



Developmental origins of health and disease (DOHaD) and its impacts on children's health: a systematic review

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Abstract

The general objective of this study is to elucidate how studies linked to the Developmental Origins of Health and Diseases (DOHaD) relate to pregnancy, children's health, and the possibility of developing non-communicable diseases (NCDs). The research method chosen for its scope was based on bibliographic, qualitative, and descriptive research. Among the results obtained, it was possible to show that since the 1980s when the first studies within the DOHaD scope were published to the present, numerous advances have been consolidated and there is still a vast field of study to be developed. It is concluded that the external environment can affect the development of the fetus in the intrauterine environment, increasing vulnerability to the development of non-communicable diseases (NCDs) in adult life, such as type II diabetes, malnutrition, and obesity, among countless other problems. that can manifest in adulthood. Therefore, it is essential that the pregnant woman has specialized care from the first months, at birth, and then as the child grows and develops.

Keywords: DOHaD. Health. External factors. Children.

Introduction

The mother's internal and external environment during the developmental stages of the fetus affects the health of the offspring. According to the developmental origins of health and disease (DOHaD) theory, environmental factors influence offspring and also affect health in adulthood [1,2]. Recently, studies based on this theory have gained prominence due to its clinical utility in identifying risk groups for various diseases.

Neurodevelopmental disorders (NDDs), such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), can be caused by exposure to certain prenatal environments during pregnancy [3].

The most recent findings on the effect of the prenatal environment on the initiation mechanism of NDDs based on DOHaD theory show strong evidence [4]. Unraveling the molecular mechanisms underlying the pathogenesis of NDDs is important because there are no therapeutic drugs for these disorders. Furthermore, elucidating the relationship between DOHaD theory and NDDs will contribute to the popularization of preventive medicine [5].

The topic addressed in this article covers a branch of scientific knowledge named Developmental Origins of Health and Disease (DOHaD) which had its first publications in the 1980s through the work of Barker and Osmond (1986). The elaborated studies consider environmental exposures, as well as other factors, experienced at the beginning of life, even during pregnancy, which have an impact on the greater vulnerability of this individual to develop certain diseases in adult life [6].

The justification for choosing the topic of this study comes from the understanding that the greater the knowledge of epigenetics and its impact, the greater our responsibility as physicians to teach about a healthy lifestyle since several diseases can be developed. This is because "[...] epigenetic changes, such as DNA methylation, are associated with measures of metabolic health and potentially predict future metabolic health status" [7].

Thus, the general objective of this study was to

elucidate how studies linked to Developmental Origins of Health and Disease (DOHaD) relate to pregnancy, children's health, and the possibility of developing non-communicable diseases (NCDs). The specific objectives were to define DOHaD, highlight the contributions of epigenetic studies in DOHaD, and discuss the influences of external factors on intrauterine development and the susceptibility of developing later non-communicable diseases (NCDs).

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules-PRISMA (Transparent reporting of systematic review and meta-analysis: [//www.prismastatement.org/](http://www.prismastatement.org/)). The presentation of the main results obtained was outlined descriptively without any kind of manipulation or impression by the researcher, that is, an attempt was made to highlight the most fundamental and constitutive aspects of DOHaD and its impacts. This study also contributed to the field of scientific knowledge as it corroborates to fill the existing gap in studies that address the environment, the phenotype, and the possibility of emerging non-communicable diseases (NCDs) in the long term.

Search Strategy and Search Sources

The literary search process was carried out from September to October 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: "DOHaD. Health. External factors. Children", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and discussion

Summary of Findings

As a corollary of the literary search system, a total of 90 articles were found that were submitted to the eligibility analysis and, then, 16 of the 37 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $I^2=98.4\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 22 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

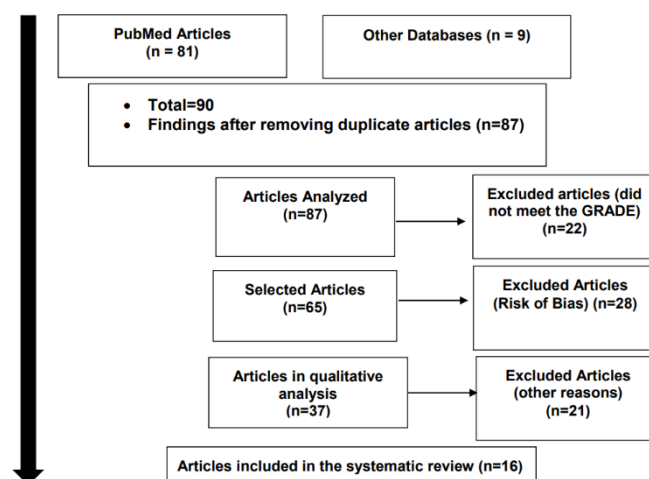
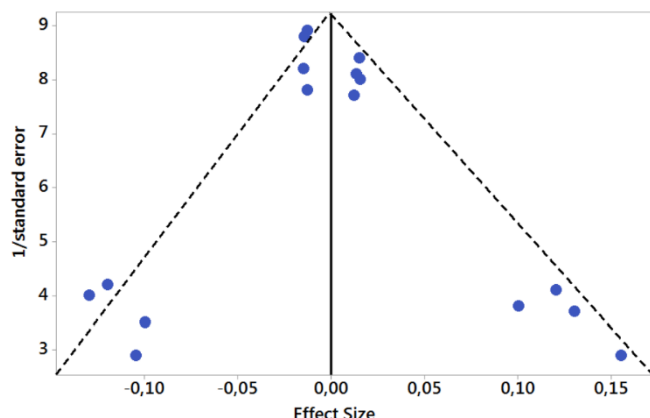


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This chart had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the chart and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=16 studies).



Source: Own authorship.

Main Clinical Findings

The Developmental Origins of Health and Diseases (DOHAD) [1-3] constitute a branch of scientific knowledge that uses knowledge from multiple areas, dedicated to the study of the existence of diseases diagnosed at the beginning of somatic development and the intensification of risk of developing chronic diseases throughout life, for example, obesity, cardiovascular diseases, and type II diabetes, among others, whose frequency has been increasing in the last decade, affecting people of different age groups [6,7].

The developed studies are based on hypotheses in which maternal, fetal, and infant growth/development factors culminate in predictive adaptive responses, as environmental factors directly influence the possibility of developing diseases in the future, as well as the vulnerability of these individuals from childhood to adulthood [7]. As an example of changes, we can mention that “[...] epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, are involved in mediating how the early life environment affects later health” [7]. Maternal health can impact the intrauterine environment, fetal development, and postnatal health. This is justified because in “[...] “immune privileged” and transient tissues such as the placenta, some mechanisms are important for the correct activation of cellular homeostasis maintenance pathways, including proteostasis” [8].

During pregnancy, it is verified that, although the intrauterine environment presents the necessary conditions for the development of the fetus, the external environment can affect this entire process, due to placental, fetal, or even maternal alterations [9]. Gene expression and how hormonal signals act on the fetus through the placenta or newborn through lactation can affect their future health condition making the child

more vulnerable to certain diseases. Therefore, babies who are born with low birth weight are more likely to have type II diabetes and a greater risk of being overweight in childhood [8]. From conception to the first two years of this little human being's life, all the phenomena that affect maternal health will also affect the baby and his health conditions in the future, due to the regulation process of the hypothalamus axis. - adrenal, through glucocorticoids. Such hormones are important throughout the process of adaptation of the maternal organism, during pregnancy until the moment of delivery [9].

The entire prenatal period, childbirth, breastfeeding process, food introduction, as well as the experiences and stimuli received by the child, can turn on or off certain genes that indicate the functioning of the body. Carrying a child marks a beautiful moment of great transformation, but it also requires a series of physical and emotional care from the mother [8]. The mission that guides and permeates DOHAD's studies is based on clarifying the physiological and pathophysiological bases that demonstrate how the environment influences human development and the onset of chronic diseases, from the earliest stages of life. given to the fetal period and the emergence of diseases [8,9].

Given this context, DOHAD is based on research methodologies that contribute to understanding the developmental influences of adverse events, the health-disease pattern that is manifested throughout the life of a given individual and that can be understood through epigenetic processes [8]. Epigenetic studies in DOHAD have shown to be very promising insofar as they can interpret:

[...] the impact of the genome on the epigenome, the tissue specificity of epigenetic marks, the stability (or lack thereof) of epigenetic changes over time, and the importance of associating epigenetic changes with changes in transcription or translation to demonstrate consequences functional [10].

These key concepts contribute to the elaboration of studies that allow designing and interpreting specific data about each child, how the health-disease process can affect them in their different age groups and levels of maturation, certain functional consequences, and epigenetic changes along the way over time, etc. [10].

During the prenatal and postnatal period, nutrition and other environmental stimuli end up influencing the development and, as a consequence, culminate in permanent transformations in metabolism, and increase

the susceptibility to the development of chronic diseases. Therefore, it is possible to link “[...] the permanent effects of transient environmental influences on the establishment of epigenetic gene regulation in development and evidence linking epigenetic dysregulation with human disease” [11].

The analysis of epigenetic studies in DOHaD is essential for the effective understanding of the causal associations that permeate early exposures, and the occurrence of long-term changes in the epigenetic regulation of diseases, since they enable the implementation of specific interventions at the beginning of life with the objective is to improve human health and its consequences during its existential course [11].

The first studies linked to DOHaD date back to the end of the 1980s, carried out by Barker and Osmond (1986) who were able to demonstrate a link between some diseases present in adults, such as stroke, type 2 diabetes, and dyslipidemia in due to factors related to in utero development [11,12]. Since the publication of his innovative reports, many studies on DOHaD have been developed and improved based on his methodology, analyzing in a more detailed way the events that occur at the beginning of life and their subsequent consequences [13].

Considering that the environment has a direct influence on the phenotype, it is possible to cite some examples of how this happens, parental nutrition and obesity increase the possibility that their children will have metabolic and cardiovascular diseases when they reach adulthood. This is because the known underlying mechanisms go through an “[...] altered development of tissues that adapt to the maternal metabolic condition and placental dysfunction, which in turn affects fetal growth and development” [12].

At the same time, epigenetic mechanisms provide new developments for gene expression without modifying the DNA sequence, among the most common epigenetic marks are “[...] DNA methylation and post-translational modifications of histones” [12]. Although such marks are erased and configured during gametogenesis and development to ensure cell identity, there may be early memorization of the environment that culminates in long-term changes in cell and tissue functions, therefore, it is easier for them to have non-communicable diseases in your body [12]. As the placenta is a programming agent of adult disease, it appears that in pregnancies where smoking or psychosocial stress are common, the possibility of epigenetic processes occurring “[...] such as the expression of small RNAs and methylation of the DNA” [12].

As the adverse intrauterine environment can later culminate in a series of non-communicable diseases (NCDs), in Pakistan a series of studies began to be developed to reduce “[...] the magnitude of early fetal programming and the subsequent risk of diseases ” [13]. In 2016, the Pakistan DOHaD Society was founded, which proposed to carry out early screening and intervene to reduce “[...] the burden of NCDs, mental health problems and lifelong learning disorders” in its population [13].

Among the advances already achieved is research into diseases “[...] such as diabetes, maternal malnutrition and pre-eclampsia in fetal programming in two major lines of research, that is, cardiovascular and cerebrovascular programming” [13]. Through the results obtained, it became possible to considerably improve the quality of life during early childhood. DOHaD assumes that strategies are adopted even during pregnancy so that there is no adverse programming in utero, preventing the occurrence of NCDs in the programming of the organism of the fetus that is in formation. During this period, it is essential to avoid unhealthy diets, environmental chemicals, bad habits, the use of drinks, and various drugs, among other behaviors and lifestyles that can affect pregnancy and increase the fetus' predisposition to NCDs [14].

Among the strategies that can be adopted to reduce the occurrence of NCDs, there is also an active medical approach that supports direct changes in utero programming in addition to personalized programs to be carried out during pregnancy, improving the mother's lifestyle and, reducing the possibility of the child being affected by NCDs in the future [14].

According to the DOHaD model, susceptibility to the development of type 2 diabetes is linked to intrauterine life through fetal environmental programming. Thus, both child malnutrition and being overweight increase the individual's risk of developing diabetes in the future. In both cases, there is high adiposity. The imbalance in the diet also plays an important role in the possibility of developing the disease in the future [14]. Associated with this, when the person maintains an unhealthy lifestyle, the risk of the disease manifesting even earlier is increased [15].

Maternal nutritional disorders, as well as “[...] a disordered metabolism, infections, maternal stress, extreme atmospheric temperature, etc” are factors that significantly corroborate the occurrence of fetal programming that is more susceptible to the development of diseases [15]. When mothers have diabetes, their children also tend to experience childhood obesity and diabetes at a young age, so the best window of opportunity to prevent the fetal

programming of NCDs is during the periconceptual period, when “[...] gametogenesis, fertilization, implantation, embryogenesis and placentation” [15]. Therefore, it is essential to improve your diet and habits, corroborating to reduce cases of NCDs worldwide. Prevention marks the main window of opportunity, as well as the correct follow-up of the child from its first years of life by specialized professionals such as pediatricians in their child care [15].

Another example that is in line with the discussions presented above refers to Dutch men who experience “winter hunger” in the first trimester of their life in the womb, showing a greater willingness to be obese in their adult life due to intrauterine “programming”. On the other hand, it was identified that Indian newborns have poor muscle and visceral mass, but greater adiposity for a given weight when compared to other white Caucasian newborns [16].

Adiposity is very important because [...] it can be an integral part of the orchestrated adjustments made to support “brain preservation” during intrauterine growth because brain tissue is predominantly fat”. In this sense, maternal nutritional intake and the concentration of nutrients that circulate throughout pregnancy must occur within parameters considered normal [16].

Conclusion

The data collected in the literature review demonstrated the importance of studies developed based on the DOHaD line of research, whether in the Biology of Reproduction, among other areas, contributing to the adoption of measures to prevent non-communicable diseases, early understanding of the mechanisms of this conditioning and its possible consequences. NCDs are characterized as a great challenge for the most diverse countries, since they culminate in high health expenses and, as studies linked to DOHaD have shown, it is necessary to prevent the occurrence of adverse effects even in the uterine environment, as they can increase the predisposition for its appearance due to the high malleability of development. Among the limitations identified in the preparation of this article is the fact that there are still relatively few published epigenetic studies on DOHaD, that is, there is still a vast field of investigation in this area, providing more subsidies for professionals such as, for example, pediatricians to who can adequately guide parents during childcare consultations.

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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