Review Article

# Developmental origins of adult diseases

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ABSTRACT

There is considerable evidence for the fact that early life environment in human beings are associated with future development of various metabolic diseases. Fetal programming and perinatal events appear to exert effects on later life that are independent of environmental risk factors in adults. Our understanding of the underlying mechanisms are limited and remains unclear. However several animal models and epidemiological studies have shown this association, and it is assumed secondary to the penalties of developmental plasticity. In this review, we amalgamate facts from several disciplines to support this hypothesis.

**Key words:** Coronary artery disease, catch-up growth, developmental origins of adult disease, epigenetics, intrauterine growth retardation, short for gestational age, type 2 diabetes mellitus

*"The devil has put a penalty on all things we enjoy in life. Either we suffer in health or we suffer in soul or we get fat."*

Albert Einstein, 1879–1955

## Background

Insulin resistance, the key component of type 2 diabetes mellitus (T2DM), is linked to a multitude of diseases like obesity, hypertension, coronary artery disease (CAD), and dyslipidemia. These diseases exert a major toll on resources across the world with wide ramifications on physical, psychological, and financial well-being. The prevalence of diabetes is projected to be 7.7% in 2030, affecting 439 million adults.[1] The enormity of the problem has necessitated a shift in focus from treatment of diabetes and related diseases to primary prevention. Intrauterine environment provides an individual with a sneak preview of the conditions one may be exposed to during childhood growth and adult life. This information in turn leads to an adaptive response in metabolism, which provides a survival advantage. Some brilliant epidemiologic studies from the latter part of the last century were instrumental in bringing out the association of body size at birth with various adult disorders including diabetes and cardiovascular disease. In this article, we have attempted to give a comprehensive review of the existing literature on developmental origins of adult disease (DOAD).

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## Epidemiological Evidence

The pathophysiological effect of adverse intrauterine life on adult health was a relatively unresearched area, till epidemiological studies revealed an association between intrauterine fetal health and adult life. Ravelli *et al.* studied a population cohort born during the Dutch famine of 1944–1945. Infants who were subjected to mid or late gestation calorie restriction had a lower birth weight and impaired glucose tolerance (IGT) as adults. Infants of mothers who endured the famine in early gestation had a normal birth weights, but had obesity and atherogenic lipid profile as adults.[2,3] Studies from Hertfordshire, UK, and Helsinki, Finland, showed that poor fetal nutrition and low birth weight are related to adult diseases, namely, CAD, obesity, and insulin resistance.[4,5] In the Leningrad siege study of the Leningrad famine which extended for 800 days, the subjects were exposed to malnutrition during fetal life and infancy. The Leningrad cohort did not show increased incidence of diabetes, hypertension, and CAD.[6,7]

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Based on the overwhelming epidemiological evidence, Barker and associates proposed the Barker hypothesis which suggested that an environment which produces poor fetal and infant growth is followed by an adult environment that determines high risk for ischemic heart disease. This hypothesis came to be known as fetal origins of adult disease or developmental origins of adult disease.[5,7-10]

Low birth weight has been consistently associated with adult-onset diabetes in various published literature from the developed world and Asia.[11-14] However, a study done from Mysore in South India suggested that shorter body length and higher ponderal index at birth were related to IGT and type 2 diabetes at age 45, while low birth weight was not.[15] The birth weight in turn is dependent upon a variety of factors like maternal nutrition, parity, mother's birth weight, mother's adult size, and mother's birth weight.[16]

## Genetic Mechanisms in Developmental Origins of Adult Disease

The evolution of the human species through a process of survival of the fittest has necessitated a complex interaction between maternal and fetal genotypes. The thrifty genotype theory suggests that the relative scarcity of food during the early periods of human evolution leads to an adaptive response of enriched thrifty genes, which is conducive in a nutritionally poor environment. However, with relative easy availability of food and nutritional enrichment, this adaptation becomes counterproductive.[17] The epidemiologic studies mentioned earlier revealed that this adaptive response is detrimental as low birth weight was associated with increased risk of obesity, dyslipidemia, hypertension, ischemic heart disease, Type 2 diabetes, and polycystic ovarian syndrome (PCOS) in adults. Thrifty phenotype hypothesis suggested that in a nutritionally deprived environment, the fetus undergoes intrauterine programming and channels the nutrient resources toward the development of vital organs like brain at the expense of other organs like beta cell islets.[18,19] The response to these adaptations in later life is based on an environmental mismatch with respect to the nutritional availability and requirement. The intrauterine programming in a nutritionally challenged environment provides a survival advantage in a nutrient-deficient extrauterine environment and becomes detrimental in a nutrient-rich environment. Hence, there is a developmental plasticity by which a single genotype may give rise to different phenotypes by adjusting their phenotype to match the environment they have to survive in.[20,21]

The complex interactions of environment and nutrition with maternal and fetal genotypes influence maternal and fetal well-being. We also do know that nutrition, stress, and other environmental factors can modify the epigenome. There are excellent review articles published recently which highlight the relationship between epigenetic changes and metabolic diseases like insulin resistance, obesity, hypertension, and cardiovascular disease. Twin studies have revealed that the heritability of birth weight may range from 30 to 70%.[22] The Avon Longitudinal study of Parents And Children (ASPLAC), which was a longitudinal study of pregnancy and childhood, reported a mitochondrial variant associated with thinner babies at birth. Interestingly, the same babies had increased postnatal weight gain.[23]

The two key concepts to be considered while discussing the genetic factors influencing birth weight and postnatal metabolic diseases are epigenetics and genomic imprinting. Epigenetics is defined as the study of heritable changes other than those in the DNA sequence that encompass two major modifications of DNA or chromatin namely DNA methylation, the covalent modification of cytosine, and post-translational modification of histones including methylation, acetylation, phosphorylation, and sumoylation.[24] The epigenetic modifications can influence the selective expression of maternal and paternal alleles. This process of silencing one parental allele is called genomic imprinting.

DNA methylations are instrumental in long-term silencing of gene expressions. On the other hand, histone modifications may be short standing and flexible.[25] Gametogenesis studies reveal a differential methylation, which is before birth in the male germ line and after birth in the female germ line.[26,27] In a recent article, Gluckman has reviewed the genetic machinery of the epigenetic modification of gene expression.[25] In an active gene, the CpG dinucleotides in the gene promoter area are unmethylated, which gives the transcription factors and RNA polymerase a free run and exon transcription will occur [Figure 1]. In the presence of DNA methyltransferases (DNMTs), methylation of CpGs occurs, which in turn leads to the binding of methyl CpG binding protein 2. These events bring forward the histone modifying enzymes (HMEs), namely, the histone deacetylase and histone methyltransferase, which deacetylates the histones and methylates the lysine residues, respectively. The end result is a conformational change in the chromatin strand which prevents the action of transcription factors and RNA polymerases. An inactive state ensues, which results in silencing of DNA.

There are many animal models illustrating how specific environmental situations induce epigenetic modifications, like agouti viable yellow ($a^{vy}$) mouse. Hypermethylation of

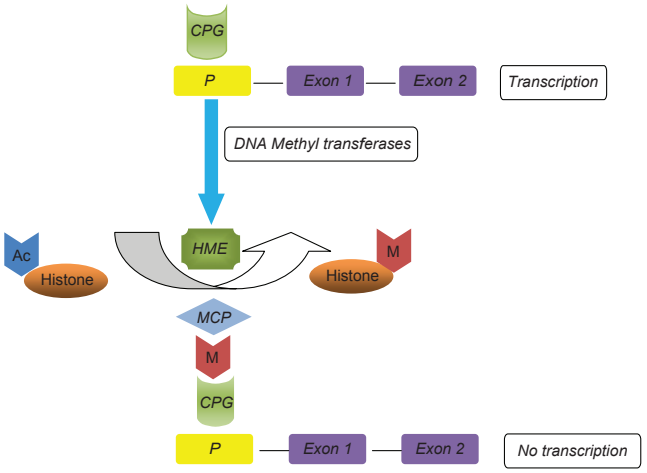


**Figure 1:** Epigenetic modifications and gene expression. TF: Transcription factors, P: Promoter, HME: Histone modifying enzymes, M: Methyl group, Ac: Acetyl group, MCP: Methyl CPG binding protein

the gene promoter decreases agouti expression which by its effects on hypothalamus gives rise to mice with normal weight and brown coat color. Agouti-related protein is an orexegenic peptide which plays an important role in hypothalamic control of feeding behavior. Hypomethylation results in increased agouti gene expression and mouse develops obesity and yellow colored coat. Hypomethylation occurs with maternal deficiency of methyl donors and cofactors like folate, while hypermethylation can be induced by maternal intake of soy isoflavone genistein.[28,29]

In another animal model, pregnant rats were given a low-protein diet. Low-protein diet induced promoter hypomethylation of peroxisome proliferator-activated receptor (PPAR)α and was associated with decreased methylation of CpG dinucleotides. This modification resulted in overexpression of PPARα receptors in the offspring.[30] In the adipose tissue, there was a decreased expression of PPARγ2 receptors. PPARα and γ receptors are involved in fatty acid oxidation and regulation of insulin sensitivity. These epigenetic modifications can result in increased triglycerides and nonesterified fatty acids in offspring, and finally insulin resistance.[31] Histone modifications and promoter hypomethylation result in overexpression of the hepatic glucocorticoid receptors. In the liver, increased glucocorticoid activity can induce phosphoenol pyruvate kinase expression which induces gluconeogenesis.[32] The pancreatic growth factor insulin-like growth factor 2 (IGF2) was shown to be reduced in neonatal rats when mothers were exposed to low-protein diet. In fact, taurine deficiency was also proposed to play a role.[33,34]. Low-protein diet also reduced the methylation of the promoter gene of type 1B adrenal angiotensin receptor and in turn overexpression of the receptor. Constellations of these changes are known to produce hypertension and endothelial dysfunction in the offspring.[25,35] In a recent article, Simmons reviewed the epigenetic modifications in intrauterine growth retardation (IUGR) islets.[36] In normal pancreatic β cells, the promoter for Pdx1 is in an unmethylated open chromatin state, which in turn promotes USF-1 and is associated with acetylated H3, H4, and trimethylated H3K4. In IUGR islets, mSin3A–HDAC1–DNMT1 repressor complex is recruited with gradual loss of histone acetylation and trimethylated H3K4. On the other hand, dimethylated H3K9 starts appearing from birth. When one looks at the IUGR adult islets, there is an inactive chromatin with dimethylated H3K9 and high DNA methylation which is not conducive for transcription and hence *pdx* gene is silenced. A key initiator in this methylation process could possibly be the oxidative stress found in IUGR.[37,38] GLUT-4 expression has also been examined in IUGR subjects. IUGR increases MEF2D binding to GLUT-4 promoter which is an inhibitor and decreases MEF2A and MyoD (activator and co-activator, respectively) binding to the GLUT-4 promoter in skeletal muscle tissue, which in turn promotes insulin resistance.[39]

Genomic imprinting also plays a role in epigenetic modifications. *IGF2* gene is imprinted and plays a major role in placental nutritional transfer. Placental insufficiency can decrease the production of pancreatic transcription factor product of pdx1 by CpG methylation in animals and they can develop diabetes at a later date.[40] *IGF2* polymorphisms are known to influence adult height.[41] The role of genomic imprinting in birth weight can be understood by studying two fetal growth disorders associated with 11p15 *H19/IGF2* imprinted domain. Methylation of this imprinting region can result in silencing of *H19* and the expression of *IGF2*, and if methylation does not occur, silencing of *IGF2* and the expression of *H19* is the result. Normally methylation occurs in the male germ line and is prevented in the female germ line. Absent DNA methylation in the paternal allele leads to biallelic expression of *H19* with silencing of *IGF2*, which in turn results in IUGR and Russell Silver syndrome. On the other hand, a gain of DNA methylation on the maternal allele results in silencing of *H19* and biallelic expression of *IGF2* with fetal overgrowth and Beckwith–Wiedemann syndrome.[20] In fact, several imprinting disorders including Beckwith–Wiedemann is more commonly seen associated with assisted reproductive technology as a result of epigenetic changes.[42]

Epidemiological studies have recorded a subnormal mitochondrial function in patients with hypertension and diabetes. Since mitochondrial DNA is inherited from the mother, it may be a player that determines the transfer of maternal nutritional stress to fetus. So it is not surprising that mitochondria contributes to thrifty phenotype.[43] The

central mechanism here is possibly free radical induced mitochondrial DNA damage. Studies have associated IUGR with increased oxidative stress in fetus.[44,45] Reactive oxygen species (ROS) can induce several intramitochondrial changes like shutting down of mitochondrial energy production and various other cellular changes.[36] An apt example of free radical induced mitochondrial damage occurs in β cell. The β cells have a high oxidative energy requirement for their normal function. The antioxidant machinery of β cell is suboptimal, which makes it more prone for free radical induced injury.[46] Islets affected by IUGR have increased oxidative stress secondary to increased ROS production. Complexes I and III of the electron transport chain are shown to function below par. IUGR is associated with decreased mitochondrial gene content and progressive damage of the mitochondrial DNA content with free radicals.[38,47] These dysfunctions can manifest functionally as decreased glucose-mediated insulin secretion and cell death, with diabetes as the end result.[48,49]

Human studies, though few, are also remarkable in showing the effect of nutritional modification of epigenome. In a study by Yajnik *et al.*, increased insulin resistance was observed in children whose mothers were vitamin B12 deficient with folate sufficiency. In fact, folate levels during pregnancy were positively associated with child's adiposity and insulin resistance, while vitamin B12 levels negatively correlated with the same.[50] These findings demonstrate the power of methyl donors and their cofactors to change the epigenome and ultimately affect the adult phenotype. In subjects with hyperhomocysteinemia, *S*-adenosylhomocysteine, an inhibitor of DNA methyltransferases, accumulates. This leads to lower levels of DNA methylation and a shift from monoallelic to biallelic expression for some imprinted genes (including *H19*). Folate supplementation normalizes DNA methylation levels and restores monoallelic expression of the *H19* gene.[51] There is evidence that tells us that the effect of nutritional modifications can persist through a number of generations despite nutritional correctional measures.[52]

## Socioeconomic Factors in India Pertaining to Developmental Origins of Adult Disease

India is rapidly undergoing a demographic, economical, and health transition as it is advancing through the 21st century. There is a reduction in the crude death rate, birth rate, infant mortality rate and there is an increase in the population of age group between 15 and 59 years. There is also a steady increase in per capita income, with reduction of poverty. The rural urban migration has resulted in a steady growth of urban population and creation of megacities. The maternal and perinatal problems in India are still high and non-communicable diseases like diabetes and cardiovascular disease are rapidly increasing.[53]

Over the years, there has been a relative decrease in the cost of the cereals. However, consumption of cereals has not increased except in the lowest income group. Rural populations consume more cereals, fewer pulses, and less oil, fat, and sugars, compared with urban populations. With the advent of fast food operators with high-energy density food and sedentary lifestyle in urban population, obesity is on the rise.

Osmani and Sen have discussed the hidden penalties of gender inequality on fetal origins of adult disease in an excellent review.[54] In the developing countries and especially in India, gender inequality influences birth rate, mortality, and male female ratio which is steeped against female gender. It is no secret that the poor health of mother adversely influences fetal health. The world is moving through an epidemiological transition by which mortality and morbidity through infectious diseases are decreasing while the mortality and morbidity due to non-infectious diseases are slowly increasing. In India, there is a paradox and the population suffers from high incidence of infectious and non-communicable diseases.

Statistical evidence shows that though girls and boys have similar nutrition at birth, as they grow up, an inequality creeps in with girls falling behind boys. As these girls reach the reproductive age group, they suffer from undernourishment and anemia. Multiparity and relatively young age at the time of marriage also contribute to the low birth weight of children born to these mothers. It is not surprising that children born to these women have low birth weight. If undernutrition persists during childhood, it puts the patient at high risk for infectious diseases. However, the economic and social transition combined with relative nutritional affluence during childhood puts these patients at risk for obesity, CAD, and insulin resistance, as adults.

## Intrauterine Growth Retardation and Catch-up Growth

Various studies across the globe have shown that excessive postnatal weight gain can have additional adverse influences on adult health. Considerable body of evidence has come from studying and following up children who were born short for gestational age (SGA). Most of these children exhibit good catch-up growth in the initial few years of

life, while some of them have a smaller degree of catch-up growth and remain short.[55] SGA children have elevated levels of growth hormone,insulin like growth factor binding proteins 1 and 2 (IGFBP1, and IGFBP2), with low levels of IGF-1 and IGFBP3, which is a pattern consistent with growth hormone insensitivity and insulin resistance.[56-58] In most of these children, growth hormone dynamics normalizes in the initial few months of life.[59] SGA children who have weight gain are at risk of developing insulin resistance, PCOS, premature adrenarche during adolescent period, and hypertension, diabetes, and cardiovascular disease in adulthood.[60,61] The abdominal adipose tissue of these infants shows resistance to the actions of insulin and catecholamine hyperresponsiveness.[62,63] Low birth weight may be associated with decreased number of glomeruli, which when exposed to hyperfiltration associated with weight gain can accelerate glomerulosclerosis and contribute to hypertension.[64] Pro12Ala polymorphism of the *PPARγ2* gene has been shown to increase the risk of type 2 diabetes in IUGR patients.[65] It is important to note that those infants who do not have significant catch-up growth are not at risk for most of these diseases.[66]

In the Pune Maternal Nutrition Study,[67] Indian babies were found to be lighter, shorter, and thinner, compared to British babies. However, there was a relative preservation of subscapular fat and a paucity of non-adipose tissue. In another study by the same group, the cord leptin concentrations in the British babies and Indian babies were found to be similar despite the fact that Indian babies were thinner and lighter.[68] These findings suggest a higher adiposity in the Indian babies, paving way for the concept of thin fat Indian baby. Yajnik and group also studied body size, glucose tolerance, insulin resistance, and cardiovascular risk factors in children. At 4 years of age, glucose, insulin, and IGF-1 levels were inversely related to birth weight after considering the effect of current weight.[69,70] However, they also found that growth velocity of children from 4 to 8 years was a stronger predictor of insulin resistance and cardiovascular risk than measurements at 8 years.[71] These concepts become important in children undergoing rural to urban migration, adoption, and those stepping up on the economic and affluence ladder, which ultimately increases nutritional availability.[72]

Although majority of the evidence points out insulin resistance as the primary pathology behind diabetes in children with IUGR, some evidence also points toward decreased insulin secretion. Studies have thrown mixed results with some showing an association between low birth weight and defective insulin secretion while others not showing a similar association.[71,73] An earlier study reported that the pancreatic β cell number was reduced in infants with IUGR.[74] In an interesting experiment, insulin secretion and insulin sensitivity of young men, who were small for gestational age, was compared to controls, taking care to eliminate confounders. Although insulin sensitivity was normal, insulin secretion was decreased by 30% when controlled for insulin sensitivity. Hence, it is also possible that there is an insulin secretory defect compounded by insulin resistance, which comes into play when they accumulate body fat.[75]

The adaptational response in a fetus to a nutritionally challenging environment is preservation of its vital organ function, namely the brain, at the expense of other organs in the body.[76] The mechanisms by which the fetus achieves this include blood and nutritional diversion to the brain, along with insulin and growth hormone resistance in the periphery. Starvation or nutritional deficiency is associated with reduced basal metabolic rate (BMR). If energy is stored when BMR is low, there is a relative preference to fat storage. The insulin resistance associated with reduced lean muscle mass along with hyperinsulinemia directs the excess glucose toward fat storage in adipose tissue.[77-79] Though fat can act as an energy reservoir for vital organ functions, in a nutritionally rich environment with limited energy expenditure, fat deposition occurs. This fat deposition promotes insulin resistance, inflammation, and finally diabetes and coronary vascular disease.[72] Haguenau cohort of SGA and Appropriate for gestational age (AGA) subjects looked at metabolic syndrome components at 22 years of age. Metabolic syndrome was six times more common in SGA individuals when compared to AGA individuals.[80]

## Role of Hormonal Adaptations

Last few decades have shown a high activity in decoding molecular and cellular mechanisms underlying DOAD.[81] The hormonal programming concept points out that an adverse intrauterine environment leads to metabolic and endocrine adaptations programmed toward energy conservation. These adaptations prove counterproductive in adulthood as the body finds it difficult to adjust to a nutritionally enriched environment and excess nutrients become deposited as adipose tissue. Abnormalities in GH-IGF axis have already been described in an earlier part of the article.

Experimental studies in animals have shown that those that are born small are prone to adult-onset hyperglycemia, blood pressure, anxiety, and increased hypothalamic pituitary adrenal (HPA) axis activity.[82,83] However, the HPA axis activity may vary depending on the sex of the fetus, and time and nature of the stimulus.[84,85] Placental

corticotropin-releasing hormone (CRH), sympathoadrenal system, and glucocorticoid and mineralocorticoid receptors in the hippocampus and other areas of brain are supposed to play a role in the programming of HPA axis.[84] One of the key regulators of fetal cortisol levels is placental 11 Beta Hydroxy Steroid Dehydrogenase 2 (11βHSD2) enzyme which converts cortisol to cortisone and keeps fetal cortisol levels at a lower level. Studies have demonstrated that 11βHSD2 levels are low in IUGR and preeclampsia.[86,87] Preeclampsia and early-onset adiposity have been associated with PCOD and hyperandrogenism.[88,89] High morning cortisol levels are seen in adults who are born as preterm or with low normal gestational age.[90,91] It is interesting that different, but normal environmental changes can result in individual variations of HPA axis to stress.[92] Studies using stimulated cortisol have shown an association between low birth weight and hyperactive HPA axis, with adult cardiovascular disease, glucose intolerance, and higher systolic and diastolic pressures.[93-95]

Recent researches have brought out an exciting interplay of adipocytokines and subsequent development of adult disease in IUGR. Most studies have demonstrated a low leptin levels in neonates with IUGR.[81,96] Subsequently, when they progress to childhood and adulthood, the leptin levels are higher compared to normal cohort. This leptin resistance may be an adaptive response which may serve as a stimulus for food intake and promote catch-up growth.[97] Studies examining adiponectin levels have failed to show any significant differences between IUGR neonates and normal cohort, although conflicting reports exist.[98-100] However, SGA infants show a shift to a higher molecular form adiponectin, which is more related to insulin sensitivity. The idea behind this shift is an enhancement of insulin sensitivity and promotion of neonatal catch-up growth.[101] Ghrelin can stimulate appetite and promote growth hormone secretion. Ghrelin levels are elevated in IUGR, which again may help in postnatal catch-up growth.[102,103] Other adipocytokines under active investigation for their role in IUGR and subsequent adult-onset adiposity and insulin resistance include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), resistin, apelin, and visfatin.[81]

## Maternal Obesity and Diabetes

Current evidence points toward the fact that maternal diabetes predisposes to adult-onset obesity and diabetes in the fetus even after other influencing factors are adjusted for. Evidence for the influence of intrauterine metabolic derangements secondary to maternal diabetes comes from the study on Pima Indians. Children born to mothers who were diabetic at the time of pregnancy were found to be more obese than their siblings who were born before the onset of diabetes.[104] It was also seen that diabetes was more common in children who were born to mothers who had diabetes at the time of pregnancy when compared to infants who were born to mothers who did not have diabetes at the time of pregnancy, though they developed diabetes subsequently.[105] Infants with high birth weight are also prone to develop obesity and insulin resistance later in life.[106] A study by Yajnik *et al.* showed that higher birth weight in children was associated with adiposity in the parents and metabolic syndrome in mother 8 years after the child birth.[107]

Even obese women with normal glucose tolerance were shown to beget babies who had increased percentage of body fat.[108] So, how does this happen? The metabolic abnormalities that are present in the obese and diabetic mothers are transferred to the fetus during intrauterine period, conferring a risk of subsequent obesity.[109] Multiple pathways including upregulated placental transporters and altered fetal gene expression are proposed.[110] Another interesting mechanism is probably early-onset endothelial dysfunction. Studies have shown that the levels of endothelial progenitor cells are reduced in neonates born to mothers with type 1 diabetes mellitus.[111] Endothelial progenitor cells play an important role in vascular repair and neovascular formation, and endothelial dysfunction plays a pivotal role in the development of cardiovascular diseases.[112,113] Existing literature gives us some insight on islet cell function in an environment of hypercholesterolemia. Hypercholesterolemia has been shown to induce islet cell apoptosis and glucokinase downregulation, resulting in decreased insulin secretion.[114,115] Further studies are required to highlight the effects of hypercholesterolemia and a nutrient-rich environment on fetal insulin secretion.

## Conclusion

The alarming rise in diabetes and other communicable diseases has necessitated a focus shift from treating the non-communicable diseases to their prevention. There is enough evidence at present to demonstrate an intrauterine origin of communicable diseases. The mysteries behind these intrauterine origins are solved by current understanding of epigenetic modifications and hormonal adaptations. The future research on fetal origins of adult disease needs to be focused on expanding our current knowledge on molecular mechanisms. Ultimately, the horizon may open up preventive nutritional modifications with genomic and hormonal targets for disease prevention.

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