Growth and nutrition in early life and risk of type 2 diabetes

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Abstract

The traditional model of type 2 diabetes encompasses genetic susceptibility and precipitation due to lifestyle factors. The idea of prevention revolves around changing the lifestyle of adults with impaired glucose tolerance, a method supported by many trial results. As the epidemic of diabetes matures, this rather limited idea will prove less and less effective. The risk factors for diabetes (obesity and insulin resistance) are increasingly seen in children and the age at diagnosis of diabetes is falling rapidly. The burden of disease is shifting to a younger population and the focus on prevention must anticipate this changing epidemiology. The concept of the developmental origins of health and disease (DOHaD) makes much sense. Although the medical profession has been slow to embrace this concept, the World Health Organization has endorsed the idea in its life-course model of non-communicable disease.

This review article traces the history of the DOHaD concept and summarizes current thinking. Both fetal undernutrition (low birth weight) and overnutrition (the baby of a diabetic mother) increase the risk of future diabetes. Children who grow rapidly in childhood are also at increased risk of type 2 diabetes, especially if they were born small. Earlier age at adiposity rebound (the age at which BMI starts rising) has been shown to be a particularly powerful risk factor for type 2 diabetes. Thus type 2 diabetes may be regarded as malnutrition-related diabetes, especially when associated with undernutrition in early life.

The DOHaD idea thus represents a paradigm shift in the model for prevention of chronic disease. The next challenge is to translate this knowledge into practice. The focus is on the health of young girls. We need to understand the specific aspects of maternal nutrition that influence adiposity in the offspring, as well as the factors that influence a child's age at adiposity rebound. Special efforts will be needed to change current practice, especially of overfeeding low-birth-weight babies to 'normalize' their growth.

Key words:
Fetal programming, developmental origins of health and disease (DOHaD), birth size, childhood growth, insulin resistance, type 2 diabetes

Introduction

Traditionally, susceptibility to type 2 diabetes has been ascribed to 'thrifty genes', selected during the hunter-gatherer period of our evolution and believed to promote obesity and type 2 diabetes in the modern world [1]. Few thrifty genes have been demonstrated, however. In 1992, Nick Hales and David Barker proposed an alternative explanation [2]. They suggested that poor nutrition of the fetus increased its susceptibility to type 2 diabetes. The idea arose from their finding that low birth weight is associated with type 2 diabetes and the metabolic syndrome. They proposed that small size at birth represented a 'thrifty phenotype', reflecting intrauterine undernutrition, which predisposes to type 2 diabetes when food supply is adequate. Later research showed that patterns of growth in infancy and childhood may also predispose to type 2 diabetes [3, 4]. Thus the original concept of fetal origins has now been expanded to the concept of developmental origins of health and disease (DOHaD) (*Fig. 1*). An international council has been set up to promote the idea and four dedicated international congresses have discussed and promoted the DOHaD concept (http://www.mrc.soton.ac.uk/dohad/index.asp).

We begin our life as a single cell that grows, divides and differentiates to form an embryo (*Fig. 2*). Further growth and differentiation form

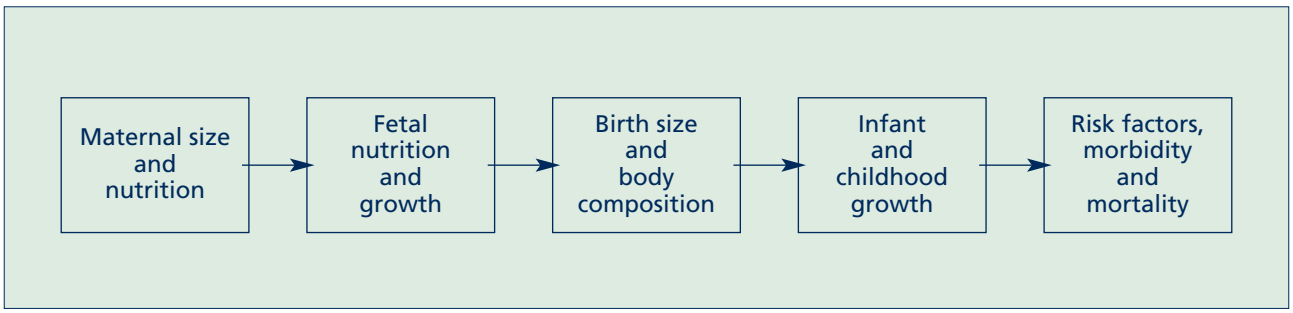

Fig. 1: *DOHaD, the developmental origins of health and disease.*

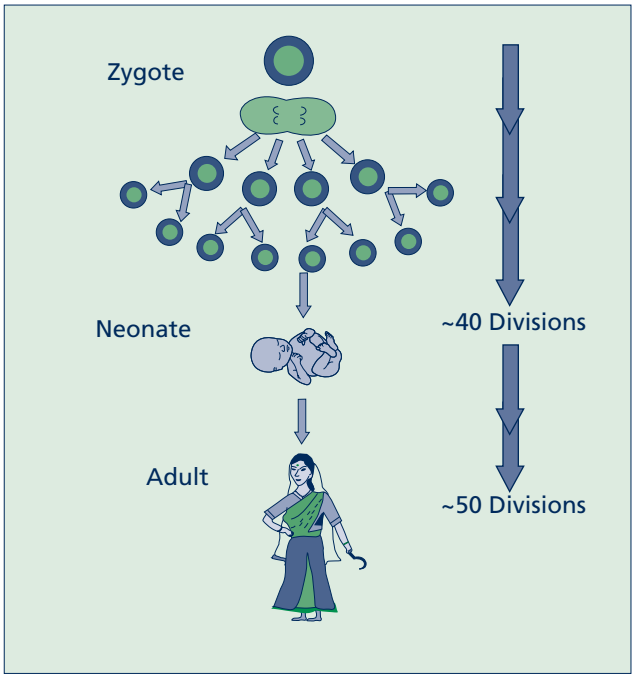

Fig. 2: *Cell divisions during the lifetime of an individual. Cells in the human body undergo approximately 50 divisions during a lifetime. Of these, about 40 take place before birth. A large part of our development, therefore, is over before we are born (adapted from [5]).*

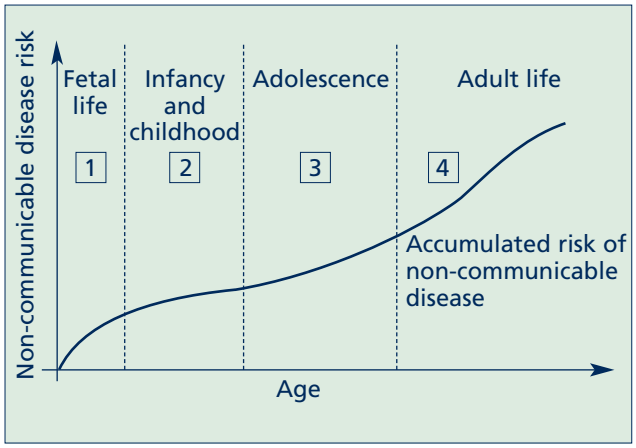

Fig. 3: *The World Health Organization's life-course model of non-communicable disease. The model suggests that non-communicable diseases have their origins in early life. The risk progressively accumulates throughout the life course and the disease becomes manifest in later life.*

systems and the embryo develops into a fetus. At birth we are a miniature adult with most of the systems in place. The fastest growth during life occurs *in utero*, making this is a very vulnerable period for environmental influences. It is estimated that an average cell divides approximately 50 times during a lifetime, more than 40 of these divisions occurring before birth [5].

An insult during intrauterine life would thus have a profound and permanent effect on the structure and function of the developing organism (programming) and will be reflected in future health and disease [6]. Depending on the timetable of development there are windows of time when an insult may cause more severe damage to a particular system. Our ancestors knew about programming: Hindu mythology has stories related to intrauterine programming (for example, Abhimanyu, who learned about advanced warfare from listening to the discussions when he was in his mother's womb) [7].

The medical profession has been slow to appreciate the importance of fetal life for future health. Thanks to Professor Barker and his team, there is now a perceptible shift in thinking about how to prevent type 2 diabetes and cardiovascular disease [8]. Late Professors Joe Hoet and Nick Hales contributed elegant animal models to support the idea [9, 10]. The World Health Organization has endorsed the concept in its life-course model of non-communicable disease (*Fig. 3*) [11]. These issues are discussed below in three parts: the original studies relating birth size to adult outcomes; subsequent studies in children; and prospective studies from conception and birth.

Size at birth and type 2 diabetes

Barker and colleagues used birth and growth records in the UK [2, 12, 13], India [14, 15] and Finland [16] to report a series of associations between size at birth and subsequent morbidity and mortality. The results were dramatic and showed that small size at birth (low birth weight and low ponderal index [thinness]) predicts future type 2 diabetes and the metabolic syn-

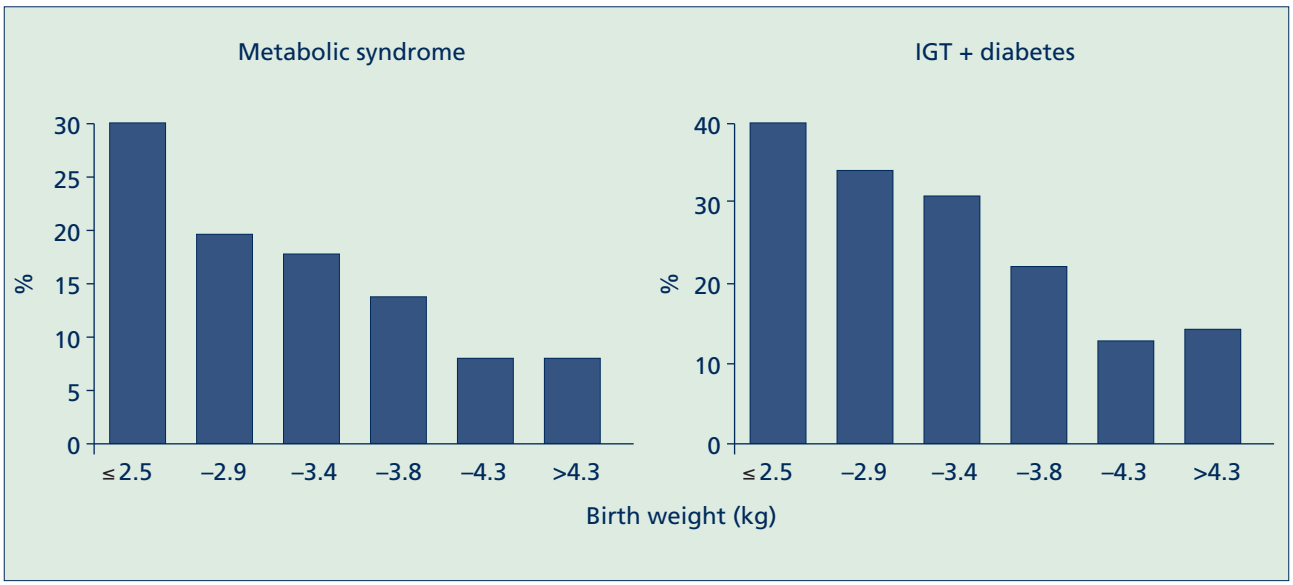

Fig. 4: *Relationship between birth weight and adult diseases. Hertfordshire studies showed an inverse association between birth weight and glucose intolerance (IGT + diabetes) as well as the metabolic syndrome (glucose intolerance + dyslipidemia + hypertension)*

drome, independently of later obesity (*Fig. 4*). Similar findings were reported from many other countries, including studies from Europe and North America [17], and the concept of the small baby syndrome was established [13]. Barker and colleagues stressed that the associations reflected growth retardation rather than preterm delivery. The new idea was contrary to the clinician's expectation that a large baby born to a diabetic mother (intrauterine overfeeding) is at increased risk of obesity and diabetes [18–20].

It was expected that the contribution of low birth weight to diabetes might be more important in developing populations, where low birth weight is common. However, this was challenged by a study in Pima Indians which showed that both low and high birth weights were predictive, i.e. the relationship between birth weight and future diabetes was U-shaped [21]. Large birth weight was thought to reflect the effect of maternal hyperglycemia, though maternal obesity could also contribute. In Taiwan, both low and high birth weight predicted type 2 diabetes in the young [22], but two Indian studies failed to show a relationship between birth weight and type 2 diabetes [4, 15]. In Mysore, short length and high ponderal index (obesity) at birth predicted future diabetes. A study in Canadian Indians showed that high birth weight predicted type 2 diabetes but low birth weight was not predictive [23]. Overall, these findings suggest that both small and large size at birth are predictive: both fetal undernutrition and fetal overnutrition could be responsible.

These studies focused attention on the importance of fetal life for future health, but there is a danger of overinterpreting the results. The retrospective design, large number of dropouts and inability to adjust for a number of important confounders mean that interpretation must be cautious. An important issue is that the etiological role of nutrition is presumptive, as there were no nutritional measurements (intake or circulating nutrient levels) in these studies. Where information was available, the results are confusing [24, 25] or negative [26]. It is important that the relationship between nutrition and size is variable and is influenced by a number of factors including genetics [27]. Moreover, size does not reveal body composition, which is more important for susceptibility to type 2 diabetes.

The relationship between maternal nutrition and fetal nutrition is complex and influenced by the placenta [28]. Thus the obvious implication that improving maternal nutrition will reduce the risk of type 2 diabetes and cardiovascular diseases in the offspring demands more evidence. Only long-term prospective follow-up and properly designed interventions will provide an answer. Animal studies can be supportive, although they will have their own problems of interpretation and applicability to humans.

Birth size and cardiovascular risk factors in childhood

The next set of studies looked at the relationship between birth weight and risk factors for type 2 diabetes and cardiovascular disease in prepubertal children. The Indian studies are informative. The Pune Children's Study showed that in

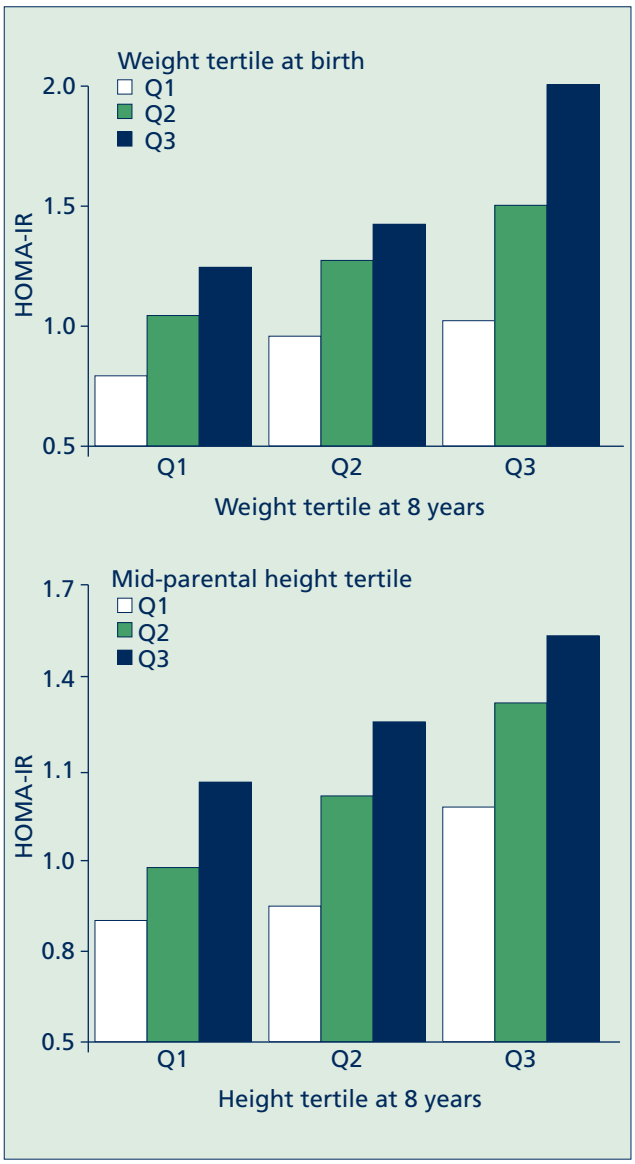

Fig. 5: *Relationship between size and insulin resistance. The highest levels of HOMA-IR were seen in children who were born light and had grown heavy, as well as in those who had short parents but had grown tall. Thus, relative excess growth within a lifetime or between generations is associated with higher insulin resistance.*

4-year-old children, plasma glucose, insulin and insulin-like growth factor (IGF)-I concentrations were inversely related to birth weight when adjusted for the strong effect of current size [29]. At 8 years, the cardiovascular risk factors (homeostasis model assessment of insulin resistance [HOMA-IR], plasma cholesterol and triglyceride concentrations, blood pressure and central adiposity) were highest in children who had a low birth weight but had subsequently grown heavy or tall (*Fig. 5*) [30]. Growth velocity between the ages of 4 and 8 years was a stronger predictor of cardiovascular risk than size at 8 years [31].

Another set of studies (in Finland and India) [3, 4, 32] showed that individuals who developed type 2 diabetes had slower growth in infancy but a progressively accelerated weight gain starting in childhood.

The Pune Children's Study made an intriguing observation: children born to short parents had higher body fat and HOMA-IR, and those who had grown taller in relation to mid-parental height were the most insulin-resistant (*Fig. 5*) [30]. The results suggest an intergenerational influence on insulin resistance in the offspring. It would appear that a rapid transition invites insulin resistance and increased cardiovascular risk. These ideas are captured in the predictive adaptive response explanation [33].

In addition to a small or large size at birth, subnormal growth rate in infancy and rapid childhood growth are associated with an increased risk of type 2 diabetes

Thus, in addition to a small or large size at birth, subnormal growth rate in infancy and rapid childhood growth are associated with an increased risk of type 2 diabetes. This seems to be true both of babies born small and thin as well as those born big and fat. The common denominator in these two phenotypes may be the high adiposity (percentage body fat) at birth. Appropriate body composition measurements may improve our understanding of the relationship between birth size and future disease.

Prospective studies

These studies begin before or during pregnancy, make serial observations during *in utero* and postnatal life, and relate the observations to risk factors, morbidity and premature mortality. The prospective design allows measurement of relevant exposures as well as confounders to test well-defined hypotheses. Prospective studies are necessarily long term, difficult to carry out, expensive and require special expertise. Prominent studies are the Pune Maternal Nutrition Study [34], the Parthenon Study [35] and the Southampton Women's Study (http://www.mrc.soton.ac.uk/sws/default.htm).

The Pune Maternal Nutrition Study [34] was the first such study. It began in 1993 in six villages near Pune and is now in its 12th year of follow-up. Investigators studied approximately 2700 women before conception and over 800 pregnancies in this study. Measurements included: maternal size before conception, and

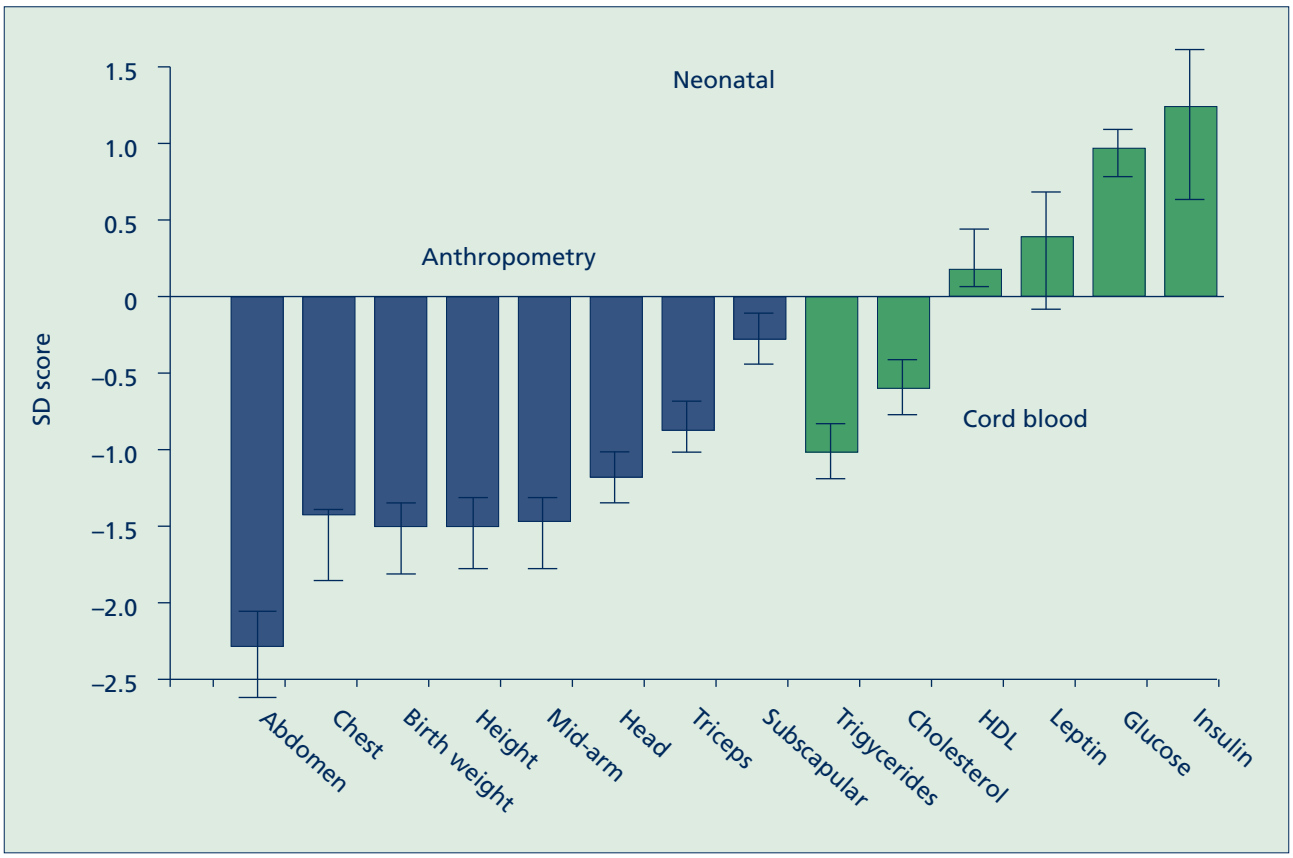

Fig. 6: *Comparison of Indian and UK babies. UK measurements are used as a reference (0). The Indian babies were smaller than the British babies in all measurements of size. Cord plasma leptin concentration was similar and cord plasma glucose and insulin concentrations were higher in the Indian babies.*

nutrition, physical activity, metabolic and endocrine parameters and clinical events during pregnancy. Babies were measured in detail at birth and every 6 months thereafter. Body composition, nutrition and cardiovascular risk factors in the children were studied at intervals. This enables investigation of the relationship between maternal nutrition and offspring risk of type 2 diabetes and cardiovascular disease.

Body composition at birth may be a more important risk factor for future type 2 diabetes than size itself

The Pune mothers were small (42 kg, 1.52 m, BMI 18.1 kg/m^2) and gave birth to small, thin babies (2.7 kg, ponderal index 24.3 kg/m^3). Comparison of these babies with those born in Southampton (3.5 kg, 27.5 kg/m^3), however, revealed an astonishing pattern. Despite their smaller size, the Indian babies had comparable central subcutaneous fat (subscapular skinfold thickness). In other words, they were 'thin but fat' (*Fig. 6*) [34]. Indian babies had higher concentrations of insulin and leptin in the cord blood [36]. These findings suggest that body composition at birth may be a more important risk factor for future type 2 diabetes than size itself. Maternal intake of macronutrients (calories, protein, etc.) was found to have little effect on the size of the baby, but intake of micronutrient-rich foods (green leafy vegetables, fruit and milk) and circulating concentrations of vitamin B12, folate and vitamin C were strong determinants of offspring size [37]. Higher maternal circulating homocysteine concentrations (due to low vitamin B12 status) predicted intrauterine growth retardation [38]. At 6 years of age, the adiposity and insulin resistance of these babies were predicted by low circulating concentrations of vitamin B12 and high concentrations of folate in the pregnant mother [39]. This is the first demonstration that maternal nutrition is an important determinant of risk of type 2 diabetes in the offspring.

The Parthenon Study (Mysore, S. India) confirmed the thin-fat phenotype of the Indian baby. The babies of gestational diabetic mothers were heavier and more adipose at birth in comparison with those born to normoglycemic mothers. They lost the extra weight and adiposity in the first 2 years of life but had an earlier adiposity rebound to become more adipose, insulin-resistant and hyperglycemic at 5 years of age [35].

Finally, follow-up of Hertfordshire adults who were born with a low birth weight has shown that the low-birth-weight babies grew into thin-fat adults [40], supporting the idea that small size at birth may indeed be a surrogate for higher adiposity.

Mechanisms of DOHaD

Fetal programming may operate through a number of mechanisms [41]. Some of these have been demonstrated in humans, some in animals. A change in endocrine axes is one of the major mechanisms. This has been convincingly demonstrated for the insulin-IGF [41] and the hypothalamic-pituitary-adrenal axes [42]. At cellular level, programming involves a change in number as well as in the basic aspects of cellular function including cell cycle dynamics and apoptosis [43]. At molecular level, telomerase shortening and altered function of different enzyme systems have been demonstrated [44]. A comparatively recent development is the recognition that epigenetic changes are an important component of programming. In animal experiments this has been demonstrated for the *agouti* gene [45] and the PPAR-α gene [46], both of which affect adiposity and insulin resistance. Methylation is a major mechanism of epigenetic regulation and suggests that 1-carbon metabolism and its regulators (vitamin B12 and folate) may be important in nutritional programming. Change in the offspring phenotype by treatment of *agouti* mothers with a methylating cocktail (vitamin B12 + folate + betaine + choline) provides direct proof. The Pune results linking maternal vitamin B12 and folate nutrition with offspring adiposity and insulin resistance assume special significance. It is interesting that epigenetic modifications are inherited [47].

The role of genetics in DOHaD was suggested in the fetal insulin hypothesis [48]. This hypothesis proposes that genes which affect susceptibility to diabetes also influence birth weight by influencing the fetal insulin response to nutrients. Thus birth weight might be a surrogate for a diabetes-predisposing genotype (for example, glucokinase). A further role for genetic factors in DOHaD was suggested by a relationship between paternal diabetes and low birth weight in the offspring [49], postulated to be an effect of insulin resistance genes. However, a direct relationship between paternal insulin resistance and offspring birth weight has also been demonstrated, challenging the idea [50]. In the final analysis, a gene–environment interaction seems to be at the heart of intrauterine programming.

Future of DOHaD

Twenty years on, the DOHaD concept is well established and flourishing. It represents a paradigm shift in thinking about the etiology of health and disease. Arguably, this is the most important public health message that has been made in the last few decades. There is currently only limited knowledge about specific exposures in intrauterine life that may be acted upon. The role of specific aspects of nutrition is beginning to be understood and there is a growing realization that micronutrients may be particularly important. One-carbon metabolism might be crucial and vitamins which control these pathways (vitamin B12, folate, pyridoxine and riboflavin) may have special significance. There is a need for worldwide research on local nutritional factors of importance for fetal health. It is time to recognize that type 2 diabetes is related to malnutrition.

The DOHaD concept represents a paradigm shift in thinking about the etiology of health and disease

The next step will be an intervention to target intrauterine growth retardation. However, the history of feeding undernourished mothers during pregnancy to improve fetal growth is chequered. The effects vary according to the stage of pregnancy and the quantity and quality of macronutrients and their balance with micronutrients. The fetal supply line is complex and governed by many factors, so feeding the mother cannot always be equated with feeding the baby. Genetics plays an important part in determining the requirements and response to nutrition [51]. Moreover, promoting fetal growth in a small mother may cause difficulties during delivery and harm both the mother and the baby [52]. Thus, improving young girls' nutrition during their formative years may be the ideal strategy. More than one generation of improved nutrition and growth may be needed to optimize fetal outcomes. Postponing age at marriage and childbearing would allow Indian mothers to embark on pregnancy better prepared.

Controlling maternal obesity and treating hyperglycemia are other potential targets to

reduce the risk of type 2 diabetes in the offspring. Treatment of obesity has been overall disappointing and as yet there is little evidence that treatment of maternal diabetes reduces the offspring's risk of diabetes. Indeed, aggressive diabetes management pushes some babies into growth retardation, which may further increase their risk of type 2 diabetes and cardiovascular disease [53]. There is an urgent need to study long-term fetal outcomes in trials of diabetes and pregnancy. A substantial proportion of 'gestational' diabetes may in fact be 'pregestational' and fetal programming may be over by the time it is diagnosed and treated. Future research should therefore concentrate on screening and treatment of even minor degrees of metabolic abnormalities before pregnancy.

The hand that rocks the cradle may hold the key to curtailing the growing epidemic of type 2 diabetes

The hand that rocks the cradle may hold the key to curtailing the growing epidemic of type 2 diabetes. History will not forgive those who close their eyes to this simple truth of nature.

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