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Invited review article

# Early environmental factors, alteration of epigenetic marks and metabolic disease susceptibility

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ABSTRACT

The environmental conditions that are experienced in early life can profoundly influence human biology and long-term health. Early-life nutrition and stress are among the best documented examples of such conditions because they influence the adult risk of developing metabolic diseases, such as type 2 diabetes mellitus (T2D) and cardiovascular diseases. It is now becoming increasingly accepted that environmental compounds including nutrients can produce changes in the genome activity that in spite of not altering DNA sequence can produce important, stable and transgenerational alterations in the phenotype. Epigenetic changes, in particular DNA methylation and histone acetylation/methylation, provide a 'memory' of developmental plastic responses to early environment and are central to the generation of phenotypes and their stability throughout the life course. Their effects may only become manifest later in life, e.g. in terms of altered responses to environmental challenges.



## 1. Introduction

The environmental conditions that are experienced in early life can profoundly influence human biology and long-term health. Early-life nutrition and stress are among the best documented examples of such conditions because they influence the adult risk of developing metabolic diseases, such as type 2 diabetes mellitus (T2D) and cardiovascular diseases [1–4]. Individuals who are born small for gestational age have an increased risk of cardiovascular morbidity and mortality when they are adults [2,5,6] (Fig. 1). This epidemiological evidence is now supported by an extensive experimental literature in animals [7]. Evidence on the importance of prenatal and early postnatal growth for later morbidity suggests the existence of a link between developmental responses to early environments and adult biology.

## 2. The developmental origins of health and disease (DOHaD) concept

In light of epidemiological data, Barker and Hales proposed the thrifty phenotype hypothesis in 1992 to explain the relationships between patterns of early growth and long-term health [8]. This suggested that the relationships between birth weight and metabolic disease arose because of the response of a growing fetus to a suboptimal nutritional environment. Central to this hypothesis was the suggestion that during times of nutritional deprivation, the growing fetus adopts a number of strategies to maximize its chances of survival postnatally in similar conditions of poor nutrition. Such adaptations include the preservation of brain growth (at the expense of other tissues such as skeletal muscle and the endocrine pancreas) and the programming of metabolism in a manner that would encourage storage of nutrients when they were available. This has no detrimental effect and is in fact beneficial to survival if the fetus is born into conditions of poor nutrition. Thus, in populations where there is chronic malnutrition, these adaptations are beneficial and the prevalence of metabolic disease is low. However, detrimental consequences of developmental programming were proposed to arise if the fetus was born into conditions that differed from those experienced in utero (Fig. 2). The imbalance between the early and postnatal environments may then conflict with the programming that occurred during fetal life and predispose the offspring to the subsequent development of metabolic diseases in adulthood. To reflect the evidence that the critical periods of vulnerability to environmental influences extend beyond the fetal period, the concept that events in early life affect long-term health is now generally referred to as

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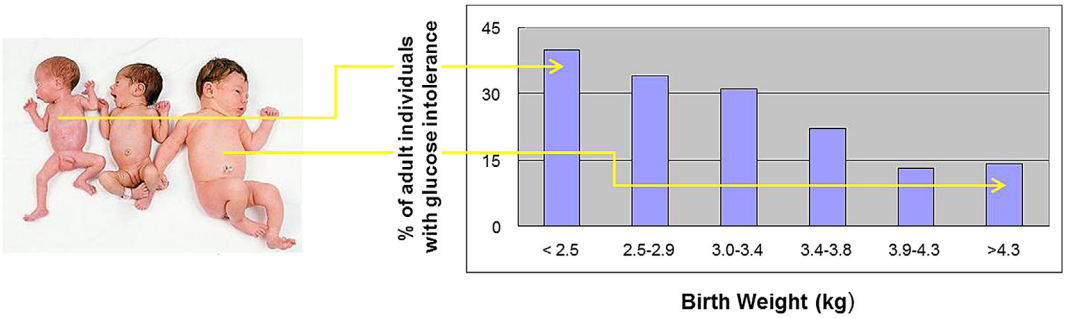


**Fig. 1.** Epidemiological evidence for a fetal programming of metabolic diseases. Although the concept of programming had been suggested prior to the work of Barker and colleagues, it was their epidemiological studies in the U.K. in the late 1980s that led to the proposal that events in fetal life could influence long-term risk of metabolic disease. Using a cohort of 64-year-old men born in Hertfordshire (UK), they identified an inverse relationship between systolic blood pressure and increased cardiovascular mortality and birth weight. Using the same cohort of men, they demonstrated a similar inverse link between birth weight and glucose tolerance and insulin resistance. They demonstrated that the individuals with the lowest birth weights were 6-fold more likely to develop type 2 diabetes or impaired glucose tolerance when compared with those who were heavier at birth. These findings have now been replicated in a variety of populations with differing ethnicities. [adapted from Ref. [2]].

the developmental origins of health and disease (DOHaD) hypothesis.

Various terminologies have been proposed to describe biological phenomena relevant to DOHaD. Lucas [9] proposed the term "programming" to refer to permanent or longterm effects of a stimulus or insult at a critical or sensitive period. Barker [1] referred to the fetal origins hypothesis. Realization that developmental plasticity extends into the postnatal period led to a change in nomenclature to the developmental origins hypothesis [10]. Waterland and Garza [11] proposed the term "metabolic imprinting" to describe adaptive responses to specific nutritional conditions early in life that occur during limited periods of sensitivity and persist to adulthood. Metabolic imprinting refers to phenomena in which both the exposure and outcome are specific and measurable and exhibit a dose–response or threshold relation.

Some of the strongest evidence in support of the role of the environment in underlying the relationship between fetal growth and metabolic disease in the adult (in this case, type 2 diabetes) has

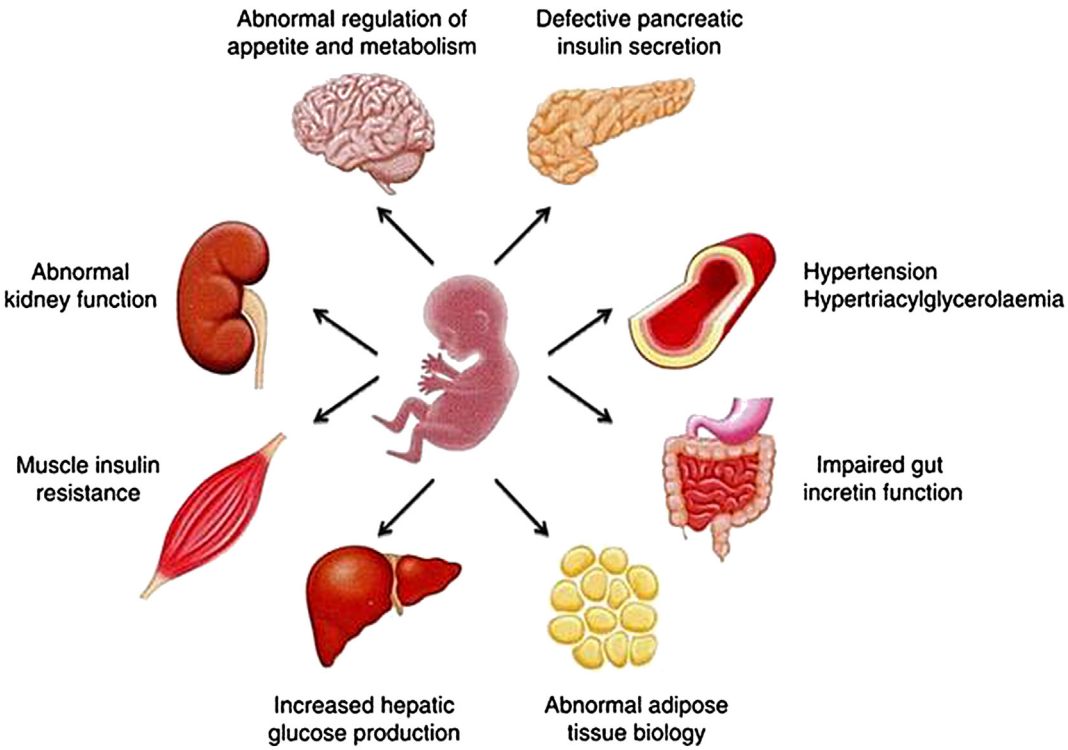


**Fig. 2.** Environmental factors acting in early life have consequences that become manifest as an altered disease risk in later life. It has been suggested that the baby receives from its mother a forecast of the environment it will encounter after birth and modifies its metabolism, whole body physiology, and growth trajectory appropriately to maximize its chances of survival postnatally. However, these adaptations become detrimental if the conditions after birth are not the same as the ones encountered during early life. These adaptations include metabolic and endocrine changes that may lead to lifelong changes in the function and structure of the body, a concept termed programming. There exists uniform agreement that glucose intolerance, ranging from the prediabetic states of impaired glucose tolerance to overt type 2 diabetes, constitutes heterogeneous dysmetabolic states, involving the dysfunction of multiple organs, including the liver, muscle, pancreas, adipose tissue, gut, kidney and brain. The concept of developmental programming provides a conceptual framework to explain the multiple organ dysfunctions in type 2 diabetes, changing with time and age, and differing in magnitude between patients within and between societies. [reproduced from Ref. [139]].

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