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Article

Child Health Beyond Survival: Linking Developmental Origins to Lifelong Disease Risk

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Abstract: Child health strategies have historically emphasized survival; however, increasing evidence demonstrates that early-life conditions significantly influence long-term health outcomes. The Developmental Origins of Health and Disease (DOHaD) framework provides a basis for understanding how prenatal and early postnatal exposures affect physiological development and disease susceptibility. This review examines current evidence on the mechanisms linking early-life environments to adult disease risk, focusing on epigenetic modifications, endocrine and metabolic regulation, and structural organ development. Key determinants, including maternal nutrition, intrauterine conditions, psychosocial stress, and environmental exposures, are evaluated in relation to their impact on developmental programming. The review also analyzes the mismatch hypothesis, highlighting how discordance between early-life adaptations and later-life environments contributes to the development of non-communicable diseases such as cardiovascular disease, type II diabetes, and obesity. Furthermore, intergenerational influences and socioeconomic factors are considered to contextualize population-level health disparities. Despite advances in understanding, challenges remain in establishing causal pathways and translating evidence into effective public health interventions. The findings support a life-course approach to health, emphasizing the importance of early-life interventions in reducing long-term disease burden and improving population health outcomes.

Keywords *Fetal programming; early-life exposures; epigenetics; life-course approach; maternal health; developmental programming*

INTRODUCTION

Childhood mortality has been significantly mitigated through global child health programs through better immunization, maternal care, sanitation and control of infectious diseases. In spite of these successes, modern child health issues are becoming more and more based on lifelong health trajectories as biological and environmental exposures encountered in early life are increasingly recognized as determinants of health in the long term. The recent global recovery efforts that have focused on immunization and preventive treatment further underscore the need to safeguard developmental health at critical developmental phases (World Health Organization [WHO], 2023). As a result, child health systems have experienced a gradual transformation in terms of no longer focusing on reducing mortality but rather on optimizing the developmental quality, physiological resilience and healthy aging across the life course

Though the survival-oriented strategy has enhanced the pediatric outcomes, they usually have an insufficient response to the long-term consequences of adverse developmental exposures during prenatal life, infancy and early childhood. The traditional child health models had a primary focus on acute illness prevention and short-term survival with a relatively less emphasis on how developmental conditions play a role in the susceptibility to non-communicable diseases such as cardiovascular disease, obesity, type 2 diabetes, neurodevelopmental disorders and immune dysfunction later in life. This restriction is becoming of increasing importance as most low- and middle-income countries are going through rapid epidemiological and nutritional transitions and enduring maternal and child health inequities

The introduction of life-course epidemiology has offered a significant framework in understanding the interaction of biological, environmental and social exposures throughout development to influence lifelong health. Life-course models focus on the fact that health is a dynamic development process that is shaped by critical and sensitive periods that encompass preconception to adulthood. The existing research on early childhood development also emphasizes the significance of nutrition, cognitive stimulation, emotional security, and supportive caregiving in influencing the developmental outcomes in the long-term (Black et al., 2017). Evidence around the world also proves that investments in early childhood development enhance education levels, economic performance, and health of adults, making developmental health an important element of sustainable development (Richter et al., 2017).

In this view, the Developmental Origins of Health and Disease (DOHaD) paradigm has turned into an influential framework connecting early developmental exposures with subsequent risk of disease. The DOHaD model suggests that environmental exposure during critical developmental periods (including maternal nutrition, psychosocial stress, placental function, and environmental toxicants, and infant feeding practices) may trigger long-term biological adaptations to metabolism, endocrine regulation, immune functioning, organ development, and epigenetic programming. Whilst such adaptations could be helpful in the short-term in adverse environments, their incompatibility with more-adapted environments in adulthood may lead to increased susceptibility to chronic disease in adulthood.

The combination of developmental biology, epidemiology, neuroscience, public health, social medicine has given rise to increasing attention to the role of early-life conditions in contributing to global disease-burden and health-inequality. The current life-course models are more and more focused on interactions between biological vulnerability, environmental exposures, social determinants, and policy structures in the formation of developmental paths (Halfon & Forrest, 2017). The discourse on international policy also acknowledges that health in early development is a key determinant of attaining long-term health, equity, and sustainable societal growth (Clark et al., 2020). Against a backdrop of increasing mechanistic and epidemiological data, this narrative review will critically synthesize existing knowledge on the developmental origins of a lifetime risk of disease. The review will combine biological, epidemiological, and policy approaches to explore the impacts of exposures in early-life on long-term health outcomes and the future of preventive and public health strategies.

2. Conceptual Foundations of Developmental Origins of Health and Disease

2.1 Historical Evolution

The Developmental Origins of Health and Disease (DOHaD) paradigm came to light as a way to explain how unfavorable fetal and early developmental environments contribute to the susceptibility of chronic diseases in adulthood. The early epidemiological research attributed the low birth weight to higher risks of cardiovascular disease, high blood pressure, and metabolic imbalance, that conflicted with the traditional models of biomedical research that largely relied on the adult lifestyle factors as the main determinants. The DOHaD model further developed into a multidisciplinary field that incorporates the disciplines of developmental biology, epidemiology, nutrition, environmental sciences, and public health to explain how developmental environments determine lifelong physiological functioning and disease risk (Gluckman et al., 2016).

The focus of DOHaD research has increasingly moved towards observational associations to mechanistic insights into developmental programming. Recent research in the fields of molecular biology and epigenetics have demonstrated that environmental exposures during and around conception and during early embryonic development can cause long-lasting changes in endocrine regulation, metabolic pathways, and epigenetic signaling. The developmental programming is thus becoming more and more known as a dynamic process that goes beyond the fetal growth restriction and involves a series of developmental stages (Fleming et al., 2018).

2.2 Life-Course Health Framework

The life-course health model is the interaction of biological, environmental, and social exposures across developmental periods to impact long-term health pathways. There is a major difference between critical period which involves exposures that can cause irreversible physiological changes, and sensitive period which is a period during which developmental responsiveness is increased. The period of prenatal life, infancy, and early childhood is incredibly vulnerable because of the active development of organs and the nervous system, an individual is susceptible to various nutritional deficiencies, psychosocial stress, and environmental exposures (Nobile et al., 2022).

Another aspect of life-course models is the accumulation of risk due to repeated exposures across development. Biological embedding may be involved in endocrine, metabolic, immune and neurological dysregulation in response to maternal malnutrition, psychosocial adversity, environmental toxicants and socioeconomic disadvantage. The growing body of evidence further shows that the nutrition of preconception and the lifestyle of parents have profound effects on the developmental patterns prior to pregnancy and, thus, increases the chances of preventive treatment and preventive health policies (Stephenson et al., 2018).

2.3 Developmental Plasticity and Predictive Adaptive Responses

Developmental plasticity explains how organisms can alter developmental paths, in response to environmental conditions at vulnerable developmental stages. In the DOHaD paradigm, adaptive fetal responses are regarded as evolutionary survival mechanisms that maximize short-term fitness during such conditions as maternal under nutrition, placental insufficiency or psychosocial stress. Such adaptations can include a changed energy distribution, metabolic efficiency, endocrine control, and

growth patterns. But in cases when prenatal adaptations are out of tune with subsequent life situations characterized by nutritional plenty or immobility, vulnerability to obesity, cardiovascular disease, and type 2 diabetes may be exposed (Rosenfeld, 2017).

Although developmental plasticity and predictive adaptive response models are important, and have been discussed extensively. There has been a focus by some researchers on fetal environmental prediction as the centre of importance in developmental programming, and an emphasis by others on the importance of postnatal exposures, structural inequalities, and cumulative social disadvantage. In addition, there is still a challenge of empirical validation of fetal prediction in human populations. However, it is a combination of developmental biology, environmental exposures and social determinants that strengthens the notion that disease susceptibility is a product of interaction among developmental biology, environmental exposures, and social determinants as opposed to genetic determinism.

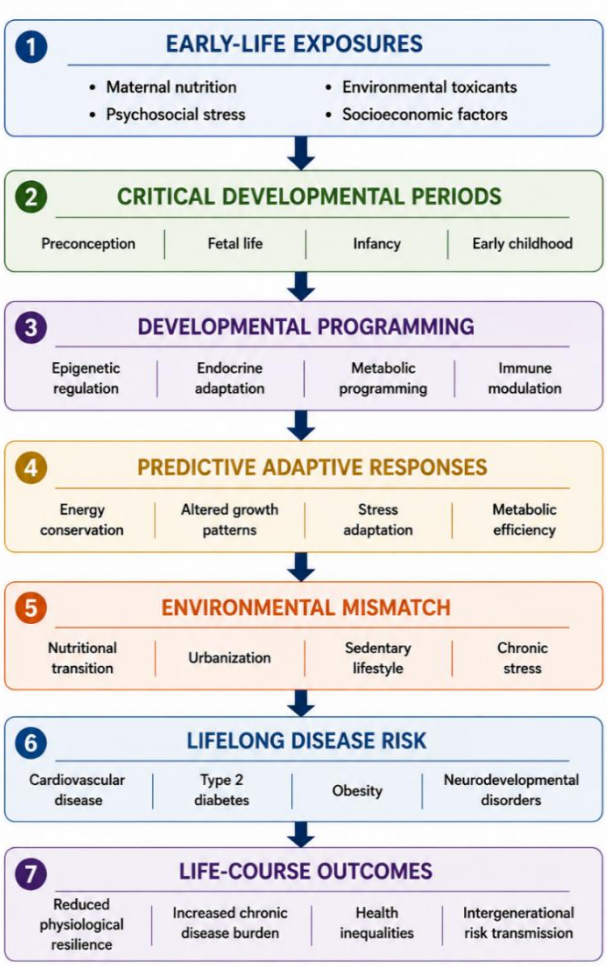

Figure 1. Conceptual Framework of the Developmental Origins of Health and Disease (DOHaD) Paradigm

Figure 1 illustrates how early-life environmental exposures during critical developmental periods induce biological programming through epigenetic, endocrine, metabolic, and immune adaptations. When developmental adaptations become mismatched with later-life environments, susceptibility to chronic diseases increases, ultimately influencing life-course health outcomes, population health inequalities, and intergenerational transmission of disease risk.

3. Biological Mechanisms Underpinning Developmental Programming

3.1 Epigenetic Regulation

One of the most widely studied processes that constitute the underlying developmental programming and lifelong disease susceptibility is epigenetic regulation. Exposures to the environment at age sensitive stages can cause irreversible changes in gene expression that do not involve a change in the sequence of the DNA. The key epigenetic mechanisms are DNA methylation, histone modification, and microRNA-mediated regulation that play a role in cellular differentiation, metabolic signaling, and physiological adaptation. There is growing evidence that prenatal nutrition, psychosocial stress, environmental toxicants, and maternal metabolic status can modify epigenetic patterns related to risk of chronic diseases later in life, and hence contribute to long-term biological embedding of developmental environments (Sharp & Relton, 2017).

Additional evidence on the effects of developmental exposures on aging trajectories includes experimental and epidemiological data that points to effects on epigenetic regulation of cellular metabolism, oxidative stress, and inflammatory control. In animal models, a lifespan, mitochondrial activity, and metabolic homeostasis can be changed due to long-term epigenetic changes in response to maternal dietary imbalance and prenatal stress. Human cohort studies also indicate that there are associations between adverse developmental conditions and accelerated biological aging, but causal pathways are

hard to determine. Notably, there is an emerging view that epigenetic programming is not fixed but dynamic and may be amenable to some developmental changes via nutritional, environmental, or behavioral interventions (Vaiserman et al., 2018).

3.2 Endocrine and Metabolic Pathways

Another key pathway that connects early-life exposures to long-term risk of diseases is based on endocrine and metabolic pathways. Stressors in development can alter the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which in turn can change the cortisol secretion and affect the metabolic adaptation throughout the life course. Endocrine signaling during fetal development may also be dysregulated, which may further affect the insulin-glucose metabolism, appetite regulation, adipogenesis, and energy balance, making them more susceptible to obesity and metabolic syndrome. Biological embedding models also postulate the existence of repeated developmental exposures, which become physiologically embedded within neuroendocrine systems, and which shape metabolic responses to chronic stress and stress reactivity (Aristizabal et al., 2020). Childhood exposure to toxic stress also partially leads to endocrine and neurodevelopmental dysregulation. Prolonged activation of stress-response systems may result in disruption of immune, metabolic, and neurological development as a result of chronic exposure to psychosocial adversity, poverty, family instability and environmental stressors. The chronic cortisol and inflammatory activations have the potential to disrupt emotional regulation, neural connectivity, and cognitive development and increase the risk of cardiometabolic disorders later in life. However, the mechanisms are still complex and interplay based on the interactions between genetics, caregiving environments, socioeconomic conditions, and ecological factors (Magalhães-Barbosa et al., 2022).

3.3 Organ Structural Programming

Developmental programming can cause enduring structural changes in key organ systems, and thus potentially lead to chronic disease vulnerability throughout the life course. Prenatal nutritional deficiency, placental insufficiency and maternal metabolic disturbances may cause impairment of organogenesis in critical developmental windows producing permanent losses in functional capacity. Developmental insults in the kidney can lead to fewer nephrons and result in increased risks of hypertension and renal dysfunction in later life. Likewise, the impacted fetal development can modify the cardiovascular remodeling by endothelial dysfunction, decreased vascular elasticity, and cardiac alterations. Adverse developmental environments also may mediate the long-term physiological resilience and organ-system functioning.

3.4 Inflammation and Immune Programming

Inflammation and immune programming have become a growing area of interest as an important connection between early-life exposures and lifelong health outcomes. The immune maturation may be influenced by the developmental conditions through immune imprinting, whereby prenatal and early-life exposures shape the inflammatory responsiveness and immunological control later in life. The prenatal inflammatory states, maternal obesity, nutritional imbalance, and neuroendocrine dysregulation have been linked to alterations in cytokine profiles, metabolic dysfunction and neuroendocrine dysregulation in offspring. Experimental models also indicate that maternal metabolic disturbances could impact on the regulation of appetite, the functioning of adipose tissues, and the effect of hypothalamic signaling pathways in relation to obesity and chronic inflammatory disease. Nevertheless, despite the considerable amount of mechanistic evidence in animal studies, it is challenging to translate this information to human populations due to the interactions between environmental exposures, genetic variability, and postnatal social determinants (Reynolds et al., 2017).

Table 1. Biological Mechanisms Underlying Developmental Programming and Associated Long-Term Outcomes

Mechanism	Key Process	Early-Life Trigger	Long-Term Outcome	Supporting Reference
Epigenetic regulation	DNA methylation and altered gene expression	Maternal nutrition and environmental stress	Obesity, diabetes, cardiovascular disease	Sharp & Relton (2017)
Epigenetic aging programming	Oxidative stress and mitochondrial alteration	Prenatal nutritional imbalance	Accelerated aging and metabolic dysfunction	Vaiserman et al. (2018)
Endocrine dysregulation	HPA axis and cortisol imbalance	Psychosocial adversity and toxic stress	Metabolic syndrome and stress disorders	Aristizabal et al. (2020)
Toxic stress and neurodevelopmental programming	Chronic stress-response activation	Poverty and psychosocial instability	Cognitive dysfunction and cardiometabolic disease	Magalhães-Barbosa et al. (2022)
Immune and inflammatory programming	Cytokine imbalance and immune imprinting	Maternal obesity and prenatal inflammation	Asthma and chronic inflammatory disease	Reynolds et al. (2017)

Table 1 summarizes the major biological mechanisms involved in developmental programming and highlights how early-life environmental exposures influence long-term physiological function and disease susceptibility. The table demonstrates the interconnected roles of epigenetic regulation, endocrine adaptation, metabolic alterations, toxic stress, and immune programming in shaping lifelong risks of chronic non-communicable diseases.

4. Early-Life Determinants of Long-Term Health

4.1 Maternal Nutritional Status

The nutritional status of the mother is a key determinant of fetal growth, organ development, and metabolic health during adult life. Undernutrition and overfeeding during pregnancy can interfere with developmental homeostasis by metabolic and epigenetic programming. Maternal nutrient deficiency has been linked to impaired fetal growth, altered endocrine signaling, and increased susceptibility to cardiometabolic diseases whereas maternal obesity and excessive gain of gestational weight have been associated with predisposing offspring to insulin resistance, obesity, and chronic inflammation. Gene regulation and developmental adaptation may also be affected by micronutrient imbalance, such as deficiencies in folate, iron and vitamin D, during fetal development (Godfrey et al., 2016).

In low- and middle-income nations where nutritional deprivation is often overlapping with poverty, infectious disease and limited access to healthcare services, adolescent undernutrition continues to be a major issue of public health concern. During adolescence, poor maternal nutrition can impair placental functioning and fetal transfer of nutrients, and increase the risks of low birth weight, stunting and adverse developmental outcomes. Nonetheless, the context of nutrition transition has both heightened susceptibility to maternal obesity and nutritional excess in most populations. These contrasting nutritional conditions show that deficiency and overnutrition of nutrients can disorient the development trajectories due to overlapping biological pathways (Christian and Smith, 2018).

4.2 Intrauterine Environment

One of the key factors that dictate the growth and developmental adaptation of the fetus is the intrauterine environment. Placental insufficiency, hypoxia, maternal illness and failure to deliver nutrients may alter fetal physiology at sensitive developmental periods, and thus, increase susceptibility to chronic disease later in life. Adverse in uterine conditions, could limit fetal development and result in compensatory metabolic adaptation maximizing short-term survival in low resource environments. Nevertheless, such developmental responses can be maladaptive when the postnatal environments are characterized by significant differences with the prenatal environments. The growing body of literature confirms the fact that intrauterine exposures have the potential to affect endocrine regulation, cardiovascular development, immune development, and metabolic functioning through interrelated biological pathways that extend across the lifespan (Heindel and Vandenberg, 2015).

4.3 Maternal Stress and Psychosocial Factors

It is possible that maternal stress and psychosocial adversity in pregnancy have significant long-term effects on fetal neurodevelopment and long-term physiological regulation. Persistent stimulation of maternal stress-response systems can elevate prenatal exposure to glucocorticoids like cortisol, and thus influence the development of hypothalamic-pituitary-adrenal (HPA) axis, emotional and stress responsiveness in offspring. Prenatal psychosocial stress has also been linked with disturbed immune function, poor cognitive development, anxiety-related behaviors, and high cardiometabolic risk in adulthood. However, these developmental outcomes depend on a number of interacting factors, such as maternal mental health, good caregiving, socioeconomic disadvantage, and postnatal environmental conditions (Hoffman et al., 2017).

4.4 Environmental and Chemical Exposures

Prenatal and early postnatal environmental and chemical exposures could have long-term consequences on physiological regulation and predisposition to disease. Air pollution, exposure to heavy metals, neurodevelopmental dysfunction, metabolic dysregulation, and altered immune responses have been linked to impaired fetal growth. The degree of developmental vulnerability to toxicants is especially high during fetal life due to the increased sensitivity of the external exposures. Nevertheless, the evidence of the long-term toxicant effects stays heterogeneous in all populations because of variations in the intensity of exposure, socioeconomic conditions, nutrition, access to healthcare, and genetic vulnerability.

4.5 Infant and Early Childhood Nutrition

Infant and early childhood nutrition are the key factors that determine developmental health and long-term physiological functioning. Breastfeeding has been linked to the better immune maturation, cognitive development, metabolic regulation, and reduced risks of obesity and chronic disease in adulthood. Bioactive compounds and immunological factors present in human milk play a role in gut maturation and immune programming in early development. Complementary feeding habits also have the potential to affect the diet, metabolic regulation, and developmental patterns. Nevertheless, correlations between breastfeeding and long-term health outcomes are not consistent across all populations due to the potential influence of socioeconomic status, maternal education, cultural behaviors and access to health services. There is also evidence that early exposure to breastfeeding has a positive effect on renal functioning in childhood (Miliku et al., 2015).

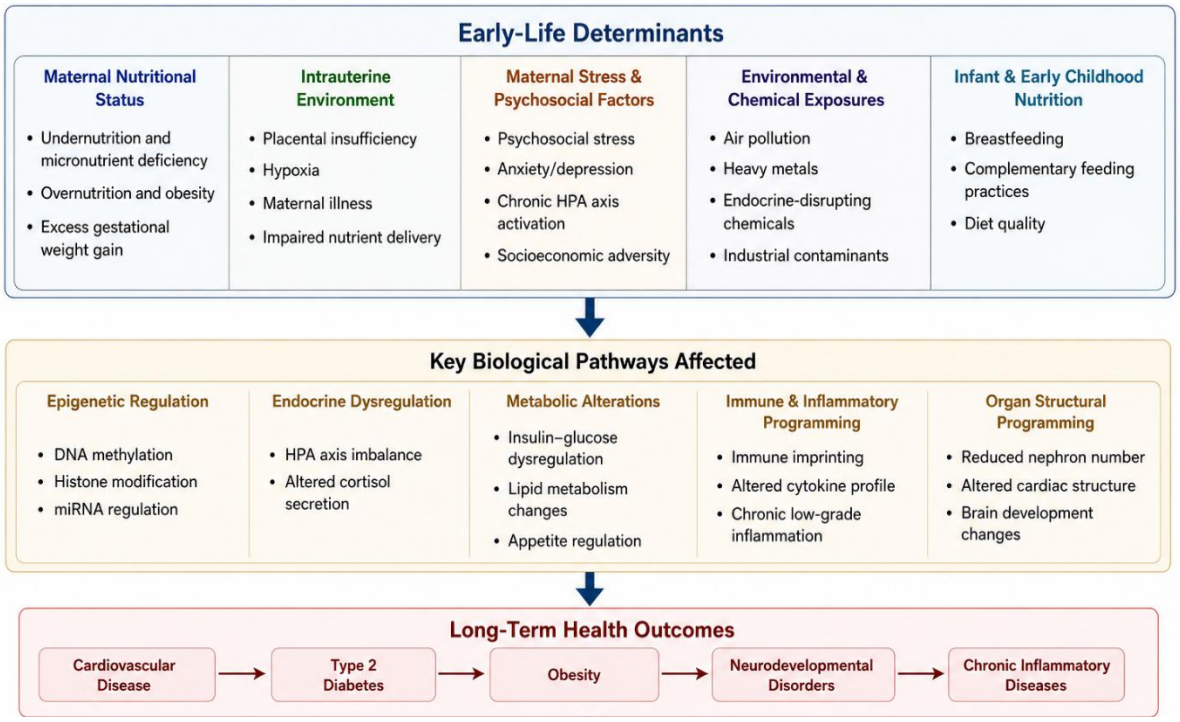

Figure 2. Early-Life Determinants Influencing Developmental Programming and Long-Term Health Outcomes

Figure 2 illustrates how maternal nutrition, intrauterine conditions, psychosocial stress, environmental exposures, and infant nutrition influence key biological pathways involved in developmental programming. These early-life determinants affect epigenetic, endocrine, metabolic, immune, and structural mechanisms, thereby increasing susceptibility to chronic diseases and adverse life-course health outcomes across generations.

5. The Mismatch Hypothesis and Adaptive Programming

5.1 Predictive Adaptive Responses

The mismatch hypothesis suggests that developmental adaptations in early life can become maladaptive when there is a significant difference between the prenatal environment and the postnatal environment. Predictive adaptive responses are those where the fetus modifies the physiological processes in response to the future environment, especially when there is a nutritional scarcity of the mother or maternal stress. These adaptations can include a change in metabolism, endocrine signalling, and energy allocation that enhances short term survival. Nonetheless, resource-optimal adaptations can subsequently make one more susceptible to obesity, insulin resistance, and cardiovascular disease in nutritionally rich environments (Lea et al., 2017).

5.2 Adaptive Developmental Plasticity

Adaptive developmental plasticity postulates that an organism can alter developmental pathways to environmental signals during sensitive developmental stages. This plasticity probably evolved to be a survival response that allowed physiological and behavioral adaptation to the predicted ecological conditions. Nonetheless, it has been difficult to pinpoint genuinely adaptive responses in humans because outcomes of development are influenced by genetic factors, environmental exposures, socioeconomic factors and culture. Also, not all developmental changes are necessarily adaptive responses to developmental stress, but may represent pathological consequences (Nettle and Bateson, 2015).

5.3 Urbanization, Nutritional Transition, and Lifestyle Shifts

Rapid urbanization, nutritional transition, and lifestyle modification have intensified interest in the mismatch hypothesis within global health research. Many populations now experience coexistence of prenatal undernutrition with postnatal exposure to calorie-dense diets, sedentary lifestyles, and chronic psychosocial stress. This environmental discordance may contribute to increasing rates of obesity, metabolic syndrome, and non-communicable diseases, particularly in low- and middle-income countries. Nevertheless, individuals exposed to adversity may also develop adaptive cognitive, behavioral, and social strategies that improve resilience under unstable conditions (Frankenhuis & Nettle, 2020).

5.4 Critical Perspectives and Population Variability

While the mismatch hypothesis has made substantial contributions towards understanding developmental programming, it is not clear that it holds true across populations. Biological embedding models imply that experience during childhood can affect the regulation of the neuroendocrine system, immune system and stress sensitivity in a long-term physiological adaptation. The impact of these, however, is different in social, cultural and environmental contexts. Access to health care, quality of care, education, nutrition, and social protection policies can significantly impact developmental outcomes of exposure to early adversity. Therefore, developmental programming is not just "biological determinism" but rather a dynamic interplay between the biology, environment and social experience (Berens et al., 2017).

Table 2. Key Concepts of the Mismatch Hypothesis and Adaptive Developmental Programming

Concept	Description	Potential Consequence	Supporting Reference
Predictive adaptive response	Fetal adaptation to predicted environment	Metabolic mismatch	Lea et al. (2017)
Developmental plasticity	Flexible developmental adjustment	Physiological adaptation	Nettle & Bateson (2015)
Nutritional transition	Prenatal scarcity with postnatal excess	Obesity and T2DM	Frankenhuis & Nettle (2020)
Biological embedding	Long-term physiological adaptation to adversity	Chronic disease risk	Berens et al. (2017)

The main ideas behind adaptive developmental programming and the mismatch hypothesis within the DOHaD framework are outlined in Table 2. The table highlights how developmental adaptations to early-life environmental conditions may become maladaptive when postnatal environments differ substantially, thereby contributing to long-term metabolic dysfunction, chronic disease susceptibility, and population-specific health outcomes across the life course.

6. Lifelong Disease Risk: Epidemiological Evidence

6.1 Cardiovascular Disease

There is epidemiological support to show that negative developmental environments play a significant role in the risk of cardiovascular disease throughout life. In adulthood, hypertension, endothelial dysfunction and ischemic heart disease have been linked to early-life exposures which include fetal growth restriction, maternal malnutrition, prenatal stress and placenta insufficiency. Results of Helsinki Birth Cohort and Dutch Hunger Winter studies also confirm the relationship between prenatal adversity, low birth weight, and increased cardiovascular risk in adulthood. Nevertheless, these impacts are diverse among populations due to the fact that socioeconomic situations, access to health care, nutrition, and environmental exposures have a strong influence on developmental outcomes (Suzuki, 2018).

6.2 Type 2 Diabetes and Metabolic Syndrome

There is substantial epidemiological evidence to support associations between negative intrauterine environments with later in life increased risk of type 2 diabetes and metabolic syndrome. Deviations of placental transfer of nutrients during pregnancy, maternal obesity, gestational diabetes, and developmental programming may influence insulin sensitivity, pancreatic development of 8 cells, adipogenesis, and glucose metabolism through developmental programming mechanisms. There are longitudinal studies that have shown that there are increased risks of obesity, insulin resistance, dyslipidemia, and impaired glucose tolerance among people who experienced adverse prenatal metabolic conditions. Still, the causal explanation is complicated by variations in maternal nutrition, ethnicity, postnatal way of life, and genetic predisposition (Fernandez-Twinn et al., 2019).

6.3 Obesity and Adiposity Patterns

Developmental programming has been strongly implicated in obesity and altered adiposity patterns across the life course. Prenatal exposure to maternal overnutrition, excessive gestational weight gain, endocrine disruption, and nutritional imbalance may alter appetite regulation, adipocyte differentiation, and metabolic efficiency. Evidence suggests that both fetal undernutrition and maternal obesity may predispose offspring to increased adiposity, while rapid postnatal catch-up growth may further increase obesity risk. However, obesity susceptibility is also influenced by postnatal diet, physical activity, urbanization, and socioeconomic conditions.

6.4 Neurodevelopmental and Mental Health Disorders

Early stress and poor developmental contexts could have a profound effect on brain development and predispose children to future neurodevelopmental and mental health disorders. Early life stress, such as high levels of maternal stress, psychosocial stress, inflammation, and environmental stressors, have been linked to changes in neural connectivity, emotional control, and risk for depression, cognition, and attention disorders. In addition, prenatal stress has been found to impact brain regions related to emotional processing and executive functioning in the brain through neuroimaging studies. But caregiving quality and social support and education also play a strong role in neurodevelopment outcomes (Van den Bergh et al., 2018).

6.5 Immune and Inflammatory Conditions

There is growing evidence that developmental exposures can impact immune maturation and inflammatory regulation that in turn can lead to asthma, allergic disease, autoimmune dysfunction, and chronic inflammatory conditions later in life. Maternal psychosocial stress during pregnancy has been linked to increased asthma and allergic disease in childhood by various mechanisms, such as modifications in fetal immune function. Systematic reviews and meta-analyses also show significant links between prenatal stress exposure and children's immune outcomes. But the interpretation of this is complicated by the fact that there is heterogeneity in stress measures, in exposures to the environment, genetic susceptibility, and access to health care (Flanigan et al., 2018).

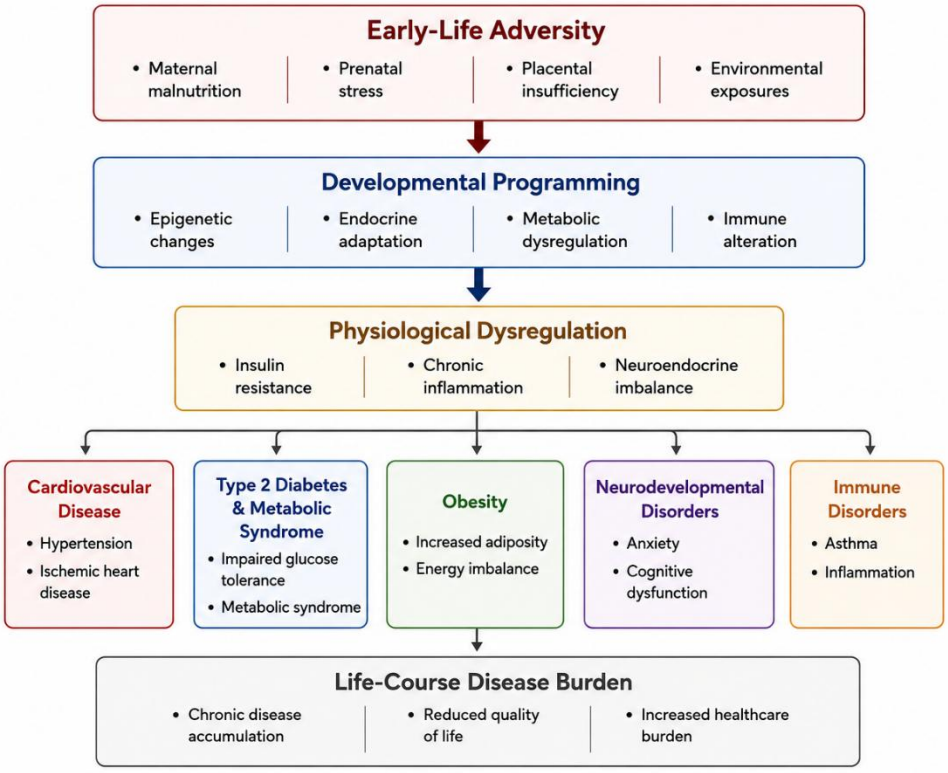

Figure 3. Developmental Programming Pathways Linking Early-Life Adversity With Lifelong Disease Risk

Figure 3 illustrates how adverse early-life exposures induce developmental programming through epigenetic, endocrine, metabolic, and immune alterations. These biological adaptations contribute to physiological dysregulation and increase susceptibility to cardiovascular disease, type 2 diabetes, obesity, neurodevelopmental disorders, and immune dysfunction, ultimately contributing to long-term life-course disease burden and reduced health resilience.

7. Intergenerational and Transgenerational Effects

7.1 Maternal–Fetal Transmission of Risk

Intergenerational transmission involves the direct biological, environmental or social exposure to a health risk that is passed on from one generation to the next. During pregnancy, maternal nutrition, metabolic status, stress physiology, toxicant exposure and placental function may have direct effects on the development of the fetus and disease susceptibility later in life. The multigenerational cohort studies also indicate that grandmaternal exposures could have impacts on reproductive timing and adiposity-related outcomes in grandchildren, but caution is required to interpret such effects given that multiple generations may be involved during pregnancy. The results show how the developmental paths are linked to each other, both biologically and socially, via the maternal and grandmaternal environments (Cirillo et al., 2021).

7.2 Distinguishing Intergenerational and Transgenerational Evidence

It is crucial to differentiate intergenerational and transgenerational inheritance in DOHaD studies. An intergenerational effect is an effect seen in the exposed parent, fetus or fetal germ cell while a true transgenerational effect must be seen in generations not directly exposed to the environmental exposure. This distinction is especially relevant when considering human studies as the foetus, mother and developing germline can be affected at the same time during pregnancy. Many of the observations of transgenerational effects may therefore be attributed to intergenerational exposure, a shared environment, or socioeconomic continuity instead of to epigenetic transmission through unexposed generations (Horsthemke, 2018).

7.3 Paternal Origins of Health and Disease

While maternal–fetal pathways have always been a focus of DOHaD research, paternal influences are now known to play an important role in offspring health. In the Paternal Origins of Health and Disease (POHaD) framework, the paternal nutrition, obesity, toxicant exposure, age, and psychosocial stress may affect offspring development by modifying the epigenome of the sperm, by altering the composition of seminal fluid, or by sharing the same postnatal environment. Such paternal determinants can interact with maternal and social determinants to influence developmental conditions and/or susceptibility to disease later in life. Incorporating fathers into DOHaD science is more complete and not assigning all responsibility for DOHaD solely to mothers (Soubry, 2018).

7.4 Epigenetic Inheritance Evidence

Epigenetic inheritance has been shown to be more consistent in experimental animal models than in humans due to environmental influences. Research in animals indicates nutrition imbalances, toxicant exposures, endocrine disruptions, and stress may induce generational changes in DNA methylation, histone modification, and non-coding RNA. The results support

the hypothesis of germline transmission of disease susceptibility. Extrapolation to humans is however limited as studies are influenced by long generation time, ethical issues, heterogeneous exposures, genetic variability and shared environment. Therefore, epigenetic inheritance needs to be taken with a grain of salt in the research field of developmental programming (Nilsson et al., 2018).

7.5 Socioeconomic and Nutritional Cycles Across Generations

In addition, socioeconomic and nutritional intergenerational cycles influencing developmental environment have been identified as a mechanism of disease risk transmission across generations. Poor nutrition, poverty, low literacy, maternal undernutrition, obesity, and inadequate health services can be passed down in families and communities, leading to repeated exposures to development in prenatal environment, childhood development and increased risk for disease in adulthood. In addition, paternal metabolic health may play a role via environmentally responsive sperm epigenetic patterns—environmental influences in the pre-conception period and nutrition and their impacts on developmental outcomes in offspring. The pathways show the strong links between structural inequalities, family environments and population level nutritional transitions in the intergenerational health transmission.These pathways illustrate how deeply intergenerational health transmission is rooted in structural inequalities, family environments and population level nutritional transitions (Donkin & Barrès, 2018).

Table 3. Intergenerational and Transgenerational Pathways Influencing Developmental Health

Pathway	Key Mechanism	Evidence Type	Health Implication	Supporting Reference
Maternal–fetal transmission	Prenatal metabolic and environmental exposure	Human cohort studies	Obesity, metabolic disease	Cirillo et al. (2021)
Intergenerational inheritance	Direct exposure across generations	Epidemiological evidence	Chronic disease susceptibility	Horsthemke (2018)
Paternal influences (POHaD)	Sperm epigenetic modification	Emerging human evidence	Offspring developmental risk	Soubry (2018)
Epigenetic inheritance	DNA methylation and non-coding RNA alteration	Experimental animal models	Multigenerational disease risk	Nilsson et al. (2018)
Socioeconomic transmission	Poverty and nutritional cycles	Population-based evidence	Recurrent developmental adversity	Donkin & Barrès (2018)

The main intergenerational and transgenerational pathways that shape developmental health from one generation to the next are summarized in Table 3. The table shows some examples of maternal, paternal, epigenetic and socioeconomic explanations for susceptibility to disease, and identifies key differences between direct intergenerational exposure and true "transgenerational" inheritance in developmental programming research

8. Contextual and Socioeconomic Dimensions

8.1 Inequality and Health Disparities

Inequalities in nutrition and health services, quality of care, education, and safety of the environment influence early childhood development. Undernutrition, infectious disease, social and emotional situations, and poor developmental stimulation are disproportionately experienced by children living in poverty, and may affect cognitive, emotional and physical development. According to global estimates, millions of children in low and middle income countries continue to be at risk of not reaching their developmental potential due to the continued socioeconomic disadvantage. These inequities are linked to chronic disease risk, lower educational status and lower economic productivity throughout the life course (Lu et al., 2016).

8.2 Connecting Biology with Social Determinants

Developmental programming needs to be understood in terms of the interplay between biological mechanisms and other social determinants of health. Commonalities in environmental, behavioral and structural factors between early life adversity and chronic disease make it difficult to draw causal conclusions. The developmental exposures could be influenced by socioeconomic conditions that can include pathways of maternal nutrition, psychosocial stress, environmental toxicants, access to healthcare, and intergenerational disadvantage. So, developmental outcome is not only a biologically reductionistic phenomenon. To provide the full picture of life course health, biological vulnerability needs to be understood in the context of social and environmental conditions and public policy (Pearce & Lawlor, 2016).

8.3 Urbanization, Stress, and Inflammatory Responses

Rapid urbanization and social transition have increased exposure to psychosocial stressors associated with poverty, overcrowding, instability, and environmental adversity. Childhood neglect, chronic stress, and social deprivation may influence long-term immune and inflammatory regulation through biological embedding processes. Evidence suggests that early-life adversity may contribute to exaggerated inflammatory and stress responses during adulthood, thereby increasing susceptibility to cardiometabolic disease, psychiatric disorders, and immune dysfunction. However, these physiological consequences are also shaped by continuing social disadvantage, supportive relationships, and cumulative environmental stressors across the life course (Schreier et al., 2020).

8.4 LMIC Burden and Lifestyle Transitions

Low- and middle-income countries face a complex developmental health burden due to coexistence of undernutrition, infectious disease, urbanization, and increasing non-communicable diseases. Lifestyle transitions involving dietary change, environmental pollution, reduced physical activity, and psychosocial instability may interact with developmental vulnerability established during early life. Furthermore, adverse caregiving environments and chronic stress exposure during infancy may influence hypothalamic–pituitary–adrenal (HPA) axis functioning and immune development, thereby increasing susceptibility to respiratory and inflammatory conditions during childhood. The results show developmental programming is not a purely biological phenomenon, but must be interpreted in the context of a wider social and ecological context (Frost et al., 2021).

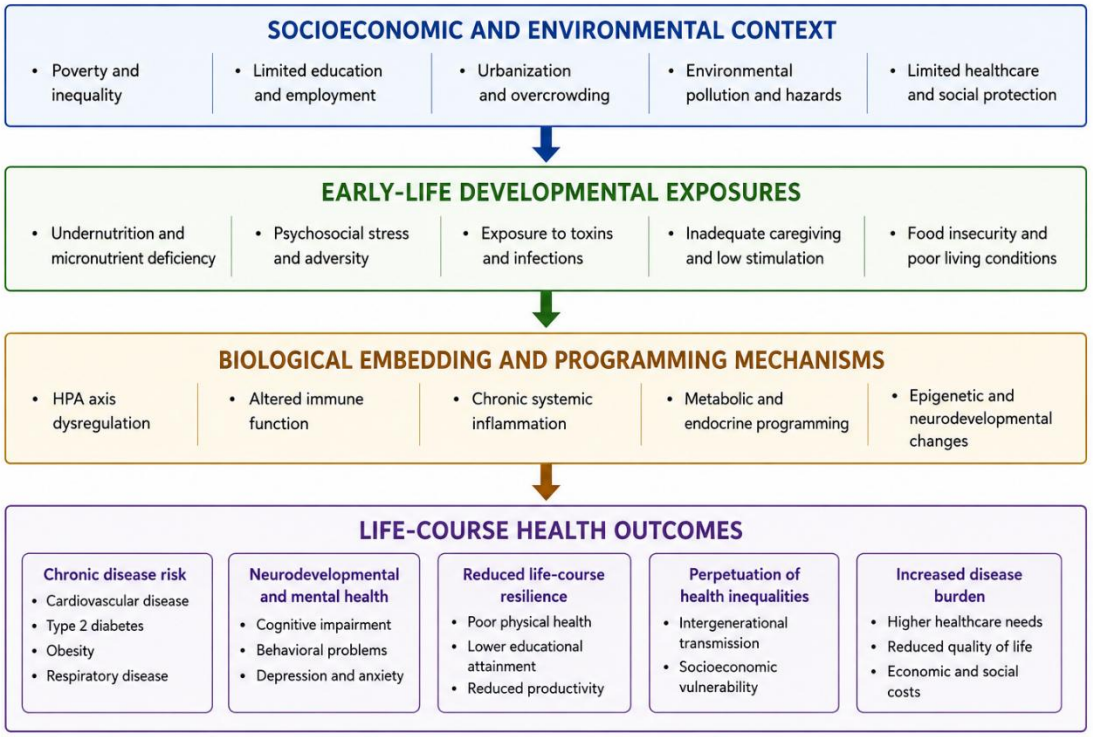

Figure 4. Socioeconomic and Environmental Contexts Influencing Developmental Programming and Life-Course Health Outcomes

Figure 4 illustrates how socioeconomic disadvantage, environmental adversity, urbanization, and limited healthcare access shape early-life developmental exposures. These conditions become biologically embedded through immune, metabolic, endocrine, and inflammatory mechanisms, thereby increasing vulnerability to chronic disease, neurodevelopmental disorders, reduced resilience, and persistent health inequalities across the life course.

9. Public Health and Policy Implications

9.1 Reframing Child Health Beyond Survival

The current context of child health policy is more aware of the need to go beyond the reduction of child deaths to achieve long-term population health and human development. Despite progress in immunization, infectious disease control, and maternal care, too many children are still at risk for developmental problems as a result of their nutritional status, poverty, environmental challenges, and lack of social and emotional stimulation. Developmental quality, cognitive development, emotional health and life-long physiological resilience are now recognized as key areas of child health in global health frameworks. The importance of early childhood development to educational results, economic productivity, and social sustainability has therefore grown increasingly important and is viewed as a determining factor (Daelmans et al., 2017).

9.2 Maternal and Preconception Health Strategies

Disease prevention strategies for the health of mothers and children should be focused on developmental disease prevention as developmental programming starts before conception and extends throughout pregnancy. Nutritional interventions, antenatal monitoring, micronutrient supplementation and mental health support of the mother may enhance fetal growth and developmental outcomes. Emerging public health strategies increasingly emphasize the need for integrated maternal care, dealing with nutrition, psychosocial stress, environmental exposures, and reproductive health prior to and during pregnancy. However, there are variations in implementation between countries due to the unequal access to maternal health care, lack of skilled health care workers, socio-economic and demographic disparities, and poor health care infrastructure, especially in low-resource countries (World Health Organization [WHO], 2023).

9.3 Early Childhood Development Programs

Childhood development initiatives that combine nutrition with cognitive and psychosocial stimulation have proven significant benefits for life-long development. Parenting practices, responsive caregiving, early learning and nutritional

adequacy during infancy and early childhood interventions could result in better cognitive functions, emotional regulation, school outcomes and future socioeconomic outcomes. Longitudinal data also indicate that benefits for development might continue into adulthood via educational outcomes and economic involvement. However, cultural adaptation, involvement of caregivers, ongoing funding and community support networks all play a critical role in successful implementation (Grantham-McGregor & Smith, 2016).

9.4 Integration into Global Health Frameworks

The need for ECD is increasingly recognized as part of the sustainable development and public health agenda at the global level, especially within the Sustainable Development Goals (SDGs). Parenting interventions that incorporate nutrition, caregiver responsiveness, psychosocial stimulation and developmental support during the first three years of life have been shown to be beneficial in various developmental domains. Yet, in many countries, policy implementation is weak due to a lack of coordination between health, education, nutrition and social protection systems. Despite these developments, there are ongoing inequalities in recognising health development priorities, financial investment and policy integration that remain limiting longer-term effectiveness and scalability of early childhood development interventions globally (Jeong et al., 2021).

10. Emerging Directions and Future Perspectives

10.1 Biomarkers for Early Risk Detection

The identification of developmental exposures and the development of biomarkers of these exposures has proven to be a promising approach toward detecting risk early and intervening to prevent it. Stress, nutritional status, quality of caregiving, and adverse environments might have molecular signatures that could help identify developmental vulnerabilities prior to the onset of clinical signs. DNA methylation patterns, inflammatory markers, hormones, and metabolic markers are among the biomarkers currently being studied as markers for identifying children who are at increased risk for chronic diseases. But there are ethical issues related to biological determinism, social labelling and the interpretation of molecular risk markers in different developmental and socioeconomic settings (Hein et al., 2024).

10.2 Omics Technologies and Developmental Programming

The understanding of the mechanism of developmental programming has been advanced by advances in omics technologies such as genomics, epigenomics, transcriptomics, metabolomics and proteomics. These strategies allow for study of phenotypic outcomes of exposures during developmental periods and the role of those exposures on molecular pathways that control metabolism, endocrine function, immune system maturation and reproductive health. Omics-based approaches are more increasingly being incorporated into developmental toxicology research to determine environmentally responsive biological pathways that underlie susceptibility to disease. However, the interpretation of omics data is still difficult, as developmental outcomes result from interactions between genetics, environmental exposures, and social determinants; these are not exclusively dependent on molecular changes (Scarano et al., 2024).

10.3 AI and Predictive Modeling

The use of artificial intelligence (AI) and predictive modeling in developmental health research is becoming more common, as it can help to better predict disease, stratify patients, and develop individualized intervention strategies. Combining massive amounts of epidemiological, clinical, environmental and molecular data with machine learning approaches could enable the identification of developmental patterns that are linked to the risk of chronic disease. Predictive models can also be used to identify vulnerable groups at critical developmental periods and design preventive interventions to address them. There are still worries about issues of algorithmic bias, the unequal representation of data, and the ethical concerns of predictive health surveillance (Reisinger & Hannan, 2025).

10.4 Precision Public Health and Social Context

The aim of precision public health is to combine characteristics of the individual's biology and the environment, social and population-level factors to optimize strategies for disease prevention. Developmental programming is a new research paradigm in DOHaD that is gaining recognition and has been acknowledged that social factors like social disadvantage, inequality and social adversity have a powerful influence on developmental pathways and programming. Meanwhile, researchers are not condoning a biological-only approach to explaining health disparities. The future developmental health frameworks will thus need to focus on molecular developments as well as ethical, social and structural determinants of health in a balanced way (Romijn & Louvel, 2023).

10.5 Climate Change and Developmental Health

There is growing recognition that climate change is a significant factor influencing developmental health throughout the life course. The changes in temperature, environmental pollution, food insecurity, expansion of infectious diseases, and climate related psychosocial stress could impact maternal health, fetal development, and childhood physiological resilience. Environmental perturbations that can potentially alter long-term developmental regulation are especially effective on early embryonic stages. From these results, it can be inferred that future generations can become more vulnerable to developmental outcomes and to chronic diseases due to environmental disruption driven by climate change. Incorporating climate resilience into maternal, fetal and child health policies is likely to be increasingly important in future DOHaD research and global public health planning (Čikoš et al., 2015).

11. Strengths and Limitations of Current Evidence

11.1 Heterogeneity of Studies

One of the key features of DOHaD studies is their interdisciplinary nature, combining epidemiology, molecular biology, developmental physiology and the environmental sciences. But there is significant variability between publications in terms of population description, exposure measurement, outcome description and analysis techniques. Comparisons of studies are difficult and generalizability is limited by the differences in nutrition, socioeconomic factors, ethnicity, environmental exposures and health care systems. Furthermore, the small size of the epigenetic effects is often misinterpreted, as there is evidence that relatively small molecular changes can have meaningful developmental consequences (Breton et al., 2017).

11.2 Lack of Long-Term Longitudinal Data

A number of cohort studies have identified links between exposures in the early life and the risk of disease in later life, but long-term longitudinal studies are still limited. Prospective studies are expensive and difficult to conduct due to the many years needed to gather the required information to study chronic disease outcomes. Participants may drop out of existing cohorts, vary in their exposure, and have varying follow up across developmental stages. In addition, developmental programming systems can be different depending on the environment, meaning they can only be applied to similar populations. Research investigating prenatal nutritional exposures and epigenetic changes in offspring has given insights into the mechanisms, but the repercussions of many molecular changes are not yet clear in the long term, (Küpers et al., 2022).

11.3 Challenges in Causal Inference

Causality is difficult to establish in DOHaD research due to the interactions of genetic, environmental, behavioral and social factors. Residual confounding and reverse causation, selection bias and shared family environments can affect observational studies. An increasing number of Mendelian randomization approaches aim to improve the strength of the causal inferences, and to identify developmental effects over and above confounded associations, via genetic variation. However, these have their own drawbacks because of pleiotropy, population stratification, and inadequately representing complex environmental exposures (Richmond et al., 2017).

11.4 Translational Gaps

Although there have been significant developments in mechanistic and epidemiological understanding, there are key translation issues between developmental programming research and public health implementation. Because of uncertainties about exposure limits and the time of vulnerability, the reversibility of developmental changes, and the applicability of the results at the population level, translating molecular findings into preventive interventions is complicated. The methodological challenges in the field of environmental health are also complex, because of exposure mixtures, chemical interactions, and susceptibility to development. The constraints underscore the need for standardized methodologyies, interdisciplinary connections and better mechanistic science–public health policy linkages (LaKind et al., 2017).

11.5 Integrating Environmental and Developmental Complexity

Prominent restrictions of current DOHaD evidence include a lack of environmental complexity in developmental health models. Biological exposures are not the only factors that affect developmental outcomes, but interacting developmental nutritional, psychosocial, environmental and socioeconomic exposures throughout the life course also affect development. Thus, interpretations at the molecular level can be reductionist, resulting in the neglect of structural determinants of health at a broader level. Modern approaches toward development increasingly focus on the importance of considering environmental exposures and social context, climate hazards, population disparities, and public health systems in order to better understand how susceptibility to disease is passed from generation to generation (Heindel et al., 2015).

12. Conclusion

The Developmental Origins of Health and Disease (DOHaD) paradigm has significantly shifted current perspectives on the health of children by revealing that the susceptibility to develop lifelong diseases is profoundly affected by preconception, fetal, infant and early childhood environmental exposures. The review identified the developmental programming mechanisms, such as epigenetic control, endocrine adaptation, immune modulation and structural organ development, and how these mechanisms relate with nutrition, psychosocial, environmental and socioeconomic factors to influence long-term physiological outcomes. Epidemiological evidence has been accumulating over time to link adverse early-life exposures to a higher risk for cardiovascular disease, obesity, type 2 diabetes, neurodevelopmental disorders, and chronic inflammatory diseases, throughout the lifespan. Although significant progress has been made in the knowledge of mechanisms and epidemiology, there are still many challenges, such as the lack of consistency between studies, short-term longitudinal studies, poor ability to make causal inference, and the lack of translation between research results and public health action. However, current evidence strongly supports the urgent need to shift from the survival perspective of child health to a life-course perspective that focuses on developmental quality, early intervention, and resilience to health. The potential for the future integration of omics technologies, biomarkers, artificial intelligence, and precision public health could further enhance early risk detection and targeted prevention strategies to contribute to healthier population and decrease burden of chronic diseases in the world

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