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Review

# Pathways linking the early environment to long-term health and lifespan

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ABSTRACT

The intrauterine environment is a major contributor to normal physiological growth and development of an individual. Disturbances at this critical time can affect the long-term health of the offspring. Low birth weight individuals have strong correlations with increased susceptibility to type 2 diabetes and cardiovascular disease in later-life. These observations led to the Thrifty Phenotype Hypothesis which suggested that these associations arose because of the response of a growing fetus to a suboptimal environment such as poor nutrition. Animal models have shown that environmentally induced intrauterine growth restriction increases the risk of a variety of diseases later in life. These detrimental features are also observed in high birth weight offspring from mothers who were obese or consumed a high fat diet during gestation. Recent advances in our understanding of the mechanisms underlying this phenomenon have elucidated several potential candidates for the long-term effects of the early environment on the function and metabolism of a cell. These include: (1) Epigenetic alterations (e.g. DNA methylation and histone modifications), which regulate specific gene expression and can be influenced by the environment, both during gestation and early postnatal life and (2) Oxidative stress that changes the balance between reactive oxygen species generation (e.g. through mitochondrial dysfunction) and antioxidant defense capacity. This has permanent effects on cellular ageing such as regulation of telomere length. Further understanding of these processes will help in the development of therapeutic strategies to increase healthspan and reduced the burden of age-associated diseases.



**Contents**



*Abbreviations:* 4E-BP, eukaryotic initiation factor 4E binding protein; 11β-HSD2, 11β-hydroxyl steroid dehydrogenase type 2; AC, adenylate cyclase; AGA, appropriate for gestational age; ACE, angiotensin converting enzymes; $A^{VY}$, agouti viable yellow; BAT, brown adipose tissue; CuZnSOD, copper-zinc SOD; CR, caloric restriction; CVD, cardiovascular disease; DNA, deoxyribonucleic acid; ETC, electron transport chain; GC, glucocorticoid; GH, growth hormone; GHR-BP, GH receptor binding protein; GK, glucokinase; GPx, glutathione peroxidase; GR, glutathione reductase; H2A, histone 2A; H2B, histone 2B; H3, histone 3; H4, histone 4; HDAC, histone deacetylase; HO-1, hemeoxygenase 1; HPA, hypothalamo-pituitary adrenal axis; $H_2O_2$, hydrogen peroxide; IGF-1, insulin like growth factor; IIS, insulin/IGF-like signalling; IUGR, intrauterine growth restriction; miRNA, micro RNA; MnSOD, manganese SOD; mtDNA, mitochondria DNA; NAFLD, non-alcoholic fatty liver disease; NAM, nicotinamide; NASH, non-alcoholic steatohepatitis; $O_2^-$, superoxide; $OH^-$, hydroxyl radicals; PDX1, pancreatic and duodenal homeobox 1 transcription factor; PEPCK, phosphoenolpyruvate carboxykinase; PKA, protein kinase A; PLP, postnatal low protein; PPRAα, peroxisome proliferator-activated receptor alpha; PRL, prolactin; R, recuperated; RAS, renin-angiotensin system; ROS, reactive oxygen species; RNA, ribonucleic acid; S6k1, S6 protein kinase 1; Sir2, silent information regulator 2; SGA, small for gestational age; SOD, superoxide dismutase; TERT, telomerase reverse transcriptase; TOR, target of rapamycin; TSH, thyroid stimulating hormone; WAT, white adipose tissue.

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## 1. Developmental origins of health and disease

Fetal and postnatal life are critical periods for the development and growth of major structures and organs. There is accumulating evidence that nutrition during this time window can have long-term consequences on the individual's health. During this critical period of growth and development, alterations in nutrition could cause permanent adaptations to the structure and function of specific organs. These changes appear to influence the risk of developing type 2 diabetes, cardiovascular disease (CVD), obesity and, as shown more recently, on the longevity of the organism.

## 2. Epidemiological findings

The first studies linking fetal development with adult disease arose from studies by Barker et al. in 1989 using birth weight as a crude index of *in utero* experiences. They observed that systolic blood pressure in both children and adults in Britain was inversely correlated with birth weight (Barker et al., 1989a). Additional studies in a cohort of Hertfordshire men born between 1911 and 1930 revealed an inverse relationship between birth weight and death from ischemic heart disease (Barker et al., 1989b). Using the same cohort, with an average age of 64 years, they also demonstrated an inverse relationship between birth weight and impaired glucose tolerance (a pre-diabetic state) and type 2 diabetes. This was shown by a continuous linear relationship across the birth weight range, the individuals with the lowest birth weight had a six fold increased risk of developing type 2 diabetes compared to the heaviest (Hales et al., 1991). These low birth weight individuals also had 18 fold increased prevalence of the metabolic syndrome. These relationships have been confirmed in over 40 populations worldwide.

## 3. Thrifty phenotype hypothesis

In light of their earlier observations Hales and Barker proposed that early nutrition was a significant factor mediating the relationship between early growth and the features of the metabolic syndrome. This proposal was termed the 'Thrifty Phenotype Hypothesis' (Fig. 1) (Hales et al., 1991). They theorised that if the growing fetus was malnourished during gestation due to suboptimal maternal nutrition, placental dysfunction, stress or other factors, the fetus would adapt *in utero* to increase the chance of survival if the conditions of poor nutrition were continued postnatally. The fetus would protect the development of particularly vital organs, such as the brain at the expense of other tissues, such as the endocrine pancreas. This was consistent with previous studies in humans that demonstrated that in human pregnancies complicated by severe intrauterine growth restriction (IUGR) there was a reduction in fetal endocrine pancreatic tissue and insulin producing β cells (Van Assche et al., 1977). This was further supported by studies in rodents showing that when pregnant rats were fed a low protein diet, the offspring are born smaller than controls, and detrimental effects on pancreatic development can be seen including reduced β cell proliferation, islet size (Snoeck et al., 1990) and insulin secretion (Dahri et al., 1991). The kidney, that regulates fluid homeostasis and blood pressure, was another organ that was proposed to be influenced by suboptimal nutrition in utero and consequently impact on risk of hypertension. A second key component of the Thrifty Phenotype Hypothesis was that the fetus would maximise metabolic efficiency regarding the storage and

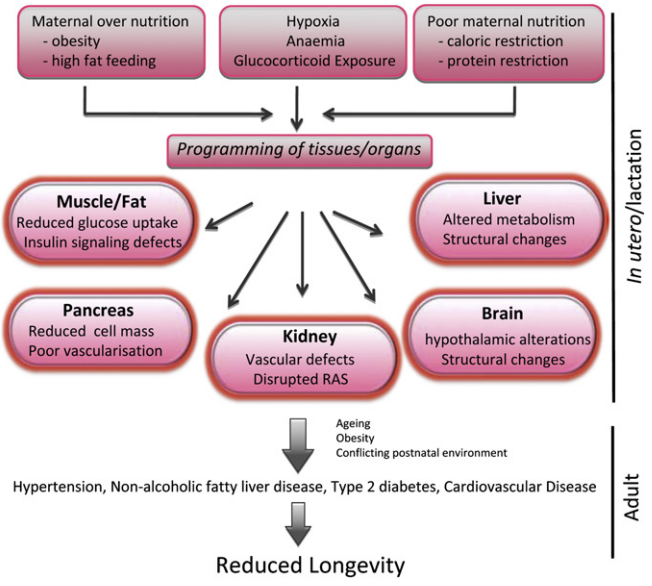


**Fig. 1.** The thrifty phenotype hypothesis in relation to longevity.