

## Developmental origins of health and disease (DOHaD)

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### Abstract

**Objective:** To present a new branch of scientific knowledge, known as the developmental origins of health and disease (DOHaD), covering its concepts, study methods and ethical considerations in addition to the prospects for this area of knowledge.

**Sources:** A non-systematic review of the biomedical literature intended to identify historical and current references related to the subject under discussion.

**Summary of the findings:** Recent studies demonstrate associations between aggressions suffered during the initial phases of somatic development and amplified risk of chronic diseases throughout life, such as obesity, diabetes and cardiovascular diseases. A variety of models have been proposed in attempts to better explain these associations, such as the thrifty phenotype, programming and predictive adaptive response theories and the concept of match or mismatch. Some of the mechanisms possibly involved in these processes are: effects of the environment on gene expression, through epigenetic mechanisms; effects of hormonal signals transmitted to the fetus via the placenta or the newborn via lactation.

**Conclusions:** DOHaD draws together information originating from many different areas of knowledge, proposing new investigative methodologies to elucidate the influence of adverse events that occur during early phases of human development on the pattern of health and disease throughout life. This new scientific field proposes new models of causality and of the mechanisms involved in the emergence and development of chronic diseases. The results of these investigations may result in a significant impact on the prevention of chronic diseases, and also on health promotion in different phases of life.

*J Pediatr (Rio J). 2007;83(6):494-504: DOHaD, programming, Barker hypothesis.*

### Introduction

Epidemiological studies in different parts of the world have related the influence of certain environmental factors in early life with alterations in the expression of individuals' genetic background, leading to a particular pattern of health and disease. Similarly, clinical and pre-clinical studies point in the same direction, suggesting a strong association between environmental aggressions suffered in utero or during the initial phases of extrauterine life and the emergence of chronic diseases throughout life. These findings indicate new bridges of

causality, inferring the possibility of early establishment of metabolic adjustments that determine morbid outcomes throughout life. In this review article, our objective is to discuss these ideas, now grouped together in a new branch of scientific knowledge under the nomenclature of the developmental origins of health and disease (DOHaD).

### Historical context

As mortality rates among preterm newborns (NB) at extremely early stages of development have fallen, new diseases have emerged and been identified. For example, in 1959

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Avery & Mead described the respiratory distress syndrome of the newborn, which is characterized by pulmonary immaturity and an incapacity to produce surfactant.<sup>1</sup> Another example is necrotizing enterocolitis, related to intestinal immaturity.<sup>2,3</sup> Other entities of a more chronic character, such as bronchopulmonary dysplasia<sup>4</sup> and retinopathy of prematurity,<sup>5</sup> emerged as a result of the development of aggressive therapies for this special population.

It was not difficult to suppose that the use of new technologies utilized to amplify the chances of survival of the pre-term or low birth weight NB affected by these new diseases could have long-term consequences. However, more distant would be to correlate responses supposedly physiological and adaptive reactions from the mother, fetus or NB faced with adverse environmental conditions with future outcomes. Towards the end of the 1930s, while studying mortality rates in England and Sweden, researchers were surprised to find that environmental conditions in utero and during childhood appeared to be determining the survival of each generation.<sup>6</sup>

During the 1970s, Ravelli et al. studied a population of 300,000 men, born from women who had been exposed to a period of food shortage (the Dutch famine), during the German blockade of Holland at the end of the Second World War. In adulthood, these individuals exhibited different patterns of body composition depending on the age at which they had been exposed to maternal malnutrition during intrauterine life. Where the mothers had suffered malnutrition during the last 3 months of pregnancy, this group exhibited a low rate of obesity incidence. In contrast, if malnutrition had occurred during the first 6 months of pregnancy, the incidence of obesity among offspring increased significantly.<sup>7</sup>

During the 1960s, Neel published the "thrifty" genotype hypothesis,<sup>8</sup> proposing that certain populations had a greater propensity towards insulin resistance, both due to selection and to genetic aspects. According to this author, a random mutation leading to insulin resistance could have been adaptive and beneficial to individuals exposed to environments with food shortages, leading to natural selection of these individuals, with the resulting transmission of the characteristic to the following generations. However, current evidence on the interaction between genetics and environment demonstrate that purely genetic considerations, considered independently from the environment, do not have a true biological correlate.

### Causal models

Following this line of reasoning, Barker et al. developed the hypothesis that adverse intrauterine and childhood conditions increase the risk of cardiovascular diseases. In order to test this theory, they correlated birth weight and environmental conditions during early childhood with cardiovascular health of adults born at the start of the twentieth century, in Hertfordshire, UK.<sup>9</sup> In these studies it was demonstrated that

people who were born with low birth weights remained biologically different from those born with normal birth weight, persisting into adulthood. They exhibited higher arterial blood pressure<sup>10</sup> and were more likely to develop diabetes type 2.<sup>11</sup> Furthermore, in later findings, these and other researchers demonstrated that low birth weight was associated with changes in plasma lipid profiles,<sup>12</sup> reduced bone mineral density,<sup>13</sup> altered responses to stress,<sup>14</sup> less elastic arteries,<sup>15</sup> specific patterns of hormone secretion<sup>16,17</sup> and a greater incidence of depression.<sup>18,19</sup> These observations resulted in the thrifty phenotype hypothesis, which proposes that the fetus is capable of adapting to an adverse intrauterine environment by optimizing the use of a reduced energy supply in order to guarantee its survival. However, this process of adaptation would favor some organs to the detriment of others, causing long-lasting alterations in the growth and function of tissues.<sup>20</sup> Although it represents an important chapter in the study of the associations between early life and the risk of chronic diseases, the thrifty phenotype hypothesis does not explain a series of findings that were described later by several researchers, such as, for example, the influence of fetal life on fluids homeostasis,<sup>21</sup> which are also persistent, but without immediate adaptive value. In other words, Barker's hypothesis does not explain persistent metabolic adjustments that take place in response to variations in the fetal environment and which are not immediately necessary for the individual's survival.

During the same period, an independent group of researchers was studying the effects of the diets fed to pre-term NB on a variety of outcomes. By means of clinical trials, these authors demonstrated the influence of different types of milk-based diet on somatic growth, immunity and neuropsychomotor development,<sup>22,23</sup> proposing the use of the term "programming" in this context. Outlined by Dörner et al.,<sup>24</sup> but widely explored by Alan Lucas, this term refers to the concept that an insult or stimulus applied during a critical or sensitive period can have long-lasting or persistent effects on the structure or function of an organism.<sup>25</sup> Therefore, the emergence and severity of many different morbid conditions depends on the genetic vulnerability of the individual, on the exposure to adverse environmental factors and also on the period during which these stressful events occur.<sup>26</sup> Both prenatal life, childhood and adolescence are critical periods that are characterized by a high degree of plasticity,<sup>27,28</sup> therefore an exposure to a significant stimulus could have consequences of an organizational order and cause persistent alterations in the body functioning.

Another important point relates to maternal restraint. Mammals' fetuses do not generally attain their maximum growth potential, primarily because they are affected by maternal and uterine factors, such as maternal size, age, nutritional status and parity.<sup>29</sup> This concept contributed to the current models for understanding the phenomena of

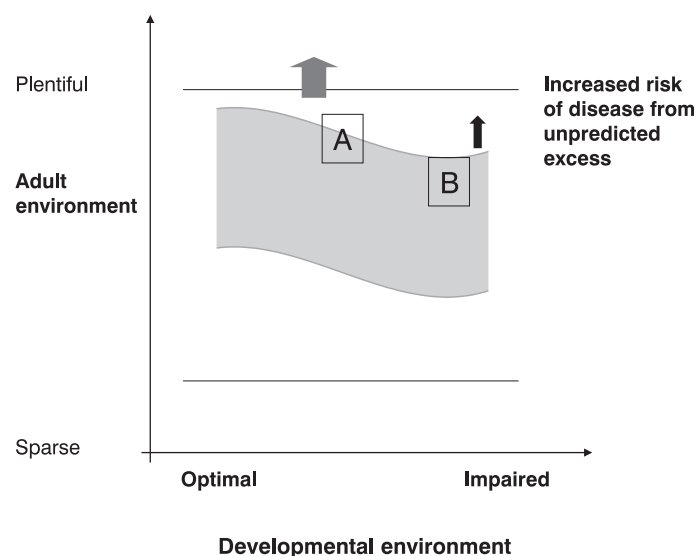
programming, which suggest that all fetal development is affected by some degree of restriction. In some cases, however, this restriction is exacerbated by other factors, such as maternal placental diseases. At birth, these restraints are alleviated and the consequences become manifest. The effect of primiparous maternal restraint on firstborn children is so evident that its impact has been compared to maternal smoking.<sup>30</sup> Furthermore, the perpetuation of low birth weight down the generations is in part explained by these mechanisms: maternal restraint will be proportionally greater where mothers have small stature, and they themselves were probably low birth weight infants.

In many animal species, environmental influences reach the fetus via the mother/placenta or the offspring via lactation, leading to physiological adaptations which increase the chance of the individual surviving in that environment. These predictive adaptive responses,<sup>31</sup> in contrast with the thrifty phenotype, do not have an immediate adaptive value, but predict long-term adaptation with the objective of guaranteeing survival, at minimum, until reproductive age. For example, maternal stress signals an adverse external environment for the fetus, leading to chronic hyperactivity of the hypothalamus-pituitary-adrenal axis (HPA) in this individual, which in turn results in a greater alert state and increased chances of survival.<sup>32,33</sup> Predictive adaptive responses cause persistent changes in the organism's functioning, probably by means of epigenetic processes, potentially transmissible from

generation to generation. Being essential factors for an individual's survival, it is to be expected that nutrition, metabolism, growth, reproduction and responses to stress would be the aspects most responsive to programming.

The predictive adaptive responses model suggests that an organism in development has the capacity to predict the environment in which it will grow, utilizing maternal hormonal signals by means of the placenta and/or lactation. These signals permit the individual to adjust its physiology in accordance with the message. If the prediction is correct, the risk of disease is low. However, if it is incorrect, there is an increased risk of diseases, which will probably manifest after the reproductive period (and, therefore, there is no "pressure" from natural selection against this incorrect prediction during evolution). The risk of disease, therefore, is the result of the degree of match or mismatch<sup>34</sup> between the environment predicted by the individual during the period of elevated plasticity and development and the actual environment in which this individual lives their maturity (Figure 1).

The match or mismatch model introduces the idea of a plasticity related to development (developmental plasticity), a phenomenon by which a single genotype can give rise to a range of diverse physiological states in response to different environmental conditions during development. Recent studies have provided support for this model by demonstrating interactions between the environment and gene expression on several levels. It is not only the cellular environment that



**Figure 1** - Relationship between developmental and adulthood environments. The horizontal lines represent the limits of the environment to which the individual is exposed; the grayed area represents the zone of appropriate predictive adaptive responses, associated with a reduced risk of diseases. Individual A, exposed to a normal intrauterine environment, is capable of tolerating a greater environmental variation in adulthood without developing morbid conditions, in contrast with individual B (adapted from Gluckman & Hanson<sup>34</sup>)

affects gene expression and protein production, but also the relationships of an individual with their environment can also influence behavioral and morphological aspects and gene expression, even within a period of hours.<sup>35</sup> Elegant studies have demonstrated that the influence of interactions that occur during vulnerable periods or periods when programming is possible can even persist transgenerationally, by means of epigenetic effects.<sup>36,37</sup> One important example illustrating these theories in humans is the presence of a prevalent polymorphism of the PPAR $\gamma$  gene and risk of diabetes, which is only evident if the individuals also have a history of shorter stature at birth.<sup>38</sup>

For the reasons given above, epigenetics, which is the study of inherited changes in gene expression that are not due to a DNA nucleotide sequence, has become a model that is fundamental to research into DOHaD. Implicit in this concept is an important process of causality on the cellular level, regulating growth and tissue differentiation and involving chemical changes to the DNA (such as methylation) or of associated proteins (such as the histones, which interact with the DNA molecule in nucleosomes to form chromatin). The pattern of epigenetic information is transmitted via mitosis and is specific to each cell and tissue type and is essential to maintenance of the organism's gene expression profile. Since epigenetic effects can suffer interference from the environment during development, they are extremely relevant to the field of DOHaD studies.

### **The hypothalamus-pituitary-adrenal axis in early life and programming mechanisms**

Exposure to glucocorticoids during the fetal period has been proposed as being one of the principal programming factors for increased risk of chronic diseases among individuals born with low birth weight,<sup>39</sup> being associated with an increased probability of later development of hypertension, diabetes and psychiatric disorders, such as depression and anxiety. Abnormal HPA axis activity during vulnerable periods of development is thought to be related to the programming of an individual's pattern of health. This abnormality is attributed to chronic exposure to maternal glucocorticoids or to stress during gestation.<sup>33</sup>

Glucocorticoids are the largest subclass of steroidal hormones that regulate metabolic, cardiovascular, immune system and behavioral responses.<sup>26,40</sup> Their physiological effects are mediated by a 94 kD cytosolic protein, the glucocorticoid receptor (GR). The GR is widely distributed throughout the brain and peripheral tissues. In its inactive state, GR is part of a multi-protein compound made up of several heat shock proteins.<sup>41-43</sup> Bound to glucocorticoids, GR moves to the cell nucleus, where it interacts with specific glucocorticoid response sites, altering the transcription of certain genes.<sup>44</sup> The activated receptor also inhibits, via protein-protein interactions, other transcription factors, such as c-jun/c-fos and NF-kB, which are positive regulators of the transcription of

several genes involved in activation and growth of immune cells and other cell types.<sup>45</sup> Furthermore, glucocorticoids alter the stability of messenger RNA and, therefore, translation of several proteins, and also neuronal electrical potential. In the majority of vertebrates, secretion of glucocorticoids follows a pronounced circadian rhythm, with peaks corresponding to the start of the active phase of the daytime cycle.<sup>46</sup> Glucocorticoid circadian rhythm is dependant on the suprachiasmatic nucleus; injuries to this brainstem structure lead to an approximately constant level that is intermediate between the circadian peak and trough.<sup>47,48</sup>

Regulation of HPA axis activity is to a great extent performed by means of negative feedback via glucocorticoids to components of the central nervous system (CNS), increasing or reducing its activity in accordance with physiological requirements.<sup>49</sup> Several cerebral structures are involved in the feedback processes, in particular the hypothalamus, amygdala, prefrontal cerebral cortex and the hippocampus,<sup>50</sup> the last of which being the structure most strongly related with regulation of the axis, as a result of its high concentration of glucocorticoid receptors.

Glucocorticoids are of fundamental importance to gestation in mammals, since they are involved in maternal metabolic adaptation.<sup>51</sup> Furthermore, they are active in coordination of readiness for birth and onset of the mechanisms of labor. During gestation, lipophilic steroids easily pass through the placenta, but levels of fetal glucocorticoids are much lower than maternal levels.<sup>52,53</sup> This is due to intense activity of the enzyme 1 $\beta$ -hydroxysteroid-dehydrogenase type 2 (11 $\beta$ -HSD-2) in the placenta, which catalyses conversion of the physiologically active glucocorticoids cortisol and corticosterone into inert forms such as cortisone.<sup>54</sup> They therefore represent a barrier which protects the fetus from exposure to maternal glucocorticoids, although around 10 to 20% are still allowed to pass.<sup>55</sup> It is interesting to note that there is a positive correlation between birth weight and the activity of this enzyme in both rats<sup>56</sup> and in humans.<sup>57</sup>

In humans, maternal plasma levels of corticotropin-releasing hormone (CRH, produced by the placenta) increase exponentially as the pregnancy progresses, reaching their peak at birth. With premature deliveries this increase is much more rapid.<sup>58</sup> Placental CRH reaches the fetus, although in lower concentrations than in the mother.<sup>59</sup> The fetus had both pituitary<sup>60</sup> and adrenal<sup>61</sup> CRH receptors. Stimulation of the fetal pituitary by CRH increases ACTH production and, consequently, adrenal cortisol production, resulting in maturation of the fetal HPA axis and inducing formation of surfactant in the lungs.

In mammals, the responsiveness of the HPA axis fluctuates during the perinatal period, being moderately responsive at the time of birth, but reducing in intensity during the neonatal period.<sup>62,63</sup> In rats, there is a peak in corticosterone

during the final fetal stage, followed by reduced responsiveness after until the end of the second week of extrauterine life, which is known as the stress hyporesponsive period.<sup>64,65</sup> Characteristically, the glucocorticoid negative feedback mechanism in the pituitary is exacerbated and adrenal sensitivity to ACTH is reduced during this period.<sup>66</sup> There is evidence that this hyporesponsive period also exists in humans.<sup>67,68</sup>

According to the concept of programming, exposure to a stimulus or stress during these first days determines neurochemical and behavioral alterations that can be observed throughout life. Although "hyporesponsive", these individuals responded acutely to the stress of being separated from their mothers even when not exposed to any other additional stressor,<sup>69</sup> and this response increased progressively over the subsequent 24 hours. Furthermore, during this phase, transcortin levels are very low and the majority of glucocorticoids circulate in plasma in their unbound and, therefore, biologically active form.<sup>70,71</sup> Thus, even though the total concentration of plasma glucocorticoids is low during the hyporesponsive period, the concentration of its biologically active form is relatively high, sufficient for the hormone to perform its biological actions and possibly to act as a programmer of the CNS in a long-lasting manner.

One interesting example of the interaction between genes and environment, with relation to the HPA axis, is the model which evaluates natural differences in maternal care among rats, demonstrating that the environment in which offspring grow up is correlated with their reactivity to stress; where the young of mothers who exhibited more caring behavior (licking and grooming) are less responsive than the young of mothers who exhibited less of these behaviors.<sup>72</sup> It has been suggested that tactile stimulation by the caring mothers acts via raphe nucleus ascendant serotonergic pathways,<sup>73</sup> which induce the expression of glucocorticoid receptors in the hippocampus.<sup>74,75</sup> Serotonin probably acts by means of the 5HT7 receptor which is regulated by glucocorticoids<sup>76</sup> and positively coupled with cyclic AMP.<sup>77</sup> Transcription factors associated with cAMP, such as Nerve Growth Factor-Inducible Protein A (NGFI-A) are then stimulated.<sup>78</sup> Although NGFI-A has a low affinity for its recognition site in the DNA sequence responsible for production of GR, tactile stimulation provokes a great increase in the levels of this transcription factor, thereby increasing the chances of binding.<sup>78</sup> The NGFI-A bond results in the recruitment of histone acetyltransferases, which increase acetylation of the histones, facilitating access for demethylases and demethylation of the GR promoter site.<sup>79</sup> The demethylated promoter site has a high affinity for NGFI-A, resulting in greater GR promoter activity induced by NGFI-A in the hippocampus, increased production of glucocorticoid receptors in this structure and, therefore, a more efficient negative feedback mechanism.

### **The importance of childhood growth patterns**

The initial studies relating low birth weight with increased cardiovascular risk were primarily based on intrauterine

growth restriction (IUGR) as the causative factor of these associations. Recent evidence suggests that a child's growth pattern during the first years of life is also strongly influenced by the pattern of fetal growth, which may determine an increase in the probability that unfavorable metabolic outcomes will occur. Abnormal postnatal growth patterns have a significant relationship with the development of chronic diseases in later life, particularly in preterm NB with IUGR.

Current practice recommends stimulation and promotion of the growth of low birth weight infants, aiming to reduce morbidity and mortality rates and to preserve neurocognitive aspects. However, some clinical studies have proposed that rapid weight gain (catch up) during this early period may be associated with increased incidence of cardiovascular disease in maturity.<sup>80,81</sup>

The risk factors for cardiovascular diseases<sup>82</sup> and for obesity<sup>83</sup> are consistently found in groups of individuals who have gained a great deal of body weight between birth and school age or preadolescence, particularly those who were born small or had low birth weight. In other words, the consequences of a given body weight are conditioned as much by intrauterine as by later childhood growth. Therefore, the growth patterns that predispose to the development of chronic diseases are complex and it is important to make a distinction between early and late catch up. While the first appears to be beneficial, as discussed above, childhood obesity is known to have harmful effects over the long term, especially in the population of low birth weight babies, and must be prevented.

For these reasons, despite having been approved by the Food and Drug Administration (FDA) in 2001 and in Europe in 2003, and despite being currently recommended in the specialist literature,<sup>84</sup> the use of growth hormone (GH) for children who are small for gestational age and those with small stature remains controversial. Around 10% of small for gestational age individuals do not exhibit catch up, remaining below the third percentile for weight and height throughout childhood, and being shorter in adulthood. It is true that the psychosocial impact of the increase in final height has been recognized, however the knowledge that late catch up may have damaging consequences for this population over the long term makes indicating this treatment an arduous decision. Even the consensus document on the management of individuals born small for gestational age, which recommends the use of GH throughout childhood and adolescence in order to increase of final height, states that it is not currently known whether treatment of people born small for gestational age with GH during childhood and adolescence is associated with benefits or with amplified risks (as metabolic consequences) in adulthood.<sup>84</sup> Despite recognizing the epidemiological studies that report increased risk for cardiac diseases, cerebral vascular accidents, hypertension, obesity and diabetes mellitus in this population, the authors argue that there is insufficient evidence to indicate carrying out any kind of follow-up



that is special or differential with relation to other children. Notwithstanding, it is important to point out that fetal growth should be considered a relevant risk factor for chronic diseases, although it cannot be treated as a causative factor. In other words, chronic diseases are not programmed in themselves, but the tendency towards the development of diseases appears to be programmed. There are countless interactions between fetal growth and variables involving the childhood and adolescent environments, however, the best way to approach the problem is to focus on the stages of life and their interactions with fetal and neonatal history.

### **Long-term consequences of nutrition during the first years of life**

The association between neonatal events and increased risk of diseases in adulthood is not necessarily linked to low birth weight alone. Here, other programming mechanisms and signals appear to be important. Of these, one of the most often studied is nutrition at the start of life, about which little is yet known.

During the beginning of the 20th century the medical literature had already demonstrated an interest with relation to the impact of postnatal nutrition on somatic growth and on specific organs by means of dietary manipulation during critical periods.<sup>85,86</sup> Currently, and primarily due to DOHaD studies, there are suggestions that nutrition during vulnerable periods can alter the structure of chromatin and gene expression, in addition to potentially influencing an individual's health over the long term.<sup>87</sup>

It is known that breastfed children exhibit growth kinetics that are different from those of children fed on formula.<sup>88</sup> The literature has proposed that breastfed NB receive sufficient calories for growth, but not more than necessary, in addition to gaining weight more slowly than formula-fed NB. Since experimental studies have demonstrated that excessive nutrition during the neonatal period is associated with increased risk of obesity and metabolic syndrome in adulthood,<sup>89</sup> it is possible that this may be one of the mechanisms by which breastfeeding is able to protect against diseases throughout life. It is also known that the compositional differences between breastmilk and artificial formula, such as the quantities of calories and proteins, are an important variable in this context.

Another factor possibly involved is the different feeding behavior of breastfed babies, which exhibit a different frequency of suckling,<sup>90</sup> and also a greater degree of control over the quantity of milk consumed.<sup>91</sup> Furthermore, constant variation in the taste and odor of breastmilk exposes the NB to a variety of gustatory stimuli, encouraging the choice of foods with similar flavors later in life,<sup>92</sup> increasing the variety of the individual's diet.

Specifically in relation to lifelong protection, it has been shown that, for example, breastfeeding preterm infants is

associated with an improved plasma lipid profile during adolescence,<sup>92</sup> and also with lower blood pressure levels.<sup>93</sup> Nevertheless, it has been more difficult to prove with clarity the effects of the postnatal diet on adult body composition. Although several different studies, including meta-analyses and employing body mass index (BMI) as categorical variable, have demonstrated that breastfeeding is associated with a lower incidence of obesity,<sup>94,95</sup> those studies that have concentrated on body composition have not been able to establish the same association, or have identified very discrete effects.<sup>96</sup> This same absence of association has also been described in Brazil.<sup>97</sup> As has been pointed out by Wells et al.,<sup>98</sup> Several methodological difficulties prevent a better evaluation of the effects of breast feeding, including a lack of precise information in large cohort studies, the influence of social factors and the fact that it is impossible to carry out randomized studies. Additionally, this author also mentions the possibility of reverse causality, i.e., that the difficulties experienced during breastfeeding may lead to the use of an aggressive diet and dietary excess among formula-fed NB, increasing their chances of developing abnormal health patterns in adulthood when compared with breastfed babies.

Although some studies indicate there are acute benefits to dietary supplementation with long chain polyunsaturated fatty acids (n-3 and n-6 LCPUFA) in artificial formula,<sup>99</sup> and also to prebiotics and probiotics given to the mother during pregnancy and breastfeeding, their long-term effects on the neurological and immunological development of individuals are not yet clear, and, in this context, further studies are needed.

### **Scientific approaches**

The study of DOHaD is an area of research that combines information from a variety of branches of knowledge, and is an interesting interface between the biological sciences and the area of health. The questions and hypotheses are investigated with a variety of scientific approaches, including:

- Epidemiological studies. Large cohort studies based on perinatal databases compiled at the start of the 20th century were the basis for the construction of the first DOHaD models, primarily through the studies of Barker et al. Although this is the most appropriate approach for highlighting associations between early events and later outcomes, epidemiological studies do not prove causality. Furthermore, human cohorts are expensive and demand a great deal of involvement on the part of the research team and also the individuals being studied, and, in the case of DOHaD research, they only produce results over the long term. Losses to follow-up during the study period, questions about the validity of associations observed in adults for the current pediatric population and about superimposition of findings in different world populations limit the application of their results.

- Clinical studies. The objective of clinical DOHaD studies is to compare individuals with diverse perinatal histories in terms of their clinical characteristics, behavior and/or response to interventions. Clinical studies are relatively quicker to carry out than cohort studies and have elucidated important questions in the area, although they are still limited by ethical considerations.
- Experimental studies. Relatively easy to carry out, less costly, faster and highly informative. Studies undertaken with animals have contributed a great proportion of the information known on the subject. However, extrapolation of the results to humans is extremely delicate and fragile. For example, many of the species used bear multiple young, making comparison with humans difficult. Species with single pregnancies have been proposed as alternatives (sheep for example), but the differences in the degree of maturity at birth also interfere with comparisons.
- Translational studies. This concept of scientific research, where researchers divide their time between "the bench and the bed", has an impressive number of followers among DOHaD researchers. With the ease of execution of basic studies, researchers apply acquired knowledge to generate hypotheses and questions relevant to human physiology, adapting protocols to tests that can be carried out with patients. Combining the advantages of epidemiological/clinical studies with those of basic studies, this new tendency has brought a large volume of relevant information and made a solid contribution to building up knowledge of DOHaD.

### **DOHaD in developing countries**

The majority of DOHaD studies have been carried out in developed countries, and the relevance of applying this evidence to healthcare in developing countries is only now beginning to be established. The match or mismatch model, where the greatest risk of chronic diseases is the result of the highest degree of contrast between the fetal environment and the environment in which the individual grows up, reflects the experience of many people who live in developing countries. The incidence of IUGR is high in these areas, partly because of the high prevalence rates of malnutrition among women. On the other hand, economic ascent and agricultural improvements have transformed the nutrition of children and adults, and the emergence of obesity in developing countries has been reported in many parts of the world. Brazil also follows this pattern of contrast, even when different social classes are taken into consideration.<sup>100</sup>

It is important to observe that, in the large cohorts from Europe which started off DOHaD studies (Hertfordshire, England and Helsinki, Finland), the association between low birth weight and cardiovascular diseases remains significant even when the current BMI of the people being analyzed is not taken into consideration. However, similar studies carried

out in Africa,<sup>101</sup> China<sup>102</sup> and India<sup>103</sup> were only able to detect the same significant association when they adjusted their analysis for adult BMI. This suggests that there is a different pattern in developing countries, where being born with low birth weight only becomes a problem when followed by obesity.

One interesting study carried out in India<sup>104</sup> demonstrates that insulin resistant adults born with low birth weight could be characterized by an increase in BMI between the ages of 2 and 12 years, even though they did not reach levels considered as overweight or obese by international standards. It is, therefore, possible that the simple recovery of weight after an initial period of malnutrition is a more important parameter in absolute terms than obesity in developing countries.

The concept of DOHaD has enormous potential implications for public health strategies in these countries and this was indeed recognized by the World Health Organization (WHO) in 2004. Nevertheless, despite the urgency triggered by the epidemic of chronic diseases in these areas, this remains an area of knowledge that has been little explored and it is not possible to propose any clear recommendations on a public health level in the current situation.

### **Ethical considerations**

Advances in fetal and neonatal medicine have been accompanied by a changed view of fetal status. The emergence of "fetus as patient" creates moral pressure both on the medical team and on the future mother. The concepts of "fetal rights", "the right to life" and "the right to be born" have now been extended to "the right to be born *healthy*". In a more or less extremist manner, the fetus and mother have been treated as two ethically and legally independent entities, and the ethical considerations involved in certain circumstances of conflict between these two entities must be carefully evaluated.

It is not rare for us to hear careless speeches aimed at public health promotion, such as those that claim that expectant mothers must have, "constant vigilance in the promotion of fetal health and wellbeing". Furthermore, the association between birth weight and chronic diseases may result in an enormous overload of responsibilities on the mother. Thus, the fetus does not just have "the right to be born healthy", but also "the right to be born and have a healthy adult life".

The key message of the DOHaD concepts is that aspects related to the early environment are fundamental in the development of diseases, and not that the individual's biology makes that disease inevitable. However, excessive emphasis on fetal growth and aspects related to pregnancy facilitates the emergence of ill-judged pronouncements, "accusing" mothers of not knowing how to choose their lifestyles and of affecting the health of their children permanently.

It is also important to mention studies that relate biological events with influences on an individual's behavior. Therefore, concepts such as "programming" take on a determinist dimension and question the capacity of the individuals affected to make choices that are appropriate for their own health, ignoring important variables such as social and economic factors. The "sentence" of having been born with low birth weight and being "condemned" to a given future is a questionable approach. More relevant than this is the quest to understand the mechanisms that lead to these associations, primarily considering social influences, in order to aid in the development of preventative measures.

## Conclusions

In a 2007 article, Gluckman & Hanson proposed future directions for DOHaD, and we shall review them here.<sup>102</sup> Although 20 years have passed since the publication of the first observations clearly relating environment with the risk of development of chronic diseases, a series of questions still remain to be answered. One important debate is related to the impact of these processes on the prevalence rates of chronic diseases. Current studies have been emphasizing relationships between perinatal variables and specific outcomes, such as insulin resistance or disorders related to cardiovascular diseases (hypertension, obesity and hypercholesterolemia, for example). However, the contribution of the influence of early variables to the genesis of metabolic phenotypes should be studied more appropriately.

The definition of "contrast" also needs to be established in a more robust manner, as does which parameters are markers of contrast. Despite being extensively used in studies, "catch up" also merits greater precision: studies should concentrate on giving details of what type of catch up (weight, lean mass, etc) they are dealing with.

The study of DOHaD has given rise to a series of studies aimed at investigating the relationship between environmental variations during early life, polymorphisms in related genes and metabolic outcomes. However, it is also yet to be discovered up to what point it is possible to establish the specifications of these variations for a given population and how these polymorphisms interact with environmental clues, influencing the risk of developing chronic diseases. Along the same lines, it is unrealistic to imagine that a single gene could be responsible for such a multiplicity of outcomes. A wide ranging perspective, integrating genetic, epigenetic and environmental variables, is needed. Studies will continue to attempt to extend their investigations into different classes of target genes and their roles in these processes, such as, for example, regulatory genes, genes related to growth and mitochondrial genes. Tissue sensitivity specific to hormones and other signaling molecules, which possibly fluctuate during development, should be characterized at different phases of life. Furthermore, cases of non-genomic inheritance, such as the

example of maternal restraint highlighted earlier, should be even better described.

It is important to point out that many other human characteristics can suffer the influence of early traumatic events, such as behavior, reproduction, thermal and liquid homeostasis and cognitive functions. It is interesting to note that, in these cases, these changes may exhibit an altered metabolic phenotype. The most important question here is the possibility of the existence of a causal link between induction of specific phenotypes in diverse domains and environmental clues that are common during early life.

Finally, to date relatively few studies have been dedicated to investigations into intervention in and reversal of phenotype. Studies with animals employing dietary supplements have demonstrated interesting results, however the applicability of these protocols to humans is delicate. More basic studies are required in order to support clinical interventions.

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