of experimental and epidemiological evidence has identified several exposures associated with promoting transgenerational epigenetic inheritance, including endocrine-disrupting chemicals, folate deficiency, stress, and substances such as alcohol and tobacco.[33] These findings highlight the central role of transgenerational epigenetic inheritance in shaping DP. As such, any definition of DP must emphasize that the consequences are not limited to the exposed individual but may extend to multiple subsequent generations.

Ontogeny

Ontogeny is the development of an organism throughout its lifecycle from fertilization to adulthood. The organism's genetic program is realized under exogenous factors during ontogenesis.[21] In situations of nutritional scarcity, vital organs, such as the brain, consume most of the limited available nutrients at the expense of other less essential organs, such as the pancreas or kidneys.[23,33] Studies have shown that alterations to cellular structure and function could remain permanent if this occurs at a critical juncture in fetal development.[33] This attribute highlights the vulnerability of fetal organ development to external influences while recognizing that environmental factors can impact health outcomes at various developmental stages.

Critical or sensitive periods

Critical periods are fundamental to DP as they are periods where an organism is more vulnerable to environmental influences that can have long-term implications for health and disease. These periods are windows of opportunity for preventative measures and interventions that may shape health outcomes. The idea of critical periods in fetal and infant life is derived from embryological studies examining the effects of exposure to toxic substances on the developing fetus.[49] The earlier the insult occurred *in utero*, the more damaging the effects. Thus, there was an inverse relationship between maturity and vulnerability.[49] Further research on critical periods came from studies where birds immediately imprinted upon or firmly attached to objects they were exposed to upon hatching.[50] However, it has been argued that the preferable term is "sensitive" periods, as this confers a degree of reversibility of detrimental programming or possible future benefit from a positive environmental influence.[51]In contrast, "critical period" conveys greater rigidity and inflexibility in the induced changes.[51] Additionally, sensitive periods have been used to refer specifically to neurobiological development and the brain's plasticity.[52]

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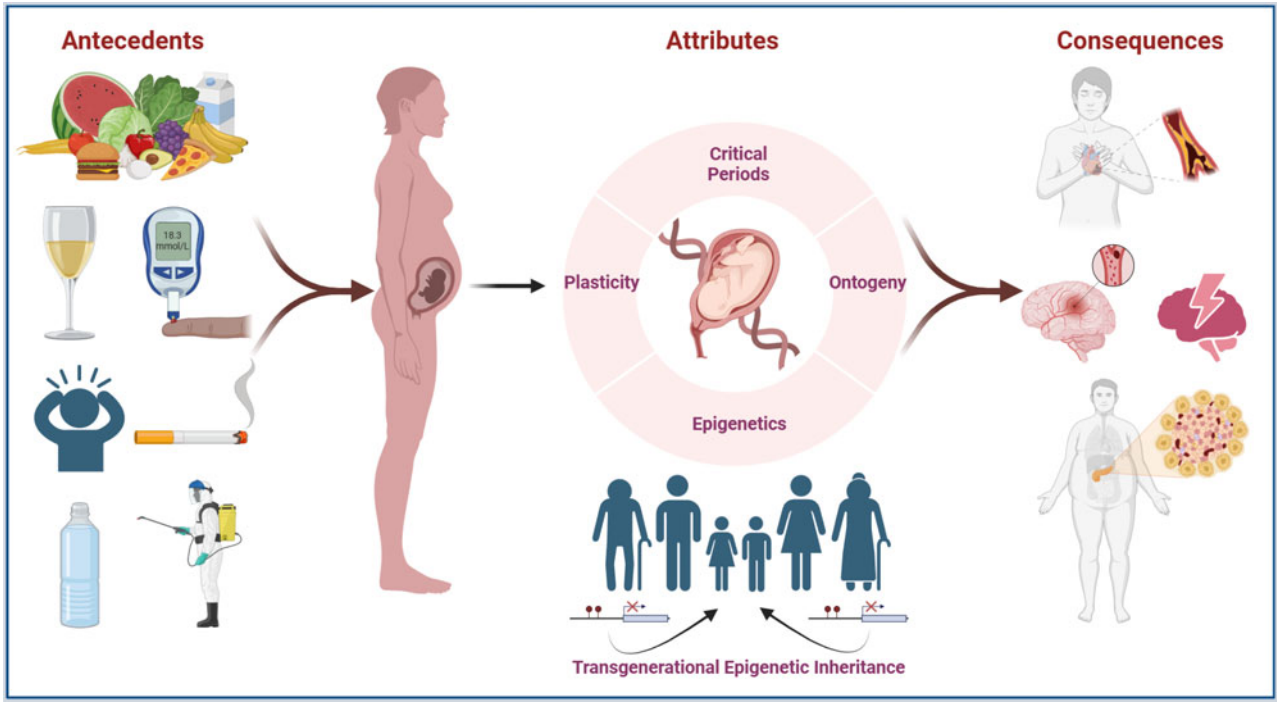

Figure 3. The antecedents, attributes and consequences of developmental programming. The antecedents of developmental programming include maternal nutrition, disease and medication, lifestyle, environmental toxins, and stress. The consequences of these exposures are in developmental programming that predispose the fetus to adverse health outcomes such as cardiovascular disease, metabolic disease, type 2 diabetes, obesity, and mental health challenges. Developmental programming is mediated by attributes such as epigenetics, ontogeny, and plasticity. Some epigenetic changes can be transmitted intergenerationally to grandchildren. Individuals are more vulnerable to the effects of the antecedents during specific sensitive periods of development. Created in https://BioRender.com.

Preconception and the perinatal period are critical for fetal development, in the context of DOHaD and DP.[51]In infancy, the period of vulnerability for the later development of physical and psychological diseases occurs during the first 1000 days (i.e., from conception to two years of age).[33,53] During this time, rapid growth and normal development will occur in the presence of appropriate stimuli or conditions.[51]

Another sensitive period is adolescence, when neuroendocrine and reproductive changes accompany puberty.[54] This is also a time of increasing independence from the family, often accompanied by freedom to make diet and lifestyle choices.[55] Adolescents may use tobacco products, drink alcohol, or ingest drugs. Patterns of physical activity are also often established in this period. Animal studies have found that a high-fat diet during puberty is associated with metabolic dysfunction in rats.[54] Including sensitive periods in any definition of DP is essential to emphasize the time-dependency of the concept. Any adverse environmental exposures during these periods may permanently impact physiological development or metabolic pathways. During these periods, organisms are thought to be more malleable.[51]

Plasticity

Despite the focus on the first 1000 days as a critical period of vulnerability, the ability of the body's organs and systems to adapt to environmental conditions extends beyond the neonatal period, throughout life, and is referred to as plasticity.[9] This allows phenotypic adaptation of the genotype to suit environmental conditions. For example, suppose the fetus develops in an environment of nutritional scarcity. It may adapt by conserving fat and glucose stores and altering the regulation of adipokines (e.g. leptin and adiponectin) within the hypothalamus to regulate metabolism,[11] and will be prepared to enter a world where food will continue to be limited in supply. If food is abundant in the post-natal environment, these adaptations can increase the risk of developing chronic diseases related to metabolism, such as obesity or type 2 diabetes.[11] Plasticity changes with age, differs for various organs and tissues, and sometimes becomes fixed.[56] Barker[10] illustrated this theory by explaining that all humans are born with the same number of non-functioning sweat glands. The number of sweat glands that become functional in the first three years of life depends on the environment the child is exposed to; hotter environments require more sweat glands. After three years, the number of glands is fixed.[10] Thus, plasticity is essential in defining DP because it is a key mechanism linking early life experiences and developmental outcomes.

The antecedents and consequences of developmental programming

According to Walker and Avant, an antecedent is an event, stimulus, or circumstance necessary for DP to manifest and be sustained, and the consequences are the effects of the concept's presence.[30] In DP, the potential consequences can be physiological or psychological and specific to each antecedent. When healthcare practitioners understand the impact of DP, they can use this knowledge to guide interventions that support positive developmental outcomes for children.

Maternal nutrition

Several factors can contribute to fetal DP (see Figure 3). Of these, maternal nutrition has been one of the most comprehensively

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studied. Nutrition is a key antecedent to DP, given that in 2022, the World Health Organization reported that 29.6% of the global population (or 2.4 billion people) did not have adequate access to food to meet nutritional requirements.[57] Further, 900 million people experienced severe food insecurity.[57] This creates a high potential that many women will not meet the daily recommended nutritional intake during pregnancy.

The studies by Barker et al. and subsequently, those in cohorts exposed to famine, demonstrated that maternal malnutrition may predispose the offspring to develop cardiovascular disease, metabolic disease, type 2 diabetes, and mental health issues.[9–11,44] Animal models and previous large-scale studies of cohorts experiencing famine also demonstrated a dose-response relationship.[56] Minor nutritional deficits or overages can exert an impact, particularly on organs or systems undergoing periods of rapid fetal development. However, more significant deviations from recommended dietary requirements have larger effects.[56]

Conversely, some studies have demonstrated that fetal *over*-nutrition, resulting from excessive weight gain in pregnancy or gestational diabetes, is also associated with adverse health outcomes. Babies born to mothers with pre-pregnancy obesity, indicated by a high body mass index (BMI), were observed to be large for gestational age and at elevated risk of developing obesity and metabolic disease, including type 2 diabetes, as adults.[11,23,34] Animal models have provided further evidence of causal mechanisms. For example, female rats given a high-fat diet produced offspring with reduced insulin hypersensitivity, hypertension, and obesity.[23] Additionally, sheep overfed in pregnancy produced dysglycemic offspring.[23]

The placenta is essential for fetal development, nutrient and oxygen exchange, and waste transportation between the maternal and fetal systems.[58]When there is nutritional scarcity, the vascular development of the placenta is reduced in early pregnancy.[58] Reynolds et al.[58] conducted studies on livestock, demonstrating that placental development is altered in pregnancy in response to over- or undernutrition. The authors found that nutritional scarcity could also decrease the expression of angiogenic factors and nutrient transporters and significantly impact gene expression in the fetal liver, muscle, and cerebrum. The authors concluded that defects in placental growth are associated with altered fetal growth and organ development. They also found that nutritional interventions had a mitigating effect on placental vascular development.[58]

Maternal nutrition may also indirectly influence fetal development through its effects on the maternal intestinal microbiota. Diet is a primary determinant of microbial composition and metabolic activity, which can influence maternal immune function, micronutrient availability, inflammatory regulation, and the production of bioactive metabolites.[2] Microbial-derived components and metabolites may interact with the placenta and influence fetal development. Evidence from human studies remains limited and does not currently support stable programming of the intestinal microbiota during the first 1000 days of life.[3] However, experimental evidence, particularly from animal models, suggests that the microbiota may act as a mechanistic relay through which nutritional exposures influence developmental trajectories or susceptibility to later pathophysiology.[3] Accordingly, microbiota-related effects can be conceptualized as intermediaries or modifiers within the DOHaD framework rather than as defining elements of DP.

Maternal disease and medication

Homeostasis of the maternal-fetal environment during pregnancy is essential to maintaining and permitting typical growth and development. Maternal diseases, particularly ones that create hormonal imbalances, such as polycystic ovary syndrome (PCOS), gestational diabetes, or pre-eclampsia, can significantly impact this homeostasis.[23] PCOS in mothers has been associated with the development of PCOS in their infants as well as metabolic disorders or reproductive issues.[23] Maternal diabetes has been linked to long-term metabolic and cardiovascular complications in offspring.[59] Further, preeclampsia affects about 2%–8% of pregnancies and is associated with premature births, intrauterine growth restriction, and increased risk of hypertension and stroke for offspring in adulthood.[23] In animals with induced diabetes, their offspring had normal glucose metabolism at birth. However, as adults, they developed diabetes during periods of metabolic stress, such as pregnancy.[23]

Medication effects can also constitute adverse exposures, which can disrupt typical developmental processes, such as organ formation and neurodevelopment, and result in atypical morphological or physiological development. An unplanned pregnancy may lead to unintended exposure of the fetus to teratogenic drugs. At times, taking medication for pre-existing or new health conditions is unavoidable during pregnancy, and the teratogenic risks of medications are not always known. A notorious example of a problematic legal drug taken during pregnancy without known risks was Thalidomide, which was given to prevent nausea in pregnant mothers and led to severe malformation of limbs in the fetus.[60] This practice was discontinued in 1962 in Canada/North America once the consequences were realized. However, one study demonstrated that from 2006 to 2017, fetuses from 1 in 16 pregnancies continued to be exposed to commonly used teratogenic drugs, such as Valproic Acid, Topiramate, and Methotrexate.[61] While rates of exposure to known teratogens declined over the study period, exposure to potentially teratogenic drugs increased.[61] Therefore, assessing exposure to teratogenic or potentially teratogenic drugs during the periods before and during pregnancy is crucial.

Maternal lifestyle choices

There is significant evidence of maternal lifestyle factors such as substance use, including smoking, consumption of alcoholic beverages, and legal and illicit drugs, as antecedents that are disruptive to DP.[9] Exposures to these substances *in utero* may be detrimental to the health of a fetus, potentially altering growth and development and predisposing the fetus to future disease development.[9]Substance use in pregnancy has been associated with low offspring birth weight, intrauterine growth restriction, neurodevelopmental disorders, and congenital abnormalities in humans.[23] Studies in pregnant animals exposed to drugs were linked to reduced birth weights and cognitive and motor deficits.[23] Additionally, maternal smoking during pregnancy increases the risk of obesity in offspring during childhood and the risk of hypertension in adulthood.[62] Conversely, optimizing pregnancy health through physical activity, which contributes to maintaining a healthy weight, regulation of metabolism, and hormone balance, may act as a protective factor to mitigate metabolic programming from environmental insults.[63–65] Physical activity has the added advantage of reducing perceived stress,[66] another antecedent of DP.

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Maternal environmental chemical exposures

Since hormones are critical components of the maternal-fetal milieu, substances that mimic hormones can alter normal fetal development.[67] Endocrine-disrupting chemicals (EDCs) can interfere with endogenous hormones, altering their production and action or even causing their elimination.[34] Thus, exposure to EDCs has been associated with DP.[34] These chemicals are commonly found in today's environment in plastics, solvents, lubricants, pesticides, and pharmaceutical agents.[23]

Animal models have shown that the EDCs to which humans are regularly exposed to, including phthalates, bisphenol A, nicotine, perfluorooctane compounds, and polybrominated diphenyl ethers (the chemical component found in household fire retardants), have been associated with a range of adverse clinical endpoints, including preterm birth, diminished immune responses, disrupted metabolism, early puberty,[34] obesity, endometriosis, type 2 diabetes,[68] and neurodevelopmental disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD).[34,68] In humans, EDCs have been associated with various adult disorders, including type 2 diabetes, cancer, obesity, male infertility, reproductive dysfunction, and metabolic disorders, with epigenetic changes believed to contribute to these outcomes.[23] Studies have associated EDCs with epigenetic changes, including alterations in DNA methylation, introducing a potential mechanistic process driving the associations between exposures and health outcomes.[68–70] Although most research has focused on EDCs, the DOHaD concept has evolved to consider other environmental chemical exposures such as pesticides, persistent organic pollutants, and heavy metals.

Maternal stress and adversity

Maternal stress experienced during pregnancy may also impact the growing fetus.[23] Maternal stressors can include daily life events, mental illness, acts of nature, war, and other traumatic experiences. This is particularly relevant as more countries are currently experiencing conflict than since the Second World War.[71] Furthermore, a staggering 1 in 8 people worldwide have a mental health condition.[72] Conditions such as anxiety and depression increased globally by 25% in the wake of the COVID-19 pandemic.[72,73] This is partly due to health disparities, where many affected people face barriers to accessing medical or psychological services.[74,75]

Stress and adversity are subjective experiences, with individual perceptions and responses based on their unique experiences and circumstances. Each person has their level of tolerance to what feels manageable or overwhelming. The ability to manage stress may depend on coping mechanisms, support, the presence of compounding stressors, and resilience. Maternal stress produces hormones such as glucocorticoids and catecholamines associated with DNA methylation changes in gene expression.[44] Similar effects have been reported in survivors of the holocaust and natural disasters.[23] Experiencing the stress of losing a loved one during pregnancy has been shown to impact the offspring's immune function and can predispose one to develop obesity or mental health issues.[23] More recent research has focused on how toxic stress from experiences of systemic racism and oppression is associated with disease development and heritable epigenetic changes.[33] Animal models have demonstrated similar findings. Rodents subjected to perinatal stress produced offspring with higher adipose tissue levels, impaired glycemic control, low birth weight, reduced glucocorticoid and mineralocorticoid receptor expression in the hippocampus, and impaired hypothalamic-pituitary-adrenal axis feedback regulation.[23]

Stress during pregnancy has also been associated with developmental delays in offspring. For example, Project Ice Storm studied the effects of maternal stress on pregnancy during the Quebec ice storm of January 1998, which resulted in more than three million people living without electricity for up to five weeks.[59]The authors found that a stressful life event experienced in pregnancy can negatively impact cognitive and language development at age two, mainly when exposure occurred in the first two trimesters, with the most significant effects experienced with second-trimester exposure and moderate-to-high stress.[59] However, given the challenges in measuring the subjective experience of stress, it remains unclear what factors might tip the balance to predispose an individual to altered health outcomes.

A model case example of developmental programming

Walker and Avant[30] describe a model case as one that illustrates the concept and incorporates all the defining attributes. A borderline case is helpful to demonstrate an example where some, but not all, defining attributes are present. A contrary case illustrates what does not constitute an example of the concept.[30]

Mariyam was a twenty-six-year-old primigravida woman. She was unemployed and had limited access to nutritious food, most of which she accessed through the food bank. The food selection available to her was primarily canned goods and other non-perishables. On occasion, the food bank offered fresh produce and dairy products. Her caloric intake was below the recommended levels during pregnancy, and her weight gain was below the typical healthy range. Mariyam lived in low-income housing and did not have a family doctor; therefore, she did not attend regular prenatal visits. In her second trimester, Mariyam experienced the death of her mother. This was a profound loss, causing significant stress, as they had a very close relationship. Her pregnancy was otherwise uneventful. Her baby boy was born small for gestational age at 2.7 kg (5.94 pounds) with no apparent health concerns.

Application of the model case

Maternal undernutrition and stress resulted in intrauterine growth restriction, predisposing the child to several health risks, including cardiovascular disease, obesity, metabolic disease, and mental health issues. During ontogenesis, vital organs would have consumed limited resources at the expense of other, less critical organs, such as the pancreas. This might contribute to impaired endocrine or exocrine (i.e., diabetes) function later in life. Epigenetic modifications through DNA methylation programmed *in utero* will have primed Mariyam's fetus to live in an environment of nutritional scarcity, with the ability to store extra nutritional factors, manifesting as noncommunicable diseases throughout the life course if exposed to nutritional abundance. This and subsequent adverse environmental exposures during sensitive periods in the child's life could have interactive effects, predisposing the child to future disease. However, due to the child's plasticity, there would still be an opportunity to mitigate risk, mainly if interventions were targeted during sensitive periods in childhood and adolescence. From a transgenerational epigenetic inheritance perspective, epigenetic changes could be passed along by the child's germ cells, priming the next generation (i.e., grandchild) for disease risk when this child has offspring. A healthcare professional working with this family can connect them to services to provide financial

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support, food security, and dedicated early child development services. From a public health perspective, addressing the social determinants of health and applying the DP model to this case can guide healthcare professionals to take an upstream approach to setting a positive developmental trajectory.

A borderline case example of developmental programming

Tanya was a twenty-one-year-old primigravida woman. She gave birth prematurely to a baby boy at twenty-nine weeks. The baby's organs at that age were underdeveloped. He had bronchopulmonary dysplasia, predisposing him to respiratory infections for the rest of his life. He was fed through a nasogastric tube for several months until he could gain weight and tolerate full oral intake. As he matured, he was delayed in meeting his gross and fine motor milestones, although he caught up to his peers early in elementary school. While these deficits were attributed to his premature birth, this case is borderline, as it includes some of the defining attributes, although not all. For example, development was interrupted at a critical period of ontogenesis. Due to an organism's plastic, malleable nature, it can rebound to a degree from the insult of prematurity. However, this does not meet the definition of DP in that there is no evidence of epigenetic changes or transgenerational epigenetic inheritance associated with these health complications.

A contrary case

Parisa was a twenty-eight-year-old primigravida woman. She had an uncomplicated pregnancy and vaginal delivery, and the baby appeared healthy. By age three, it was evident that Parisa's son was not meeting developmental milestones for motor skills, such as walking. The child eventually underwent genetic testing, revealing a genetic variant of the DMD gene on the X chromosome that encodes dystrophin. This protein is essential for muscle strength and stability.[76] The child was diagnosed with Duchenne Muscular Dystrophy. As this is an X-linked recessive genetic disorder,[77] development of DMD is not related to any environmental exposures impacting DP. Parisa could have done nothing to exacerbate or ameliorate the onset of this condition. This is a contrary example because none of the defining attributes were evident in this case.

Empirical referents

Empirical referents are the observable or measurable elements of a concept's defining attributes.[30] The ability to reliably measure a concept such as DP can contribute to research and inform clinical interventions. However, it should be noted that numerous potential confounders complicate efforts to isolate the antecedents and attributes of the concept as influencing the consequences. Furthermore, much of the epigenetic research in humans remains correlational in nature.

Epigenetics

In a research context, epigenetic changes can be observed by examining changes in DNA methylation patterns using bisulfite sequencing or nanopore technologies.[78] Histone modifications and non-coding RNAs can also be observed. Preserved methylation changes across generations might indicate that transgenerational epigenetic inheritance has occurred. Additionally, a family history of metabolic or other disease traits may be linked to common exposures to toxins, stress, or diet.

Ontogeny

Ontogeny reflects the growth of an organism throughout its lifetime. Typical physiological development can be assessed through physical assessment. Developmental milestones in infancy and childhood can be evaluated using several validated screening tools that assess psychosocial, cognitive, psychomotor, language, visual, and auditory development.[79] Critical and sensitive periods are measured by the age and stage of development. This can be quantified by calculating chronological age, measuring pubertal hormone levels, weight and height, or using screening tools for developmental milestones.

Plasticity

Plasticity is more challenging to quantify. The appropriate adaptation of an organism to its environment demonstrates plasticity. Birth weight variability due to maternal nutrition is one example. The recent application of statistical algorithms to estimate deviations in biological age from chronological age, presumed to reflect underlying cellular and molecular processes, represents an example of differential development, potentially in response to environmental influences. The empirical referents contribute to the ability to apply DP in research and practice.

Discussion

The DOHaD paradigm provides a theoretical basis for healthcare research, education, and practice pertaining to precipitating factors of adult-onset noncommunicable disease. There has been significant growth in DOHaD research over the past two decades, particularly observational studies using animal models and longitudinal human cohorts.[9,53,80] However, a standard definition is lacking for this term, and other terms that have similar meanings are used interchangeably. A conceptual definition is informed by theory and describes the concept.[81] The following proposed conceptual definition of DP is empirically grounded in the attributes, antecedents, and consequences identified through this analysis. In developing this definition, we also sought to reconcile prior conceptual critiques, including those advanced by proponents of alternative terminology, with the aim of improving conceptual clarity and scope:

> DP is the process by which environmental exposures may influence long-term health outcomes through alterations to biological pathways, occurring during sensitive periods within ontogeny when biological systems are particularly susceptible to being shaped or calibrated by these influences. To date, epigenetics is one of the most extensively characterized molecular processes underlying these alterations. While these changes may be long-lasting, individuals may also exhibit a degree of biological plasticity, allowing for partial reversibility, attenuation, or adaptive modification in response to subsequent environmental conditions or interventions across the life course. In some contexts, the effects of DP may extend to subsequent generations through inherited epigenetic modifications.

Implications for healthcare professionals

This conceptual definition of DP provides an evidence-based explanation of how early-life exposures may contribute to long-term health trajectories. This can guide clinical practice in recommending interventions targeted at sensitive periods with the most potential to influence change. However, knowledge translation strategies are needed to mobilize research findings into clinical realities. Molinaro et al.[82] interviewed healthcare providers to determine their knowledge and perception of DOHaD and how they translate theory into clinical practice. The authors found that

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healthcare providers considered DP a problematic concept for patients to understand, particularly regarding long-term implications. Healthcare providers expressed that time constraints prioritized other pregnancy concerns and led to a reactive rather than proactive approach to care. Some healthcare providers worried about causing stress or anxiety in patients by scaring them or making them feel guilty that their actions could cause harm to their baby or grandchildren over the long term, mainly if they were not able to change the contributing factor (e.g., obesity). The participants believed counseling should be empowering, supportive, and patient-centered. At the same time, healthcare providers felt that providing this information to parents could motivate changes in their health-seeking behaviors. Healthcare providers new to this information were excited by the discovery of this knowledge and acknowledged its clinical importance. They recognized that the benefits exceeded their concerns. However, they identified a need for guidelines on approaching conversations with patients. The authors suggested that better collaboration between researchers and practitioners can help bridge existing theory-to-practice gaps.[82] Healthcare professionals can apply this conceptual definition of DP by incorporating early-life histories into routine assessments and targeting preventative approaches that address prenatal and perinatal exposures. DOHaD-informed clinicians can contribute to developing evidence-informed educational resources and care models for integration in primary care and medical training.

A population health approach

A population health approach may be more practical, as it may circumvent some identified barriers in targeting individuals. In addition, many individual choices are constrained or influenced by the social determinants of health, which include income, social status, social support networks, education, employment and working conditions, social and physical environments, personal health practices and coping skills, early childhood development, biology and genetic endowment, health services, gender, and culture.[83] These determinants are intricately linked with the antecedents to DP: nutrition, stress, disease, lifestyle, and environment. A population health approach shifts the focus from the individual to examining socio-environmental factors that impact health, and addresses these determinants through upstream interventions, policies, and environmental factors. A population health approach informed by DP can prioritize early-life interventions such as maternal nutritional support, healthy environments, and responsive caregiving, through policy action and advocacy for inclusion in health services.

Areas for future research

There is a recognized need for rigorous longitudinal human studies to test and validate hypotheses of the underlying biological mechanisms of DOHaD found in animal studies.[9,53,80,82] One of the most significant challenges to conducting this research in human populations is the numerous possible confounding variables in the social and physical environment that are difficult to control.[84] The current evidence from human studies provides minimal clinical utility as it is primarily associative. There is also a need for more research on other potential mechanisms associated with DP, such as exploring the role of the microbiome. Furthermore, exploring paternal contributions to DP is important as findings may direct interventions to both parents rather than solely mothers. DOHaD research must also be broadened across various healthcare disciplines for effective knowledge translation and evidence to guide practice.[82] Finally, research is required to explore whether epigenetic changes are the cause or consequence of phenotypes. Applying a unified conceptual understanding of DP, collaborating across disciplines, and partnering with patients, researchers, clinicians, and policy makers can support the continued advancement and translation of DOHaD science.

Conclusion

The concept of DP has evolved, with varying terms utilized, sometimes interchangeably, to describe the same phenomenon. This concept analysis used the Walker and Avant method to review the existing literature and identify the attributes, antecedents, and consequences of DP. Rodgers' evolutionary perspective provided the framework for presenting the temporal and contextual evolution of DP. A conceptual definition was proposed that synthesized the theoretical elements. Common terminology used across disciplines to describe DP can aid the collaborative advancement of DOHaD science.

Targeted interventions for modifiable risk factors may mitigate adverse long-term health outcomes, particularly during sensitive periods. However, the translation of knowledge about DP within a DOHaD framework needs improvement to bridge the gaps between theory and practice. Enhanced education for healthcare professionals on the DP concept, as well as guidance on introducing conversations to patients to promote optimal offspring health during pregnancy, is needed. A population health approach addressing the social determinants of health may be a practical upstream approach to disseminate information and effect change.

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