Asian Journal of Medicine and Health

Volume 22, Issue 9, Page 123-141, 2024; Article no.AJMAH.122452
ISSN: 2456-8414

Epigenetic Pathways Linking Fetal Development to Metabolic Syndrome: Mechanisms and Implications

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Authors' contributions

This work was carried out in collaboration among all authors. Author BSO conceptualized the study and supervised the work, wrote and prepared the original draft of the manuscript. Authors BSO, LOH and AGO did validation. Authors LOH and AGO wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajmah/2024/v22i91097

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/122452

Review Article

Received: 02/07/2024
Accepted: 04/09/2024
Published: 17/09/2024

ABSTRACT

This review explores the intricate connections between early developmental environments, epigenetic mechanisms, and long-term health outcomes. The concept of fetal programming highlights how maternal stress, nutrition, and other environmental factors during embryonic and

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Cite as: *Olateju, Bolade. S., Lawal Olajumoke Habeebat, and Ayilara Gideon Opeyemi. 2024. "Epigenetic Pathways Linking Fetal Development to Metabolic Syndrome: Mechanisms and Implications". Asian Journal of Medicine and Health 22 (9):123-41. https://doi.org/10.9734/ajmah/2024/v22i91097.*

fetal development can induce physiological changes with persistent effects extending into adulthood and across generations. Evidence suggests that these early life exposures can lead to complex diseases such as cardiovascular conditions, diabetes, and metabolic syndrome. The role of epigenetic modifications—particularly DNA methylation and histone modifications—is emphasized as a crucial mechanism through which environmental factors influence gene expression and disease susceptibility. Additionally, this review discusses the significance of sex-specific epigenetic marks and their impact on disease risk, illustrating how sex chromosomes and fluctuating sex hormones contribute to sexual dimorphism in disease prevalence. The need for further research is underscored, with a focus on understanding the factors that shape fetal growth trajectories, the mechanisms by which nutrients and hormones alter gene expression, and the barriers to healthy eating among women. Addressing these issues is vital for reducing chronic disease prevalence and improving public health across generations.

Keywords: Fetal programing; maternal malnutrition; DNA Methylation; epigenetics; intrauterine environment; early life exposure.

1. INTRODUCTION

Fetal programming, also known as prenatal programming, refers to the phenomenon where environmental conditions during critical periods of embryonic and fetal development are linked to an increased risk of diseases later in life [1,2,3]. The core concept of fetal programming is that environmental events can alter crucial physiological parameters during embryonic and fetal development, with these alterations potentially persisting into adulthood and even impacting subsequent generations, thereby leading to trans-generational non-genetic disorders [4,3].

Fetal development is a highly complex process [1], and each stage can be influenced or modified by specific environmental factors [5]. Some of the changes induced by these external factors may have lifelong effects [2]. The local cellular environments within the fetus can alter gene expression during the formation of tissues and organs, leading to long-term consequences for the functioning of these tissues and organs throughout childhood and adulthood [2].

Various factors, such as altered nutrition or maternal stress, can influence fetal programming. The effects of these factors may not be immediately apparent but can manifest later in life [3]. Numerous studies suggest that early-life events play a crucial role in determining susceptibility to certain chronic diseases later in life [1,4,6,7]. These events can include over- or under-nutrition, exposure to environmental toxins, or hormonal changes, particularly stress hormones in the pregnant mother [4,6]. Recent research indicates that paternal environmental or nutritional factors can also affect the offspring's phenotype [3,8]. Maternal environmental factors influence the offspring's phenotype through epigenetic modifications of the genome [3]. For instance, studies have shown a strong association between impaired intrauterine growth and adult metabolic and cardiovascular disorders such as coronary heart disease, type 2 diabetes, and insulin resistance [4,9,10].

Clinico-epidemiological evidence points to a close interaction between the fetal and maternal environment, which modulates gene expression from very early in life and can be passed across generations [11,6,12]. Consequently, the concept of epigenetic modifications, such as DNA methylation and covalent post-translational histone modifications, has emerged as the most plausible molecular explanation for fetal metabolic programming, mediating phenomena like genomic imprinting and chromatin remodeling [11,6].

2. FETAL PROGRAMMING HYPOTHESIS

The fetal period is marked by significant neurological changes, and experiences during this time can have a profound impact on development. The fetal programming or developmental origins of disease models suggest that organisms are particularly vulnerable to environmental influences during periods of rapid development or change, and these influences can have lasting effects on health and disease risk [13,1]. The fetal programming hypothesis, which relies on the ability to study individuals throughout their entire lifespan, has a fascinating origin. Empirical support for this hypothesis partly stems from an intervention initiated by the British government in the early 1900s [14].

2.1 Barker's Hypothesis

At the beginning of the 20th century, the British government grew concerned about the declining health of the population and the poor health of young men attempting to enlist in the army. In response, they implemented a progressive intervention. Ethel Margaret Burnside was appointed as the country's first "chief health visitor and lady inspector of midwives." She led a team of nurses who traveled across the country to advise mothers on infant care. One remarkable outcome of this initiative was the meticulous record-keeping related to infant birth weights and their growth during the first postnatal year [15].

More than 60 years later, Dr. David Barker linked these birth records to death records, leading to a groundbreaking observation: a disproportionate number of deaths from coronary heart disease occurred among individuals with low birth weight [15]. This finding has since been corroborated by other epidemiological studies (e.g., Wang et al. [16]. Birth size has been found to predict a variety of later health outcomes, including heart disease, diabetes, obesity, and psychiatric disorders [15,17], underscoring the importance of considering fetal origins in the context of later health and disease.

Barker's "fetal origins" hypothesis proposed that alterations in fetal nutrition and endocrine status lead to developmental adaptations that permanently alter structure, physiology, and metabolism, thereby increasing the risk of cardiovascular, metabolic, and endocrine diseases in adulthood [13]. For example, it is believed that coronary heart disease may result from fetal adaptations to under-nutrition, which are advantageous for short-term survival but detrimental to health in post-reproductive life [13].

During fetal life, the body's tissues and organs undergo "critical" periods of development, often coinciding with rapid cell division. Similar to other living creatures, humans are "plastic" in their early life and are shaped by their environment [18]. Although fetal growth is influenced by genetics, studies in both humans and animals suggest that it is typically constrained by environmental factors, particularly the nutrients and oxygen supplied by the mother [18]. There may be evolutionary advantages to the body remaining plastic during development, rather than being solely driven by genetic instructions acquired at conception [19].

Experimental studies in animals have provided numerous examples of fetal programming. Recent research has shown that changes in maternal nutrition can have long-term effects on offspring, relevant to human cardiovascular disease [20]. For instance, feeding pregnant rats a low-protein diet results in lifelong elevated blood pressure in their offspring [21]. Additionally, rats whose mothers were fed a diet with a low protein-to-energy ratio during pregnancy exhibited a permanently altered balance between hepatic glucose production and utilization [22]. Other significant long-term effects of altered maternal nutrition include changes in cholesterol metabolism, insulin secretion, and renal development [13].

While some nutritional effects may result directly from changes in substrate availability, many are thought to be mediated by hormonal influences [13]. These hormonal effects may alter the development of specific fetal tissues during critical periods or lead to long-lasting changes in hormone secretion or tissue hormone sensitivity. Experimental studies have identified the fetal hypothalamus as a key site that can be programmed by transient changes in prenatal endocrine status [23].

3. EXAMPLES OF FETAL PROGRAMMING

3.1 The Dutch Hunger Winter

Some of the most compelling evidence for fetal programming of adult disease comes from long-term follow-up studies of survivors of the Dutch "Hunger Winter." During the Nazi occupation of the Netherlands in the winter of 1944–1945, a severe famine struck the western Netherlands due to a German embargo on rail transport combined with a harsh winter. For approximately nine months, a significant portion of the Dutch population survived on less than 1,000 calories per day, leading to widespread starvation [24].

The famine ended abruptly with the Allied liberation of the Netherlands in the spring of 1945, providing a unique opportunity to study the consequences of nutritional deprivation during pregnancy. Because the famine was limited in time and place, researchers could assess the long-term effects on fetuses exposed during specific gestational periods [18]. The national registries in the Netherlands allowed for comprehensive long-term and intergenerational

assessments of the consequences of fetal exposure to this famine.

Research findings from this extensive body of literature indicate that while many immediate effects of maternal malnutrition on newborns, such as birth weight, were not strongly predictive of later outcomes, significant latent effects were observed [25]. Adults who had been exposed to the famine in utero exhibited a significantly higher risk for various physical and mental health issues, including adult obesity, diabetes, heart disease, and schizophrenia, compared to those whose pregnancies were not affected by the famine or to same-sex sibling controls [26,25].

Many of these later outcomes are consistent with adult metabolic disorders, where biological systems function maladaptively, increasing cardiovascular risk. It seems that the period of early malnutrition led to biological adaptations in the fetus, such as decreased energy metabolism and growth rate, to prepare for a postnatal life of food scarcity [18]. However, when these children grew up in conditions of adequate food availability, their physiological systems were not adapted to this environment, contributing to the development of later health problems [27].

3.2 Ramadan Fasting

During Ramadan, which follows the lunar cycle, many Muslims worldwide participate in fasting during daylight hours [28]. This fasting typically involves abstaining from food and drink during the day throughout the lunar month. While certain groups, such as the young, sick, and elderly, are automatically exempt from fasting, pregnant women are not officially included on the exemption list, though they are often granted exemption [29]. Despite this, the majority of pregnant women choose to fast, despite the potential stress associated with this cultural and religious practice [29].

The available data on the effects of Ramadan fasting during pregnancy is limited and shows conflicting results [30,31,32,33]. The sample sizes of these studies are not large enough to provide definitive conclusions [30,31,32,33]. However, Almond and Mazumder [34] indicated that pregnancies exposed to Ramadan fasting may be more susceptible to low birth weight. Furthermore, a study by Dikensoy et al. [35] linked Ramadan fasting to elevated cortisol levels, though Riat et al. [36] noted that cortisol levels during fasting depend on the timing of measurement. The timing of nutritional deficiencies in pregnant mothers has been shown to play a critical role in long-term health outcomes for children exposed in utero, leading to increased risks of chronic illness in adulthood [37,38,39]. Specifically, fasting during the first trimester has been associated with low birth weight and placental weight [38,39]. However, a systematic review by Oosterwijk et al. [40] concluded that there is not strong evidence to support an association between Ramadan fasting and adverse health outcomes in offspring.

Research has also explored the impact of Ramadan fasting on male birth rates. Some studies suggest that Ramadan fasting may negatively affect male birth rates, leading to a skewed sex ratio at birth. Exposure to Ramadan fasting a month after conception is associated with a 13% decline in total births, with male birth rates dropping by 26% compared to a 2.5% drop in female birth rates, suggesting a potential "male vulnerability" [34].

In a study by Almond and Mazumder [34] conducted in Uganda and Iraq, it was found that individuals exposed to Ramadan fasting in utero had significantly higher rates of disability when controlling for other factors. Although the definition of disability varies by country, the impact of exposure is still evident [34]. For those born nine months after Ramadan, the likelihood of disability was notably higher than in the general population. In Uganda, where the national average disability rate is 3.8%, the rate for those exposed in utero jumps to 22%. Similarly, in Iraq, the average disability rate is 1.5%, but for those exposed during gestation, it rises to 23% [34]. Additionally, those born nine months after Ramadan were 33% more likely to be blind and 64% more likely to be deaf than those not exposed in utero. The effects of Ramadan fasting exposure extend to mental disorders as well. In Uganda, exposure early in pregnancy doubled the likelihood of cognitive disorders, while in Iraq, there was a 63% higher likelihood of cognitive disorders among those exposed compared to the national average [34].

Almond et al. [41] also observed that exposure to Ramadan fasting in utero resulted in slightly lower academic performance in offspring. Specific health effects have been noted for those exposed to fasting in utero. For example, kidney damage, which can lead to anemia, was more prevalent among adult females who were exposed to fasting during mid-gestation, while

other points in gestation showed insignificant effects [42].

4. MATERNAL NUTRITION AND FETAL DEVELOPMENT

Nutrition is the primary intrauterine environmental factor that influences the expression of the fetal genome and can have lifelong consequences. Maternal nutrition is crucial for proper fetal growth and development. Despite significant efforts to define the nutrient requirements of animals over the past 30 years, suboptimal nutrition during gestation remains a prevalent issue for many species, including cattle, pigs, and sheep, worldwide [43]. In the last decade, compelling epidemiological studies have linked intrauterine growth restriction (IUGR) to the development of various chronic diseases in adult humans and animals [44,45].

4.1 The Intrauterine Environment as a Major Factor Contributing to IUGR.

Intrauterine growth restriction (IUGR) is influenced by a combination of genetic and environmental factors. While the fetal genome plays a significant role in determining growth potential in utero, increasing evidence indicates that the intrauterine environment is a critical factor in fetal growth. For instance, embryo-transfer studies have demonstrated that the recipient mother, rather than the donor mother, has a stronger impact on fetal growth [46]. Additionally, there is evidence suggesting that the intrauterine environment of the individual fetus may be more influential in the development of chronic diseases in adulthood than the fetus's genetics [47].

4.2 Under-nutrition and Intrauterine Growth Restrictions (IUGR)

Available evidence indicates that fetal growth is most susceptible to maternal dietary deficiencies, such as inadequate protein and micronutrient intake, during the peri-implantation period and the phase of rapid placental development. Grazing ewes that do not receive dietary supplements experience substantial weight loss during pregnancy, which adversely affects their health, fetal growth, and lactation performance [48]. In pigs, an uneven distribution of nutrients along the uterine horn results in 15–20% of piglets being born with low birth weight (<1.1 kg), which significantly hampers their postnatal survival and growth performance [49]. Consequently, the suboptimal performance of certain livestock during postnatal growth and finishing phases may be linked to growth restriction experienced in utero.

In pregnant women, undernutrition can arise from inadequate intake of dietary nutrients, whether due to limited food availability or severe nausea and vomiting, a condition known as hyperemesis gravidarum. This life-threatening disorder affects 1–2% of pregnancies and typically persists beyond the 16th week of gestation [50]. Pregnant women may also face a higher risk of undernutrition due to early or closely spaced pregnancies [51,52]. Adolescent mothers, who are still growing themselves, compete with their fetuses for nutrients, while short inter-pregnancy intervals can lead to maternal nutritional depletion at the start of pregnancy. Birth weights and preterm deliveries in adolescent pregnancies occur more than twice as often as in adult pregnancies, and neonatal mortality in adolescent pregnancies is nearly three times higher compared to adult pregnancies [53,54]. Additionally, placental insufficiency reduces the transfer of nutrients from mother to fetus, resulting in fetal undernutrition and intrauterine growth restriction (IUGR).

Finally, due to nutrient competition, multiple fetuses resulting from assisted reproductive technologies are often at risk of undernutrition and consequently fetal growth restriction [55]. Thus, various nutritional and pathological conditions can lead to IUGR.

4.3 Over-nutrition and IUGR

Significant health issues for animals, particularly companion animals, as well as women of reproductive age, are often associated with being overweight or obese due to overeating. Over-nutrition, characterized by excessive intake of energy and/or protein, can have detrimental effects. Wallace et al. [56] highlighted that extensive research has shown maternal over-nutrition impedes placental and fetal growth and increases both fetal and neonatal mortality in rats, pigs, and sheep. Many overweight and obese women unknowingly enter pregnancy and continue to overeat during gestation. These women typically experience more weight gain during their first pregnancy and accumulate additional fat in subsequent pregnancies. This over-nutrition, whether occurring before or during pregnancy, frequently leads to maternal obesity,

which in turn results in fetal growth restriction and an elevated risk of neonatal mortality and morbidity [57].

5. BIOCHEMICAL MECHANISMS OF IUGR

The lack of understanding regarding the mechanisms of intrauterine growth restriction (IUGR) has hindered the development of effective therapeutic options, resulting in the current management of growth-restricted infants being largely empirical and focused primarily on determining a safe time for delivery. Since nutritional and developmental research often requires invasive tissue collections and surgical procedures, it is neither ethical nor practical to perform these experiments on human placentas and fetuses. Consequently, animal models such as mice, rats, pigs, and sheep are crucial for elucidating the mechanisms of IUGR and for developing therapeutic strategies. Evidence, discussed in the following sections, indicates that arginine, a nutritionally essential amino acid for the fetus [58], plays a significant role in the development of the conceptus, including the embryo/fetus, associated placental membranes, and fetal fluids.

5.1 Molecular Mechanisms of Fetal Programming

Nutritional insult during a critical period of gestation may leave a lasting “memory” throughout life, with some effects, such as insulin secretion and action, potentially being gender-specific [59]. Increasing evidence suggests that maternal nutritional status can modify the epigenetic state of the fetal genome, influencing gene expression through epigenetic alterations. These alterations, which involve stable changes in gene expression through covalent modifications of DNA and core histones, may persist through subsequent developmental stages.

Epigenetic effects are mediated by two main mechanisms: DNA methylation and histone modification. DNA methylation occurs at the 5′-positions of cytosine residues within CpG dinucleotides across the mammalian genome and can regulate gene expression by affecting the binding of methyl-sensitive DNA-binding proteins, thus altering chromatin conformation. Histone modification, including acetylation and methylation, can influence gene expression by altering the interactions between histones and DNA, as well as the affinity of histone binding to DNA [60,61]. DNA methylation is facilitated by DNA methyltransferases, with S-adenosylmethionine (SAM) serving as the methyl donor. SAM is synthesized from methionine and ATP by methionine adenosyltransferase. The metabolism of one-carbon units, which relies on serine, glycine, and B vitamins (including folate, vitamin B-12, and vitamin B-6), plays a crucial role in regulating SAM availability. Consequently, the overall availability of amino acids and micronutrients can influence DNA methylation and histone modifications.

This concept is supported by several lines of evidence. For example, a deficiency in amino acids leads to a significant reduction in genomic DNA methylation and aberrant expression of the normally silent paternal H19 allele in cultured mouse embryos [62]. Additionally, uteroplacental insufficiency results in hypomethylation of the p53 gene in postnatal rat kidneys, as well as global DNA hypomethylation and increased histone acetylation in postnatal rat livers [63]. Furthermore, maternal supplementation with methyl donors and cofactors (such as folic acid, vitamin B-12, choline, and betaine) enhances CpG methylation at the Avy locus in agouti mice, with these methylation patterns being retained into adulthood [64].

It remains to be determined whether maternal nutrition affects CpG methylation of genes such as NOS, GTP cyclohydrolase I (the rate-limiting enzyme for BH4 synthesis), and ODC, or alters histone modifications in the uterus, placenta, and various fetal and postnatal tissues (e.g., vascular bed, adipose tissue, liver, kidney, skeletal muscle, or pancreas). Nonetheless, epigenetics may offer a molecular mechanism to explain how maternal nutrition influences fetal programming and postnatal disease susceptibility, as well as genomic imprinting.

6. FETAL PROGRAMMING AND ADULT HEALTH

The 'fetal origin of disease' hypothesis suggests that conditions such as hypertension, insulin resistance, and dyslipidemia in adulthood—leading to significantly increased rates of cardiovascular disease and non-insulin-dependent diabetes—can be traced back to adaptations made by the fetus in response to poor early life environments, including maternal under-nutrition or placental insufficiency [65]. These adaptations involve both functional and structural changes in the newborn that typically

occur during pregnancy, but can also develop in very early childhood [66]. Barker [66] argues that events occurring during critical early periods of life can lead to permanent alterations in organ structure and function in response to environmental factors, potentially resulting in cardiovascular, metabolic, and renal diseases later in life [65].

Maternal under-nutrition or abnormal uteroplacental function reduces nutrient delivery to the fetus, which may induce secondary adaptations in metabolism and gene expression. These adaptations might be beneficial during intrauterine life but could increase disease risk in later life [65]. Insulin resistance is a key factor in the development of metabolic syndrome and its associated conditions, such as cardiovascular diseases, hypertension, and type 2 diabetes [67]. It has been proposed that adverse early life events, particularly maternal undernutrition, may program insulin resistance, leading to cardiovascular diseases and diabetes in adulthood. This hypothesis has been supported by studies in humans from two independent populations with different genetic backgrounds and eating behaviors: Caucasians and Asians, with findings showing that low-birth-weight is not just a matter of weight but also involves disproportionate intrauterine growth due to brain sparing [68,69].

Subsequent research has established a strong correlation between fetal liver volume, gestational age, and fetal biometric parameters, such as abdominal circumference [70,71]. Reduced abdominal circumference is primarily indicative of reduced liver size. In animal models of intrauterine growth restriction (IUGR) induced by uterine artery ligation, low birth weight, reduced liver weight, and lower liver glycogen storage have been observed [72]. Tissue resistance to insulin, seen as a response to malnutrition, helps maintain blood glucose levels, particularly for the brain, but compromises glucose transportation to muscles and insulin-mediated growth. This mechanism may lead to elevated plasma glucose levels, even towards the end of pregnancy, in children with low birth weight [68,69].

Other mechanisms that link early life environmental conditions to lifelong functional and structural changes include glucocorticoid exposure due to 11 beta-hydroxysteroid dehydrogenase 2 deficiency in the placenta [73] and high protein diets during pregnancy [74]. Additionally, maternal cortisol secretion has been found to be inversely related to fetal brain growth [75].

6.1 Fetal Growth and Coronary Heart Disease

At the start of this century, the incidence of coronary heart disease (CHD) surged dramatically in Western countries, becoming the leading cause of death. This steep rise has recently been followed by a decline in many of these countries, a trend that cannot be fully explained by changes in adult lifestyle alone. Meanwhile, the incidence of CHD is increasing in regions such as China, India, and Eastern Europe, where Western influences are spreading [18]. A crucial clue suggesting that CHD may originate during fetal development emerged from studies on death rates among British babies in the early 1900s [13].

At that time, low birth weight was a common certified cause of death in newborns. The death rates varied significantly across different regions, being highest in northern industrial towns and poorer rural areas. This geographical variation in death rates closely resembled today's regional disparities in CHD mortality, reflecting part of the persistent north-south health divide in Britain [13]. This observation led to the hypothesis that low fetal growth rates might be linked to the development of CHD later in life. While previous suggestions focused on childhood events influencing CHD pathogenesis [76], this new focus on intrauterine life provided a novel research perspective.

Further evidence supporting the link between adverse intrauterine environments and long-term health outcomes came from follow-up studies of individuals whose birth measurements were recorded. In Hertfordshire, UK, it was found that those with low birth weights had increased mortality from CHD in adulthood [13,77]. Among 15,726 people born between 1911 and 1930, CHD death rates declined progressively with increasing birth weight for both men and women [13,77]. A slight rise in CHD death rates at the highest birth weights in men may be attributed to macrosomic infants born to mothers with gestational diabetes. Another study of 1,586 men born in Sheffield between 1907 and 1925 found that growth retardation at birth, rather than premature birth, was associated with a higher risk of CHD [78].

The UK findings have been widely replicated, leading to broad acceptance of the association between low fetal growth and adult CHD. For instance, studies involving 1,200 men in Caerphilly, South Wales, and 70,297 nurses in the United States have confirmed this link [79]. The latter study observed a two-fold decrease in the relative risk of non-fatal CHD across the birth weight range. Similarly, a study of 517 men and women in Mysore, South India found that the prevalence of CHD among those aged 45 and older dropped from 15% in those who weighed 2.5 kg or less at birth to 4% in those who weighed 3.2 kg or more [80].

6.2 Body Proportions at Birth and Cardiovascular Disease

The Hertfordshire, Nurses, and Caerphilly studies did not include measurements of body size at birth beyond weight, which offers only a rudimentary overview of an infant's physique. Incorporating birth length allows for the calculation of the ponderal index (birth weight/length^3), providing a measure of thinness, but it does not differentiate between variations in fat and lean mass. Adding head circumference helps identify "brain-sparing" effects, where the body and trunk are smaller relative to the head, indicating fetal adaptations to under-nutrition, hypoxia, and other influences, each with distinct long-term consequences.

In Sheffield, men with a shorter crown-heel length at birth had higher death rates from coronary heart disease [81]. Specifically, the mortality ratio for coronary heart disease in men measuring 18.5 inches (47 cm) or less in length was 138, compared to 98 in those of greater length (Martyn et al., 1996). Additionally, low ponderal index and thinness at birth were linked to increased coronary heart disease risk [81]. Although low birth weight was associated with higher death rates from coronary heart disease, thinness at birth, particularly in men born at term, showed a stronger association [82]. Men with a low ponderal index had death rates twice as high as those with a high ponderal index.

In Finland, elevated death rates from coronary heart disease were associated with low placental weight. Conversely, in Sheffield, the relationship between coronary heart disease and the ratio of placental weight to birth weight was U-shaped, with the highest mortality ratios at both extremes of the distribution. Thus, predictors of coronary heart disease include small head circumference, short stature, or thinness reflecting retarded fetal growth, alongside either low placental weight or an altered placental weight-to-birth weight ratio. For stroke, reported only in Sheffield, while low birth weight was associated with increased risk, thinness or shortness were not. Instead, increased stroke rates were observed among men with a low ratio of birth weight to head circumference or a low ratio of placental weight to head circumference [81]. This suggests that normal head growth may be achieved at the expense of body growth in late gestation, coupled with inadequate placental growth.

7. FETAL PROGRAMMING AND EPIGENETICS

All cells in the body contain identical genomes, but each cell harbors a unique epigenome, a set of epigenetic instructions that establishes and maintains lineage-specific gene expression profiles. The genome is programmed to express specific genes in particular tissues at designated times throughout an individual's life. Epigenetic events create a cellular memory that preserves genomic functions, including maintaining cell identity post-differentiation, propagating crucial features of chromosomal architecture, and ensuring dosage compensation [83]. Unlike genetic information, which is highly stable, epigenetic events are reversible and responsive to both endogenous and environmental signals [84]. Experimental evidence suggests that epigenetic marks can act as a memory of early-life exposure to inappropriate environments, potentially leading to long-term changes in gene expression and disease development later in life, a concept known as the developmental origin of health and disease (DOHaD) hypothesis [85].

Recent advances in analytic technologies have made epigenome characterization a crucial component of numerous studies [86,87,88,89,90,91]. New data challenge existing perspectives on the dynamics, relevant positions, and functions of various epigenetic marks and their intricate patterns of crosstalk. The reversibility of chromatin modification states, which influence gene expression, is fundamental to the interaction between the environment and the dynamic epigenome. Nonetheless, some epigenetic marks established early in development by environmental factors must remain stable to preserve a memory of the event long after the exposure has ended [84]. This paradox—the need for both reversibility and

stability in epigenetic marks—remains an area of ongoing investigation.

7.1 DNA Methylation Dogmas

Cytosine methylation is the only epigenetic modification that directly affects the DNA molecule. It is required for correct embryonic development in mammals. The DNA of most vertebrates is depleted in CpG dinucleotides, the main target of DNA methylation. Furthermore, the role of DNA methylation in genome regulation, other than in genomic imprinting and X inactivation, remains unclear [84]. CpG islands (CGIs) and promoters have been studied in detail because they are easily accessible in terms of the techniques available and sequence specificity. However, other sequences should be taken into consideration [84].

Most DNA methylation occurs at CpG dinucleotides, resulting in the modification of cytosine to methylcytosine. However, recent findings have expanded this understanding to include hydroxymethylcytosine and methylation at non-CpG sites. Non-CpG methylation has been observed in gene bodies, promoters, and repetitive elements, though its full extent and implications require further exploration. CpG islands (CGIs) and gene promoters are often studied due to their well-defined regulatory roles. CGIs are characterized algorithmically by an observed-to-expected (o/e) ratio of CpG >0.6, guanine and cytosine content >0.5, and typically a length >500 base pairs (bp) [84].

Promoters are classified based on their CpG content into three categories: low CpG, intermediate CpG, and high CpG. Low CpG promoters have a higher probability of methylation, though this methylation correlates poorly with transcriptional activity. Conversely, high CpG promoters have a lower likelihood of methylation, but this methylation is often associated with gene expression. Additionally, gene transcription is regulated by distal elements such as enhancers, insulators, locus control regions, and silencing elements. Recent studies have also shown that gene bodies in active transcription sites are enriched with DNA methylation.

Unmethylated regions of CGIs, termed unmethylated regions (UMRs), were recently identified. These regions, initially unmethylated, undergo tissue-specific methylation during development. CGI shore sequences, which are regions surrounding CGIs, were also described. Their methylation patterns in normal tissues are highly conserved, tissue-specific, and closely related to gene expression. Furthermore, these regions are notably sensitive to DNA alterations in colon cancer compared to promoters or CGIs [84]. Other interesting targets for DNA methylation studies include highly methylated repetitive elements and conserved noncoding elements.

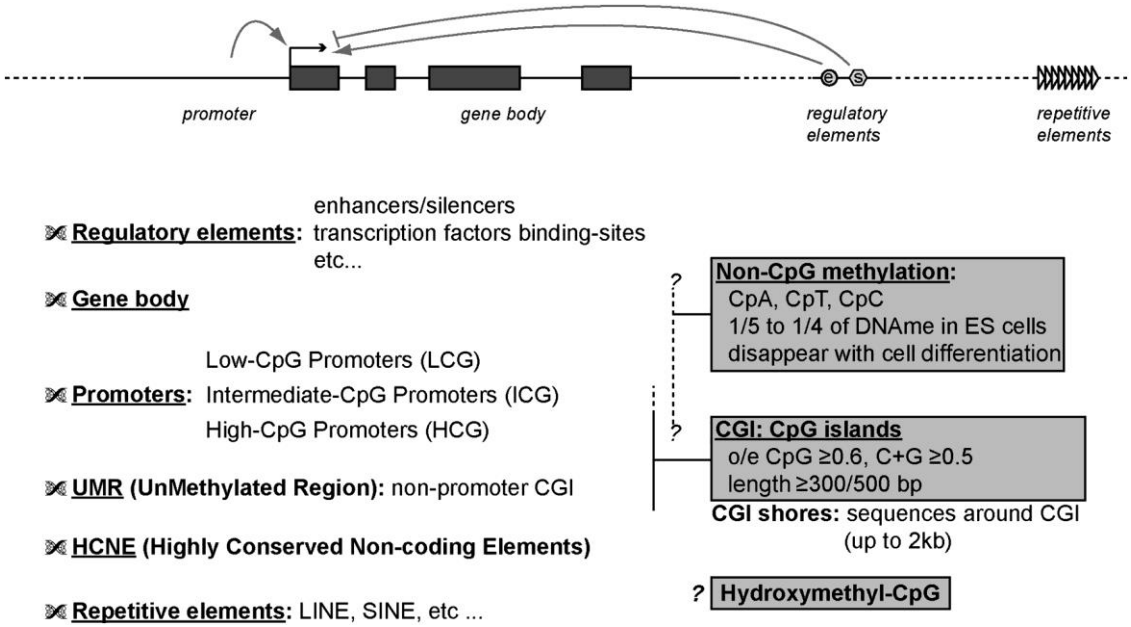

Fig. 1. Target sequence for DNA methylation studies [84]

Mammalian genomes are interspersed with CGIs, which are DNA sequences with a high frequency of CpG sites [92]. While there is substantial evidence for the role of CGI-promoter methylation in transcriptional regulation, the correlation between CGI methylation and gene expression is often poor. Irizarry et al. [93] defined CGI shores as sequences within ≤2 kb of CGIs, finding that their methylation is highly conserved, tissue-specific, and strongly related to gene expression [94].

Large-scale methylation studies have challenged some prevailing views about DNA methylation dynamics and functions. For instance, Weber et al. [95] used a methylated DNA immunoprecipitation (MeDIP-chip) approach to map DNA methylation across the genome and investigate its role in cis-regulatory regions and gene expression. Their findings revealed that: 1) Methylation of CpG-poor promoters does not necessarily inhibit gene expression; 2) DNA methylation is not a universal mechanism for gene repression, as many CGI promoters remain unmethylated even when inactive; and 3) DNA methylation is crucial for regulating key developmental genes. Thus, the density of CpG in promoters and gene function are significant predictors of promoter methylation states.

Shen and Waterland [96] found that some CGIs within key developmental gene promoters undergo tissue-specific methylation during development, a phenomenon previously observed only in imprinted and X-inactivated genes. This suggests the presence of a programmed DNA methylation mechanism. UMRs, or nonpromoter CGIs, become methylated in a tissue-specific manner during development, potentially influencing gene expression [97]. Gene-body methylation, initially noted for the active X chromosome, may serve as a hallmark of active genes throughout the genome [98,99,92].

7.2 How Early Nutrition Sculpts our Epigenomes

Throughout evolution, organisms have been faced with the challenge of sensing changes in their environment, such as food depletion and stress, and adapting to them to ensure their survival. These responses implicitly involve various mechanisms, such as chromatin targeting, for adapting the expression of fundamental genes and ensuring genome integrity. Environmental factors such as diet, nutrients, drugs, and the social environment can be linked to chromatin structure in several ways [84].

7.3 Mechanistic Pathways for Environmental Factors Involved in Epigenetic Reprogramming

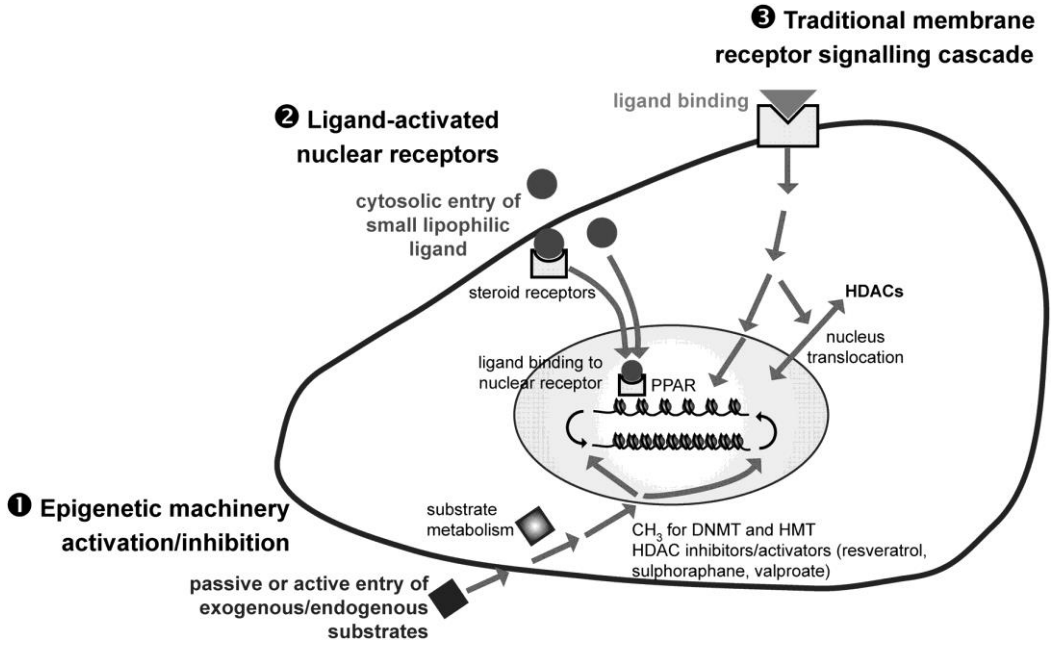

Fig. 2. Mechanistic pathways for environmental factors involved in epigenetic reprogramming [84]

The connection between environmental factors and chromatin structure can be established through three primary mechanisms, each linking external stimuli to changes in gene expression and chromatin modifications:

1. Direct Modification of Chromatin-Remodeling Enzymes: Environmental factors, including aging, sex, and specific nutrients or drugs, can influence the activity of chromatin-remodeling enzymes or alter the availability of their substrates. Once these factors cross the cell membrane, they can affect the availability or activity of critical molecules such as methyl donors (e.g., folates) or inhibitors of histone deacetylases (e.g., trichostatin A). These substances may then impact the balance of chromatin-remodeling enzymes on a genome-wide scale or in specific chromatin regions. For instance, changes in the availability of methyl donors can affect the activity of DNA methyltransferases, while the presence of HDAC inhibitors can alter histone acetylation patterns, leading to changes in gene expression [84].
2. Nuclear Receptor Signaling: Some environmental compounds act through nuclear receptors. These receptors, such as steroid receptors, peroxisome proliferator–activated receptors (PPARs), and retinoid X receptors (RXRs), bind to specific ligands (including natural polyunsaturated fatty acids or drugs) and undergo conformational changes that enable their translocation to the nucleus. Once in the nucleus, these receptors bind to their responsive elements on DNA and recruit coactivators and chromatin-remodeling factors. This recruitment leads to modifications of epigenetic marks at responsive gene promoters, thereby modulating the expression of specific genes in a tissue-specific manner depending on the presence of appropriate cofactors [84].
3. Membrane Receptor-Signaling Cascades: Traditional receptor-signaling pathways also play a role in linking environmental factors to chromatin modifications. Ligands interacting with cell membrane receptors can activate intracellular signaling cascades that influence the activity and localization of chromatin-modifying enzymes. These pathways can regulate factors such as DNA methyltransferases (DNMTs), histone acetyltransferases, histone deacetylases (HDACs), and histone methyltransferases (HMTs) or demethylases. By triggering these signaling cascades, environmental signals can induce loci-specific chromatin modifications, thus impacting gene expression patterns [84].

Each of these mechanisms highlights the complexity of how environmental factors can influence gene expression through epigenetic modifications. The interplay between these pathways underscores the dynamic nature of chromatin regulation and its response to both internal and external stimuli.

8. SEXUAL DIMORPHISM OF GENE EXPRESSION AND EPIGENETICS

The majority of common diseases, such as atherosclerosis, diabetes, osteoporosis, asthma, and various neuropsychological and autoimmune conditions, often originate early in development and exhibit a sex bias. Additionally, the likelihood of developing a complex disease can be influenced by the sex of the affected parent. This highlights the relevance of epigenetic mechanisms in explaining the physiological differences between sexes, particularly concerning drug metabolism, and supports the epigenetic theory of complex diseases [84].

This bias may be attributed to the role of sex chromosomes, different regulatory pathways involved in sexual development across various organs, and the fluctuating impact of sex hormones over a lifetime. Many tissues show sexual dimorphism in a significant proportion of their gene expression profiles [84,100].

Sex-specific gene expression appears to be regulated by distinct epigenetic marks specific to each sex. Environmental factors, including social behavior, nutrition, and exposure to chemical compounds, can modulate these epigenetic marks in a sex-dependent manner during critical developmental periods. For instance, in the developing mouse brain, histone H3 modifications are sexually dimorphic, with patterns of acetylation, but not methylation, being masculinized in females by in utero testosterone exposure [101]. Numerous studies have documented sex differences in how prenatal and early postnatal exposures impact the risk of subsequent metabolic dysfunction [102,103].

9. CONCLUSIONS AND RECOMMENDATIONS

Fetal programming suggests that environmental factors such as maternal stress and nutrition during pregnancy can alter crucial physiological parameters, and these changes can persist into adulthood and potentially affect future generations, leading to trans-generational genetic disorders. Researchers are working to establish evidence for fetal programming, which posits that early developmental disturbances—such as those caused by diet, medication, lifestyle, or social behavior—can have lasting effects, including the development of conditions like metabolic syndrome or psychiatric disorders.

Additional research is needed to uncover the factors that influence fetal growth and how maternal and placental limitations impact the supply of nutrients and oxygen to the fetus. It is also crucial to understand how the fetus adapts to restricted nutrient availability, how these adaptations affect bodily structure and function, and the molecular mechanisms through which nutrients and hormones influence gene expression. For women, understanding how their own prenatal growth, diet, and body composition influence their children's future health is important. They may seek guidance on optimizing the intra-uterine environment for their babies. Furthermore, research should focus on identifying obstacles to healthy eating among young women, as their diets are vital for both their own well-being and the health of future generations. Addressing these issues could help reduce the prevalence of major chronic diseases and alleviate health disparities.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/122452