How can the Developmental Origins of Health and Disease (DOHaD) hypothesis contribute to improving health in developing countries?[1–4]

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ABSTRACT

The relevance of nutrition during pregnancy and early infancy in defining short-term health and survival has been well established. However, the Developmental Origins of Health and Disease (DOHaD) paradigm provides a framework to assess the effect of early nutrition and growth on long-term health. This body of literature shows that early nutrition has significant consequences on later health and well-being. In this article, we briefly present the main consequences of malnutrition that affect human growth and development and consider how the DOHaD paradigm, with its evolutionary implications, might contribute to better addressing the challenge of improving nutrition. We examine how this paradigm is particularly appropriate in understanding the health and nutrition transition in countries that face the double burden of nutrition-related diseases (acute malnutrition coexisting with obesity and other chronic diseases). We focus on stunting (low height-for-age) to examine the short- as well as long-term consequences of early malnutrition with a life-course, transgenerational, and multidisciplinary perspective. We present current global and regional prevalence of stunting and discuss the need to reposition maternal and infant nutrition not only in health and nutrition intervention programs but also in consideration of the emerging research questions that should be resolved to better orient program and policy decisions. *Am J Clin Nutr* doi: 10.3945/ajcn.110.000562.

THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (DOHaD) PARADIGM

Nearly 50 y ago, it was suggested that differences in the prevalence of metabolic diseases across populations might be due to the presence of "thrifty genes" that would confer advantages in adverse nutritional environments but that might become detrimental if populations were exposed to conditions in which food would be abundant (1). Although the hypothesis has served to explain very particular cases such as the high prevalence of obesity and diabetes in the Pima Indians, it is now accepted that this is an unlikely explanation for the current epidemic patterns of chronic diseases affecting populations that evolved from hunter-gatherers and were generally not exposed to feast or famine conditions (2). Over the past decades, a body of epidemiologic evidence has shown that early-life conditions influence patterns of growth, body composition, and later risk of noncommunicable chronic diseases (NCDs) (3). Associations between low birth weight (considered a proxy of intrauterine and perinatal environmental conditions) and diabetes, elevated metabolic risk and blood pressure, and higher cardiovascular disease (CVD) risk and mortality were originally described in European countries in the 1950s but have been now replicated in almost all settings including those of developing countries (4–9). On the basis of these observations, Hales and Barker (10) coined the term, which suggests that poor nutrition during development could induce changes that would provide short-term advantage but become detrimental under conditions of energy excess and lack of exercise such as those observed in current industrialized countries. This hypothesis, a classic example of a *paradigm shift*, has guided a substantial amount of basic, clinical, and epidemiologic research addressing global health and disease patterns. More recently, the evidence that has emerged indicates that birth weight per se has a low sensitivity to assess the prenatal environment; it serves to capture only rather extreme deprivations. In recent years it has been proposed that a myriad of exposures, even within the range of normal development, might induce subtle changes that are not reflected in birth weight but yet have important implications for later health and disease patterns (11). The term *predictive adaptive responses* (PARs) has been coined to recognize responses that do not confer an immediate benefit but rather prepare the fetus for the later environment that is anticipated based on its developmental experience (12). Thus, the advantageous or detrimental consequences of PARs will depend on whether the anticipated environment is indeed encountered and prevails over time or, alternatively, if it is variable and different over the life course depending on specific exposures. PARs will be adaptive if the postdevelopmental environment is within the predicted range but may be inappropriate if the later conditions fall outside or are "mismatched" relative to the anticipated environment range (2). The mechanistic basis to support this developmental plasticity is provided by the occurrence of epigenetic changes that affect gene expression (13). Excess or deficits in nutrients, hormones, or metabolites may

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trigger changes in DNA or histone methylation, which in turn suppresses or enhances gene expression; in addition, changes in small noncoding RNA activity act by modulating gene expression. This novel, more mechanistic concept emphasizes the idea that extreme challenges during early postnatal development are not essential to elicit PARs, but rather it is the "mismatch" between the early and later environment that renders detrimental a particular phenotype. The idea that epigenetic programming could be transmitted from one generation to the next is of even greater concern (2). For example, if a mother is exposed to a nutritionally restricted prenatal environment and later on during childhood or adolescence nutrition becomes abundant she will increase her likelihood of becoming obese and of developing gestational diabetes while pregnant. Although mechanisms are far from being elucidated, there is epidemiologic and clinical evidence that shows that excess weight gain during pregnancy, gestational diabetes, and maternal obesity during pregnancy are all risk factors for offspring obesity and metabolic disturbances (14–16). In this way the cycle of disease and nonadaptive responses tends to self-perpetuate or to potentially expand in future generations.

THE DOHaD PARADIGM IN DEVELOPING COUNTRIES

Low- and middle-income countries are increasingly observing an epidemic of nutrition-related chronic diseases (NCDs) such as diabetes, CVD, and cancers (17). In fact, according to World Health Organization (WHO) estimates, >80% of worldwide deaths due to NCDs take place in developing countries, and this number is expected to increase in the next decades (18). However, at the same time, most of these countries still struggle to decrease undernutrition and infectious diseases and are now contending with the so-called double burden of diseases (19). These problems have been traditionally thought as mutually exclusive and as opposite extremes of the health and economic spectrum. However, progressive globalization, urbanization, and economic improvements have brought on a series of rapid and massive changes in diet and physical activity patterns that have allowed the coexistence of undernutrition and NCDs not only at the population level but also at the household and individual levels (20). There is now evidence that in developing countries such as Mexico or Guatemala almost 50% of the women are overweight or obese, whereas stunting (low height for age due to nutritional deficits) still affects an important proportion of the children (21). Moreover, data indicate that overweight women may live in the same household as stunted or undernourished children, showing that malnutrition problems are now intertwined and probably rooted in poverty (22). There is also evidence that undernutrition and obesity and NCDs are not only intertwined but also interact in complex ways within individuals. As mentioned previously, a body of literature from developed as well as developing countries shows that undernutrition during pregnancy and early infancy may predispose to an increased risk of developing obesity and NCDs such as diabetes, metabolic syndrome, and CVD later in life if individuals are exposed to unhealthy diets and low physical activity patterns (4, 6, 9, 23) (**Figure 1**). This underlying susceptibility given by the "mismatch" between early and later environment may explain the earlier onset and higher severity observed in the presentation of NCDs in developing countries. Moreover, increasing evidence indicates that predisposition to NCDs may be established even before birth, during the intrauterine period. Maternal diet and body composition preconceptionally and during pregnancy have been associated with a predisposition to obesity and NCDs such as diabetes, blood pressure, and lipid disorders in offspring (14–16). Given that several developing countries are presently experiencing an important maternal obesity epidemic, the potential for this transgenerational transmission of risk is of concern because it predicts a significant increase of obesity and NCDs for these countries in the near future (25). Thus, it makes sense to believe that the DOHaD paradigm applies more to the actual nutritional situation of developing countries in which patterns of the population's behaviors are rapidly changing than to that of developed countries in which changes have taken place at a slower pace. It would be then advisable to accordingly define preventive actions that have long-term implications in

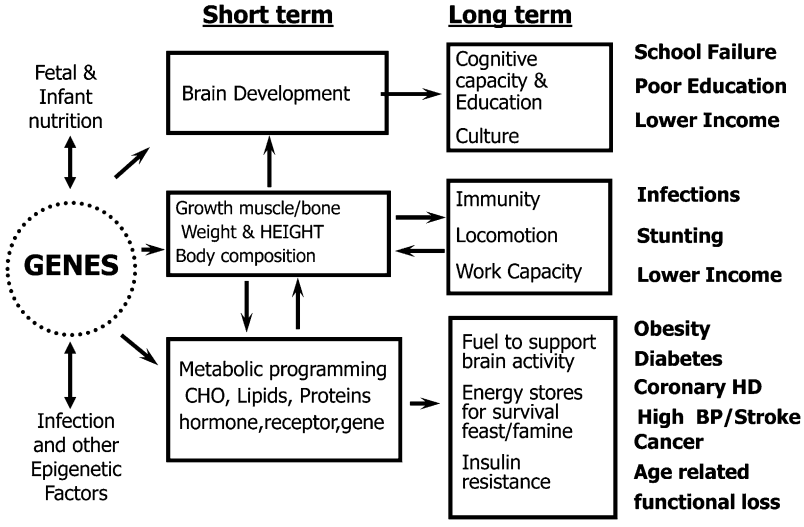

FIGURE 1. Schema representing short and long term consequences of nutrition-gene-environment conditions in early life on relevant health and disease outcomes that have potential social and economic effect. Adapted and modified from reference 25. HD, heart disease; BP, blood pressure; CHO, carbohydrates.

consideration of the life-course, multidisciplinary, and intergenerational approach that the DOHaD paradigm proposes.

STUNTING AS AN EXAMPLE OF HOW THE DOHaD PARADIGM APPLIES TO DEVELOPING COUNTRIES

Stunting is defined by an abnormally low height relative to a group of children of the same age and sex who have grown up under conditions that do not restrict growth; the WHO Multicenter Growth Reference Study conforms to these conditions. Stunting provides a cumulative record of past and present growth restrictions affecting a child's length; it is commonly due to inadequate nutrition compounded with frequent infections (particularly diarrhea). As conceptualized by UNICEF, the underlying causes are household food insecurity, inadequate care, poor sanitation, and lack of access to adequate health services. However, the true basic causes are poverty, unemployment, and limited access to all forms of capital, commonly conditioned by social, economic, and political contextual factors (26). Currently, stunting is the most prevalent form of undernutrition worldwide. Using as reference the WHO growth standards (2006) (27), in 2010 stunting prevalence among children $\leq$5 y of age reached 38.2% in Africa (for a total of 60 million children), 27.6% in Asia (for a total of 100 million children), and 13.5% in the Latin-American region (for a total of 7 million children). Given the large population of Asian countries, they account for almost 60% of the total amount of stunted children worldwide. Recent analyses of surveys from 54 countries from 1994 to 2007 using the WHO growth standard as reference indicate that the decrease in mean height-for-age in early life, expressed as an SD score (z score), occurs quite early in most regions of the world. Growth faltering takes place soon after birth and increases thereafter, reaching its lowest value close to 24 mo of age (28). After 24 mo, values remain stable in most regions with a slight catch-up in African regions. These results support the concept that the intrauterine periods and the first 2 y of postnatal life are critical for preventing malnutrition; once stunting is established, the lost length typically persists unless there are substantial delays in bone age maturation (28). This is observed in selected specific nutritional deficiencies such as in zinc deficiency. Analyses based on 5 large cohorts from developing countries (the COHORTS group) indicate that a gain of 1 z score of height-for-age at 2 y (that corresponds to a gain of $\approx$3.2 cm) was associated with an increase of 3.2 cm of attained adult height, suggesting that differences in height observed during the first 2 y of life tend to remain into adulthood (29).

In the short term, stunting has significant health consequences, increasing both mortality and morbidity, particularly due to infectious diseases such as diarrhea, measles, pneumonia, and malaria. The Lancet Series of Malnutrition reported that, in 2004, stunting directly accounted for 1.5 million deaths and for almost 55 million disability-adjusted life-years in low and middle-income countries (26). These numbers correspond to $\approx$15% of the total amount of deaths in children aged $<$5 y and $\approx$13% of the total global disease burden. These figures show the relevance of nutrition-infection interactions as a risk factor for death and disability in children aged $<$5 y. There is also a body of literature that shows that stunting is associated with impaired cognitive development and that this association is not only restricted to settings in which the prevalence of stunting is extreme (30, 31). Reasons for this association have not been fully elucidated; probable early developmental effects on brain structure and synaptogenesis may permanently affect brain function across the life span. Impaired motor development and exploratory behavior may further compromise and potentiate the early damage with consequences at later stages in terms of learning and school performance (32). However, the effect of stunting is not only restricted to the first few years of life but extends throughout childhood and beyond. Stunting has been associated with lower school performance, poorer attention in class, greater grade repetition, higher drop out of school, and lower graduation rates likely due to the lack of stimulus from deprived environments as well as the persistence of functional and behavioral damages (31, 32). Long-term consequences of stunting have been documented in terms of lower earnings and family income, which affect men and women. Regarding physical labor, there is a documented decrease in the capacity for physical work, which is likely due to reduced lean body mass and decreased productivity in manual jobs. Analyses from the COHORTS study indicate that an increase of 1 SD of height-for-age was associated with an 8% increase in income as well as an increase in assets in India (29). In terms of long-term body composition, birth length has been positively associated with attained adult height and fat-free mass. It has been suggested that stunted children would have a higher predisposition to develop obesity and metabolic complications later in life due to decreased energy expenditure; these associations have been replicated in some studies of developing countries but not in all (33–36). Thus, evidence linking stunting or linear growth and adult body composition remains inconsistent. There is scarce literature linking early linear growth to NCDs in developing countries. The COHORTS study reported for the pooled analyses a positive association between height at 2 y and blood pressure, and in adults a positive association between taller adults and some forms of cancer also has been described (37). Nonetheless, overall evidence that links stunting and NCDs in developing countries remains inconsistent perhaps due to the different stages of the nutrition transition of the populations studied. Additional studies in this area are clearly needed to arrive at more definitive conclusions. The full dimension of these effects should include the potential transgenerational consequences of stunting. It is well established that maternal nutritional status before and during pregnancy is critical for pregnancy outcomes. Worldwide, $>$10% of women of reproductive age (15–49 y) are severely stunted (height: $<$145 cm). This implies a $\geq$50% risk of cesarean delivery compared with women of normal stature (height: 164 cm) (26). It is also known that undernourished mothers [body mass index (in kg/m^2) $<$18.5] have a higher risk of presenting intrauterine growth restriction during pregnancy (26). There is also evidence that nutritional interventions in girls are associated with substantial increases in the growth of their offspring (38).

Given the actual rapid nutritional changes observed in developing countries, it is also important to assess the effect of increasing maternal obesity rates in the context of prevalent short stature. The combination of low maternal stature and large infants because of maternal obesity acts in synergy to increase the risks of cesarean delivery (39). Studies from developed countries have also shown that obese mothers tend to have a higher risk of

developing gestational diabetes as well as of delivering low- or high-birth-weight infants (14, 15). Thus, it is likely that the detrimental effects of the nutrition transition in developing countries will be amplified due to this transgenerational transmission of risks unless we intervene to break this chain of events. Altogether, these results emphasize the need to assess the consequences of stunting not only in early life but as part of a cumulative life-course perspective. Stunting may exacerbate poverty, perpetuating the vicious cycle as vulnerability to malnutrition and disease grows. From a population perspective, the evidence summarized here shows that stunting in early life has negative effects not only on children's health and educational performance but in the added burden of disease across the life course it imposes, affecting health expenditures and reducing overall productivity. Thus, the total cost of undernutrition is a function of higher health care spending, inefficiencies in education, and lower productivity.

A recent study from the Economic Commission for Latin-America and the Caribbean (ECLAC) provides estimates of the economic costs associated with undernutrition in the Central-American region (40). The analysis focuses on the consequences of infant and child malnutrition on economic development with a life-course perspective. Given the rapidly evolving nutritional and epidemiologic situation of these countries, the study provides current estimates based on extrapolations derived from previous studies from countries at early stages of the transition, as well as projected costs in the future predicted from costs and savings scenarios if interventions to control or eradicate undernutrition are effectively implemented. These 2 approaches were used in the multidimensional analysis (ie, direct health costs from treatment of malnutrition, effect of malnutrition on severity and frequency of infections, effect on income of low socioeconomic status families, increase school failure, lower potential to complete education, lost adult productivity, etc) of the economic effect of undernutrition. The first model used the incidental retrospective dimension approach that includes the social and economic consequences of undernutrition in a given year (X) for different cohorts that have been affected by undernutrition. The specific domains included on the analysis were as follows:

1) Estimates of the health costs for preschool children who are affected by undernutrition in the year of analysis
2) Estimates of the educational costs of 6–18 y old children who suffered undernutrition during the first 5 y of life
3) Estimates of economic costs derived from lost productivity of working-age individuals who suffered undernutrition in early life

The second model was based on a prospective approach that considers the projected present and future losses incurred as a result of medical treatment, repetition of grades in school, and projected lower productivity derived from undernutrition among children aged <5 y in each country in a given year. On the basis of these modeling exercises, potential savings derived from actions taken to achieve nutritional objectives can be estimated [eg, reducing undernutrition by half by 2015 (Millennium Development Goal 1: reducing poverty as measured by food insecurity and low weight for age of young children)]. Results indicate that the economic effect of undernutrition is significant, representing between 1.7% and 11.4% of gross domestic product (GDP) depending on the country studied (average = 3.4% GDP) (**Figure 2**). Higher mortality and the lower level of education accounted for $>90\%$ of the costs, whereas costs due to morbidity accounted for only 6% and school repetition for $<1\%$ (**Figure 3**). These results confirm the notion that, beyond the ethical imperative, the commitment by the governments in the region to eradicate hunger and undernutrition will yield significant economic gains and major social benefits. All of society will benefit, not just the direct recipients of the goods and services provided by these programs. Moreover, investments in nutrition in early life will benefit not only the present generation but also their children. In the context of limited resources and competing needs, economic evaluations contribute to providing valuable information to make decisions on how to spend effectively (for greatest effect) and efficaciously (for greatest benefit relative to money spent). Other considerations, such as affordability, ethical concerns, equity, and political consequences, should also be taken into account in the process of policymaking.

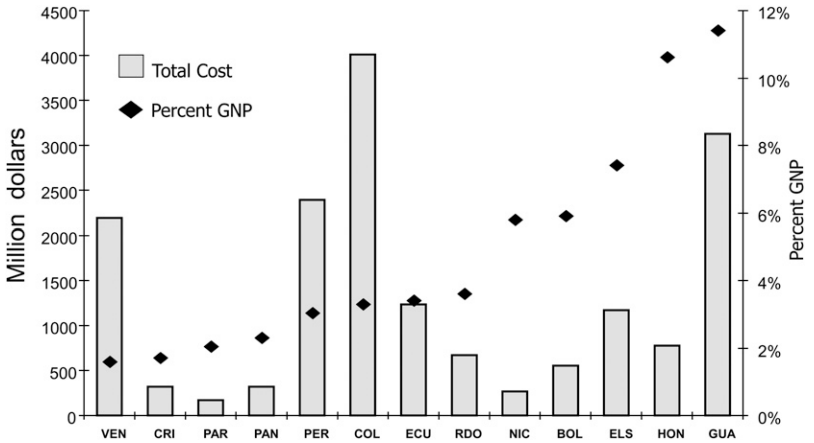

FIGURE 2. Total cost of undernutrition [in dollars and as a percentage of gross national product (GNP) 2004–2005] for selected Latin-American countries studied by the Economic Commission for Latin America and the Caribbean. Data are based on information on incomes, schooling, and educational costs of each country. Adapted and modified from references 41 and 42. VEN, Venezuela; CRI, Costa Rica; PAR, Paraguay; PAN, Panama; PER, Peru; COL, Colombia; ECU, Ecuador; RDO, Dominican Republic; NIC, Nicaragua; BOL, Bolivia; ELS, El Salvador; HON, Honduras; GUAT, Guatemala.

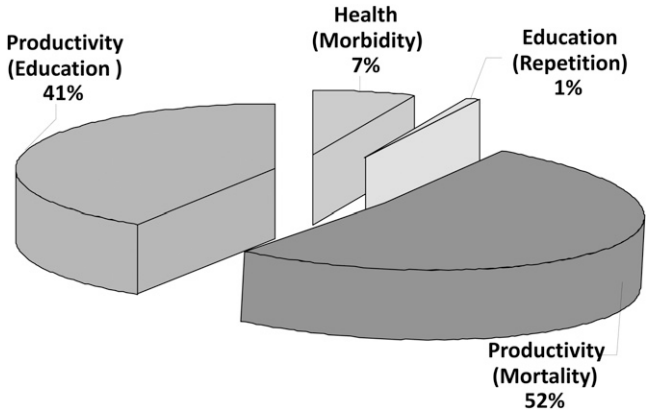

FIGURE 3. Percentage distribution of the economic costs of undernutrition by specific sector for selected Latin-American countries studied by the Economic Commission for Latin America and the Caribbean. Adapted and modified from references 41 and 42.

IMPLICATIONS OF THE DOHaD PARADIGM FOR PUBLIC HEALTH POLICIES IN DEVELOPING COUNTRIES

The vast majority of NCD-related deaths now occur in low- and middle-income countries. The fact that people in developing countries are particularly vulnerable to these diseases is even more worrisome. Men and women in developing countries are affected by NCDs at younger ages and present more severe forms than those observed in the industrialized world. NCDs affect people who are still economically productive; thus, the burden on health care costs and loss of healthy life years due to premature deaths from NCDs have profound detrimental effects on the economies of these countries (18). There is a clear need to establish early and timely preventive action to avoid the health, social, and economic burden of these diseases (41). Globalization, urbanization, and mechanization of physical work with the associated loss in physical activity and the concomitant increases in consumption of unhealthy fats and carbohydrates, which leads to body mass index gains, are now syndicated as the underlying and proximal causes for the emergence of NCDs in developing countries (20).

Most developing countries find themselves still tackling the burden of undernutrition and infectious diseases; this creates tension and potential conflict in allocating the limited available resources. However, there is growing evidence that weight, diet, and physical activity patterns are in part established or even "programmed" early in life. In the case of undernutrition there is consensus that the critical window of opportunity for effective preventive action starts from around conception through 24–36 mo (27, 42). This presents a unique opportunity to target preventive interventions focusing on the peri-conception period and the early years of life. This is the time of the greatest potential for lifelong effect, as long as we address both goals with complementary actions. In fact, recent evidence indicates that there are effective interventions that will decrease short-term undernutrition as well as contribute to preventing NCDs. A recent study in India shows that a balanced protein-calorie supplementation offered to pregnant women and children aged <5 y living in poverty had a positive effect on children's length as well as in measures of insulin resistance and arterial stiffness (43). Other interventions that may be considered in this common agenda to prevent "malnutrition in all its forms" include the following: improving weight and micronutrient status of mothers, promoting breastfeeding, adjusting protein and fat content of early diets both in terms of quantity and quality, and increasing physical activity in mothers and children where appropriate. Developing countries should start by testing interventions that might benefit both undernutrition and NCD prevention using both short- and intermediate-term outcomes, ideally under real-world conditions because effectiveness will likely be context specific. Research and effect evaluation efforts should focus on assessing the feasibility, efficacy, effectiveness, and cost-effectiveness of preventive strategies with a life-course and multilevel outcome perspective to build the body of evidence necessary to support specific policy options. At the same time, continuous monitoring of routine indicators, such as preconception weight status, weight gain during pregnancy, stunting and wasting prevalence, and progress in weight in relation to length gain during infancy should be maintained. This is necessary to chart the course of future actions in NCD prevention and to avoid the unintended consequences associated with the rapid decline in undernutrition, particularly in countries in which the transition from undernutrition/infectious diseases to obesity/NCDs is more advanced. Under the DOHaD paradigm, malnutrition in all its forms can be tackled with a common preventive agenda centered on pregnancy and the first 2 y of life. Although substantial theoretical evidence supports this proposal, there remains a need to generate local evidence on efficacy, effectiveness, and cost-effectiveness of various potential interventions. This research should serve to inform developing countries' policymakers, helping them to set priorities, as well as in implementing and evaluating preventive actions. The DOHaD paradigm provides an opportunity to understand health and nutrition transitions of countries with a life-course, multidisciplinary, and transgenerational perspective. Tackling present problems by using this novel paradigm will effectively contribute in addressing global health inequalities doing the most good while avoiding unintended harm.

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