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### Advancing Public Health through Nutrigenetics and Microbiota in Early Life: Initiating Longevity in Childhood

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#### ABSTRACT

Early life is a critical period when nutrition and environmental exposures significantly influence development and long-term health. This review examines the interactions among genetic factors, nutrigenetics, epigenetic mechanisms and the gut microbiota in early life, emphasizing maternal effects during prenatal and infancy stages. Maternal nutrition can alter fetal epigenetic marks, shaping gene expression patterns that persist into adulthood. Genetic variations in mother and child affect nutrient metabolism and requirements, influencing developmental outcomes. The infant's microbiota, seeded by maternal microbes and shaped by diet, is crucial for metabolic and immune system training. The concept of early-life programming, known as the "Developmental Origins of Health and Disease," is discussed. Evidence from both human and animal studies links early nutrition and microbial exposure to lifelong health outcomes. Immune development relies on early microbial and nutrient signals, affecting tolerance and allergy risks. By integrating epigenetics, nutrigenetics and microbiome research, this article brings the role of maternal diet quality and microbial transmission in infant development to prominence. Understanding these processes may guide strategies, such as optimized maternal nutrition and microbiota-based interventions, to improve health outcomes across generations.

**Keywords:** Genetic Expression, Epigenetics, Nutrition, Public Health, Early-life Programming, Immune Development, Environmental Inheritance

#### 1. Introduction

The developmental period spanning gestation and infancy represents a window of opportunity in which environmental factors have lasting effects on health. The Developmental Origins of Health and Disease (DOHaD) concept, rooted in observations like Barker's hypothesis, posits that early-life conditions, including nutrition, can "program" an individual's risk for chronic diseases<sup>1</sup>. In the decades since this hypothesis was introduced, substantial evidence from epidemiology and

experimental models has confirmed that maternal diet and other prenatal exposures can influence fetal development and long-term outcomes<sup>2</sup>. Early-life nutrition, through its influence on epigenetic modifications at transposable elements and imprinted genes, plays a critical role in shaping long-term susceptibility to adult chronic diseases<sup>3</sup>. Its profound significance should be emphasized in the context of public health and disease prevention strategies. An article explores the epigenetic epidemiology of the DOHaD hypothesis, which posits that early-life environmen-

tal factors, particularly nutrition, can cause lasting changes in metabolism and disease risk. While the biological mechanisms are not fully understood, growing evidence points to epigenetic changes, such as gene regulation alterations, as key mediators. The review outlines how transient early-life exposures can lead to permanent epigenetic modifications and how such dysregulation is linked to various chronic diseases. It proposes a working definition of epigenetic epidemiology and emphasizes its potential in identifying causal links between early exposures and later health outcomes. The authors advocate for future research to uncover these mechanisms and support targeted early-life interventions to improve long-term health<sup>4</sup>. Classic examples include the Dutch Hunger Winter famine: offspring of pregnant women exposed to severe undernutrition showed higher risks of metabolic disease and distinct DNA methylation patterns decades afterward<sup>5</sup>. Recent studies show that maternal factors significantly influence an offspring's risk of metabolic diseases, partly through epigenetic changes. These effects occur across all maternal environments and can be passed to future generations. Both poor and excessive maternal nutrition increase offspring's vulnerability to challenges like unhealthy diets or inactivity, raising disease risk. Considering these intergenerational effects is crucial for preventing non-communicable diseases, especially in rapidly changing populations<sup>6</sup>. These findings illustrate how early nutritional deprivation or imbalance can become biologically embedded via epigenetic changes.

In parallel, the field of nutrigenetics has emerged to study how genetic variation modulates an individual's response to diet. Nutrigenetics examines gene interactions with nutrients, recognizing that each person has a unique genetic makeup that influences nutrient metabolism and requirements. Common polymorphisms in genes involved in one-carbon metabolism, folate and methylation pathways, for instance, can alter how maternal nutrition impacts fetal development<sup>7</sup>. A well-documented example is the Methylene tetrahydrofolate reductase (MTHFR) gene<sup>8</sup>. Mothers carrying certain variants of MTHFR (677C>T) have an elevated risk of having low-birth-weight infants, particularly if their folate intake is insufficient<sup>9,10</sup>. A study explored whether the consumption of Sugar-Sweetened Beverages (SSBs) interacts with genetic predisposition to influence the risk of obesity. Researchers studied three large U.S. cohorts totaling over 33,000 participants to examine how genetic risk for higher BMI interacts with sugar-sweetened beverage (SSB) consumption. They calculated a genetic predisposition score from 32 BMI-related genetic loci and grouped participants by SSB intake levels, from less than one serving per month to one or more servings daily. The findings showed that the effect of genetic risk on BMI and obesity was significantly stronger in those consuming more SSBs. For example, in combined cohorts, each 10-risk-allele increase corresponded to a BMI rise of 1.00 for low SSB consumers versus 1.78 for high consumers. Obesity risk similarly increased with higher SSB intake. These patterns were confirmed in a separate large cohort, demonstrating that higher SSB consumption amplifies genetic susceptibility to obesity. The study concluded that the impact of genetic predisposition on adiposity is significantly amplified by higher consumption of sugar-sweetened beverages. These findings suggest that individuals with a high genetic risk for obesity may be more vulnerable to the harmful effects of consuming sugary drinks. Therefore, limiting intake of sugar-sweetened beverages could be especially important for those with a strong genetic susceptibility and may serve as an effective strategy for obesity preven-

tion<sup>11</sup>. Such evidence of gene interactions environmental factors draws attention to the importance of personalized approaches to maternal and infant nutrition, as genetic predispositions may modify the impact of diet on growth and health.

Compounding these considerations is the growing recognition of the microbiota as an integral player in early-life development. Humans are colonized by a vast community of microorganisms and this colonization begins at birth. The infant's gut microbiome is initially seeded by maternal microbes during delivery and expanded through feeding, breast milk or formula and environmental contacts. Early infancy is a "golden time" for microbiota establishment, which can have long-lasting consequences<sup>12</sup>. Numerous factors influence the composition of the neonatal microbiota, including mode of delivery, feeding practices, maternal diet, home environment and even host genetics. Over the past 5-10 years, research on bifidobacteria has significantly advanced, especially in understanding their genetic traits linked to carbohydrate metabolism and their potential role in gut colonization and diet interaction. While genome analyses have identified genes likely involved in health-promoting activities, the specific functions of individual bifidobacterial strains and their interactions within the gut microbiota remain poorly understood. In particular, *B. bifidum* has emerged as a promising species due to its potential benefits in preventing and treating gastrointestinal disorders. Further studies using advanced metagenomic techniques are needed, however, to fully uncover its functional contributions to human health<sup>13</sup>. These factors are so influential that researchers often refer to the first 1,000 days of life, from conception to age 2 years, as critical for shaping the gut microbiome and, by extension, the child's metabolic and immune trajectories. Disruptions to normal microbial colonization, for example, through unbalanced maternal diets, perinatal antibiotics or Cesarean section birth, have been associated with negative health outcomes ranging from obesity to allergies. One study examined the gut microbiota of healthy Canadian infants at 4 months, focusing on the impact of delivery mode and feeding type. Results showed high variability in microbial profiles, with breastfed infants having lower species richness than formula-fed ones, who had more *Clostridium difficile*. Cesarean-born infants, especially those delivered electively, had lower bacterial diversity, findings demonstrating how birth method and diet shape infant gut microbiota early in life<sup>14</sup>. Conversely, nurturing a diverse and beneficial microbiota in early life is thought to contribute to resilience against disease.

Food allergy is increasing dramatically worldwide, largely driven by immune tolerance defects modulated by gut microbiota alterations influenced by environmental factors such as diet, cesarean delivery, antiseptic agents, lack of breastfeeding and drugs<sup>15</sup>. Early nutrition critically shapes immune and metabolic health through epigenetic mechanisms and microbiome interactions, which contribute to heritable phenotypic traits beyond DNA sequence variation<sup>16</sup>. Breastfeeding has a protective effect by moderating the influence of the fat mass and obesity-associated protein (FTO) gene variant rs9939609 on adult adiposity, reducing BMI and fat mass among those breastfed for at least one month<sup>17</sup>. Maternal nutritional status, particularly adequate vitamin B levels during early pregnancy, impacts offspring growth and DNA methylation in growth-related genes, with elevated maternal homocysteine linked to lower birth weight in males<sup>18</sup>. Diet diversity during pregnancy, breastfeeding and early life plays a crucial role in allergy prevention by promoting overall

healthy dietary patterns and early allergen introduction combined with diverse maternal diets may reduce childhood allergy risks<sup>19</sup>. Maternal nutrient-rich diets, especially those including  $\omega$ -3 fatty acids and folate, support optimal child neurodevelopment and lower risks of neurodevelopmental disorders<sup>20</sup>. Nutritional metabolites and probiotics can induce epigenetic regulation to stimulate immune tolerance, presenting innovative approaches to allergy treatment. An article elucidates the concept of “microbiological memory,” the idea that gut microbiota can influence heritable epigenetic changes linked to metabolic diseases. While DNA carries genetic information, many chronic conditions are inherited through non-genetic mechanisms like epigenetic regulation, especially influenced by early nutrition and dysbiosis. The gut microbiome may drive long-term changes in gene expression, shaping disease risk across generations<sup>21</sup>. Early nutrition influences epigenetic aging through metabolic and microbiome pathways, with fiber-rich, antioxidant and vitamin-rich diets slowing epigenetic aging, while high glycemic and saturated fat diets accelerate it<sup>22</sup>. Research **convergently** emphasizes the essential role of early nutrition and maternal diet in shaping gut microbiota, epigenetic programming and immune development, thereby influencing allergy risk, metabolic health and neurodevelopmental outcomes.

The current article provides a comprehensive review of how maternal nutrition, the infant microbiota and genetic/epigenetic interactions collectively shape early development and long-term health. Findings are synthesized from human studies and animal models to illustrate key concepts in epigenetic programming, nutrigenetic influences, microbial contributions to immune development and the overarching paradigm of early-life programming. This review covers the interconnected roles of diet, genes and microbes in early life, through sections on epigenetics, nutrigenetics, microbiota, early-life programming and immune development. Understanding these connections is not only important for basic science, but also for designing interventions, such as improved maternal diets or microbiome-targeted therapies, that could optimize developmental outcomes and reduce disease risk in future generations.

## 2. Epigenetics: Early Nutrition and the Fetal Epigenome

Epigenetic mechanisms provide a biological link between early nutritional exposures and gene regulation in the developing child. Epigenetics refers to heritable changes in gene expression that occur without changes in the DNA sequence. The primary epigenetic modifications include DNA methylation, post-translational histone modifications and regulatory non-coding RNAs. These modifications can be influenced by environmental factors, especially nutrition, during critical periods of development. Maternal nutrition is considered one of the most powerful environmental influences on the fetal epigenome. Nutrients and bioactive food components can alter the availability of methyl groups and substrates for chromatin modification, thereby regulating gene expression in the fetus. The rapid rise in obesity can't be explained just by genetics or adult lifestyle. Evidence shows that fetal and early postnatal environments also play a key role, with both low birth weight and early overnutrition increasing obesity risk. Animal studies confirm that maternal under- or overnutrition causes lasting changes in gene expression through altered epigenetic regulation. Understanding these mechanisms suggests that early interventions, via nutrition or drugs, might reduce long-term obesity risk<sup>23</sup>. When pregnant

Agouti mice exposed to BPA were also given methyl donors like folic acid or genistein, the offspring's coat color distribution and weight outcomes shifted back toward normal, indicating prevention of BPA-induced epigenetic changes<sup>24</sup>. Folate, choline, vitamin B12 and other one-carbon donors are essential for DNA methylation; both deficiency and excess can cause abnormal methylation in offspring. Maternal diets rich in methyl donors or certain phytochemicals can increase DNA methylation at specific genes, while deficiencies can reduce it, affecting phenotype. Environmental factors impact health through epigenetic mechanisms like DNA methylation, histone modification, chromatin structure and regulatory RNAs, which regulate gene expression without changing DNA sequences. Unlike traditional gene-environment studies focusing on genetics, environmental epigenomics studies how nutrition and exposures affect epigenetic regulation during development, causing lasting effects. The Viable Yellow Agouti (Avy) mouse is a key model, where methylation of a retrotransposon affects coat color and health. Maternal genistein increases methylation and shifts coat color toward brown, reducing obesity risk, while bisphenol A lowers methylation, shifting color toward yellow and increasing risk, effects reversible by methyl donors or genistein. Early embryonic development is a critical period for stable epigenetic changes that may be inherited, though mechanisms like histone modifications and non-coding RNAs remain unclear. Epigenetics links environment, development and adult health outcomes<sup>25</sup>. In essence, the maternal diet modified the epigenetic state of a specific gene in the offspring, demonstrating how environmental toxins and nutrients can interact via epigenetic pathways. Human studies likewise support the importance of early nutritional epigenetics. Epidemiological analyses of cohorts exposed to famine or malnutrition provide natural experiments. Persistent changes were found in DNA methylation in these individuals' genomes, including at the imprinted insulin-like growth factor 2 (IGF2) gene, suggesting that severe maternal undernutrition can leave a long-lasting epigenetic “fingerprint” on the offspring genome<sup>5</sup>. Other studies have shown that maternal over-nutrition, such as obesity or a high-fat diet during pregnancy, can also lead to epigenetic alterations in the child. Research findings support that the first six months of development are the most crucial for epigenetic remodeling, showing that intrauterine fetal programming related to obesity and gestational diabetes impacts the childhood methylome after birth, altering metabolic pathways that may influence postnatal development. Maternal metabolic health also plays a key role in shaping these epigenetic changes, potentially increasing childhood obesity risk<sup>26</sup>.

Specific nutrients and dietary patterns have been associated with epigenetic markers of health. Maternal and early life diets rich in fiber, antioxidants, polyphenols, B vitamins, vitamin D and omega-3 fatty acids are linked to slower epigenetic aging, while diets high in glycemic load, fat, saturated fat and  $\omega$ -6 fatty acids are linked to faster aging. Nutrition affects epigenetic aging through one-carbon metabolism, cardiometabolic health and the microbiome. Clinical trials are needed to identify foods and supplements that can slow or reverse epigenetic aging<sup>22</sup>. These results imply that maternal diet quality not only influences specific gene loci but also affects the overall biological aging process of the child. Mechanistically, diets high in fruits, vegetables and omega-3 fatty acids may support proper epigenetic enzyme function, such as DNA methyltransferases and histone deacetylases, whereas Western-type diets might induce oxidative stress and inflammation that perturb epigenetic regulation.

Epigenetic modifications constitute a key mechanism by which maternal nutrition and other early-life exposures become biologically embedded. Through DNA methylation and related processes, transient nutritional differences can produce lasting changes in gene expression that influence an individual's physiology and disease susceptibility. This epigenetic memory of early nutrition demonstrates the need for optimal maternal diets and potential nutritional supplementation; e.g., folate, during pregnancy to ensure favorable developmental programming.

### 3. Nutrigenetics: Interactions Between Genes and Diet in Early Life

While epigenetics focuses on changes in gene expression regulation, nutrigenetics examines how genetic differences affect an organism's response to nutrients and diet. Every individual carries unique genetic variants, polymorphisms, in metabolic and signaling pathways related to nutrition. These variants can lead to heterogeneity in how effectively nutrients are absorbed, metabolized and utilized, meaning that a given diet might have different impacts on different individuals. In the context of early life, nutrigenetic factors in both the mother and the infant can significantly modulate developmental outcomes.

One of the most crucial nutrigenetic interactions involves the one-carbon metabolism pathway, which, as noted, supplies methyl groups for DNA synthesis and methylation. The enzyme MTHFR is a key player in this pathway and a common variant in the MTHFR gene (C677T) reduces its activity. Women who carry the T allele have an increased dependence on dietary folate; if their folate intake is not adequate or not supplemented with folic acid, they are at higher risk of adverse pregnancy outcomes. Indeed, studies have shown that mothers with the MTHFR 677CT or TT genotype have a greater likelihood of having infants with low birth weight or small-for-gestational-age status, especially when maternal folate intake is deficient<sup>9,10,27</sup>. Even in populations with folate fortification or supplementation, subtle effects of the maternal genotype on newborn size have been observed, suggesting that gene interactions with nutrients persist across different nutritional environments<sup>28</sup>. Polymorphisms can make certain pregnancies more vulnerable to nutrient deficiencies and conversely, how ensuring adequate nutrient intake, like folic acid, can mitigate genetic risk factors; for example, reducing neural tube defects in infants of mothers with MTHFR variants.

Another pertinent example of nutrigenetics in early life relates to childhood obesity risk and the FTO gene. Variants in FTO are well-known to influence appetite regulation and adiposity, with the A allele of SNP rs9939609 being associated with higher body mass index (BMI) in many populations. Parental-reported breastfeeding duration have been shown to influence how the FTO gene variant rs9939609 affected BMI in adolescents but not in young adults. Specifically, AA genotype individuals had higher BMI with short breastfeeding and lower BMI with longer breastfeeding compared to AT and TT genotypes. Longer breastfeeding reduced overweight risk especially in younger AA adolescents. This suggests the AA genotype is more sensitive to breastfeeding duration, supporting the idea that rs9939609 AA is a plasticity variant affected by environmental factors like breastfeeding<sup>17</sup>. The impact of this genetic risk factor can be modified by infant feeding practices. A birth cohort study with 30-year follow-up demonstrated that among individuals who were never

or briefly breastfed <1 month, those carrying the FTO risk allele showed significantly greater BMI and adiposity by adulthood. In contrast, among individuals who were breastfed for longer durations  $\geq 1$  month, the association between the FTO genotype and adult obesity was markedly attenuated<sup>29</sup>. In other words, prolonged breastfeeding appeared to buffer the genetic tendency toward obesity conferred by the FTO variant. This gene and environment interaction suggests that early-life nutrition can modulate genetic risks. A nurturing nutritional environment, breast milk, in this case, may offset some deleterious genetic predispositions, whereas an unfavorable environment might exacerbate them. Similar interactions have been explored for other genes involved in metabolism and growth, indicates the principle that genetic and dietary factors are not independent but interdependent in shaping outcomes.

Beyond these examples, nutrigenetics encompasses a broad range of gene-diet relationships. Variants in genes affecting lipid metabolism; e.g., FADS genes for fatty acid desaturases, may influence how infants respond to different fat contents in breast milk or formula, potentially impacting neural development and immune function. Polymorphisms in lactase, antioxidant enzymes, vitamin D receptors and many others can each alter nutritional needs or responses<sup>30</sup>. From a clinical perspective, recognizing these genetic differences could pave the way for personalized nutrition strategies in early life; for instance, tailoring maternal or infant diets based on genetic screening, such as ensuring a mother with certain folate-cycle variants gets high-dose folate or guiding feeding practices for an infant with higher obesity risk genes.

It is also noteworthy that genetic variation can influence taste preferences and eating behaviors even in young children, which in turn affects dietary intake. While such behavioral genetics aspects are complex, they further intertwine with nutrigenetics by determining how easily a child accepts certain healthy foods or how their appetite regulation responds to satiety cues<sup>31</sup>.

Nutrigenetics asserts that "one size does not fit all" in the context of early-life nutrition. Genetic differences in mothers and infants help explain why some children thrive on a given diet while others may be more prone to issues like growth faltering or excessive weight gain under the same dietary conditions. A thorough understanding of these gene-nutrient interactions, combined with epigenetic insights, moves us closer to predictive and personalized approaches for nutrition in pregnancy, infancy and childhood.

### 4. Microbiota: Maternal Transmission and Early-Life Colonization

The infant's acquisition of its microbiota is now recognized as a foundational aspect of early development. The gut microbiome, in particular, is intimately involved in digestion, metabolism and immune education. Unlike the genome, which is inherited fixed from parents, the microbiome is acquired and can be modified by numerous factors in early life. It represents a form of "environmental inheritance," with the mother playing a central role in seeding and shaping the infant's microbial communities.

Maternal microbiota influences begin even before birth. The womb was considered sterile, traditionally, but some studies suggest that traces of microbial DNA or metabolites from the maternal microbiome, gut oral or placental microbiota, might

reach the fetus and prime its developing immune system<sup>32</sup>. Whether or not significant colonization occurs prenatally, it is clear that delivery mode has a major impact on the newborn's initial microbiota. During a vaginal birth, the baby is naturally inoculated with the mother's vaginal and intestinal microbes. Vaginally delivered infants, consequently, have gut microbiota profiles resembling their mother's vaginal microbiome, dominated by *Lactobacillus* and other lactic acid bacteria, whereas babies born by Cesarean section are initially colonized by skin and environmental microbes such as *Staphylococcus* and *Corynebacterium*<sup>33</sup>. **One study showed that** the mode of delivery influences the early-life gut microbiome, with cesarean-born infants having delayed colonization by beneficial bacteria like *Bifidobacterium* and higher levels of potential pathogens such as *Klebsiella* and *Enterococcus*. These microbial differences were associated with a greater number of respiratory infections during the first year of life, suggesting that delivery mode may affect susceptibility to infections independent of antibiotic exposure<sup>34</sup>. Cesarean delivery is associated with delayed and less diverse gut microbiota colonization in infants. Babies born by C-section show, specifically, delayed colonization of the Bacteroidetes phylum, reduced overall microbial diversity and decreased Th1 immune responses during the first two years of life. Their intestinal microbiota is notably less diverse and often lacks beneficial *Bifidobacteria* species compared to vaginally delivered infants<sup>35,36</sup>. Epidemiological research has consistently associated Cesarean delivery with an increased risk of immune-related conditions in offspring, including asthma, allergies and autoimmune diseases; however, these findings should be interpreted with caution, as confounding factors may also contribute to or mediate these associations<sup>37,38</sup>. This is thought to arise because the infant misses the "bacterial baptism" of vaginal birth, whereby exposure to maternal vaginal microbes helps train the newborn's immune system and foster a balanced microbiome. Some interventions have even tried to simulate this microbial transfer; for example, swabbing C-section babies with maternal vaginal fluids and have shown partial normalization of the infant microbiota as a result<sup>33</sup>.

After birth, the feeding mode becomes a dominant factor influencing microbiota development. Breastfeeding has long been known to confer health benefits and one reason is its impact on the gut microbiome. Breastfed infants tend to have microbiomes enriched in beneficial microbes like *Bifidobacterium*<sup>12</sup>. Breast milk is not sterile. It contains commensal bacteria and even a core "milk microbiome" transmitted from the mother. In addition, breast milk provides abundant substrates that shape the microbiome: notably, human milk oligosaccharides, complex sugars that infants cannot digest but that selectively feed beneficial bacteria such as *Bifidobacteria*, which essentially act as prebiotics, promoting a microbiota composition that is favorable for the infant<sup>39</sup>. Breast milk also contains immune components like secretory IgA, lactoferrin and cytokines. IgA antibodies coat the infant's gut microbes and prevent overgrowth of pathogens while encouraging tolerance to beneficial flora. This helps establish a harmonious host-microbe relationship. Breastfeeding further transfers maternal immune cells and antibodies that can influence the infant's immune responses. Altogether, breastfeeding not only nourishes the infant but also "grafts" a maternal microbial legacy and critical immune factors to the baby, aligning early microbiota development with immune maturation. By contrast, formula-fed infants often show a different microbial

profile, typically more diverse in species like *Clostridia* and lower in *Bifidobacteria*<sup>14,40</sup>. Modern infant formulas are being designed to closer mimic breast milk's effects; e.g., adding prebiotic fibers or probiotic strains, but differences in microbiota remain. Diet continues to shape the microbiome beyond infancy. The introduction of solid foods, diet diversity and later eating patterns will modulate the gut microbial ecosystem, with potential implications for the child's growth and immunity.

Early life is a crucial period for the development of the infant intestinal microbiome. While postnatal factors like delivery mode, feeding and antibiotics have been well studied, the impact of prenatal exposures remains less clear. A systematic review analyzed 76 studies from 1,441 publications to examine how pre-pregnancy and pregnancy exposures affect the infant gut microbiome. Influential factors identified included maternal antibiotic and probiotic use, diet, pre-pregnancy BMI, gestational weight gain, diabetes and mood. Meta-analyses showed that maternal intrapartum antibiotic use, overweight/obesity and excessive weight gain during pregnancy were linked to lower infant microbiome diversity. Revealing the need for standardized, collaborative research to better understand prenatal influences on microbiome development<sup>41</sup>. A high-fiber diet in the mother may promote greater microbial diversity in her milk, for example, whereas a high-fat diet can alter the relative abundance of certain bacteria. These changes, in turn, may influence which microbes an infant acquires during breastfeeding. The maternal diet also affects the content of bioactive molecules in milk, such as HMOs and fatty acids, thereby indirectly shaping the infant gut microbiome<sup>42</sup>.

Beyond maternal effects, other environmental factors in early life contribute to microbiota development. These include antibiotic exposures, in mother or infant, which can disrupt microbial communities; the home environment and siblings or pets, microbial sharing among family members; and geography or cultural practices affecting diet and hygiene. Even host genetics can influence the microbiome. Certain gene variants in the infant may, for instance, affect gut environment, pH, immune factors and thereby select for specific microbial populations<sup>43</sup>. During the very early stages of life, however, environmental inputs tend to overshadow genetic influences on the microbiome composition. The significance of establishing a healthy microbiota in infancy lies in its myriad roles. The gut microbes ferment dietary components to produce metabolites, like short-chain fatty acids, that nourish intestinal cells and regulate metabolism. They also compete with pathogens, support gut barrier integrity and interact with the immune system. Early dysbiosis, an imbalance in the microbiota, has been associated with outcomes such as increased risk of atopic diseases, obesity and even neurodevelopmental differences<sup>44</sup>.

The early-life microbiota is a crucial mediator between the infant's environment and its physiology. Maternal influences on microbial seeding, through delivery mode and breastfeeding and ongoing dietary impacts suggest a tight interconnection. Maternal nutrition and microbiota together shape the child's microbiome. Ensuring that infants develop a beneficial gut microbiota, through practices like vaginal delivery when possible, breastfeeding, avoiding unnecessary antibiotics and proper maternal diet, may set the foundation for better health outcomes throughout life.

## 5. Early-Life Programming and Long-Term Health

The concept of early-life programming postulates that environmental factors during critical developmental periods can have lasting effects on an individual's health. The DOHaD theory encapsulates this idea, suggesting that many adult diseases can be traced back to developmental adaptations made by the fetus or infant in response to its early environment<sup>45</sup>.

Nutritional status, in particular, is a key programming factor. Both undernutrition and overnutrition in utero have been linked to elevated risks of chronic diseases in adulthood<sup>2</sup>. The mechanisms for this programming are complex and multifactorial, involving the interaction of epigenetic changes, hormonal and metabolic adjustments, altered organ structure and microbiome influences<sup>4</sup>. Maternal undernutrition, whether due to famine, food insecurity or micronutrient deficiencies, signals to the developing fetus that the external environment is resource-scarce. The fetus may adapt by reallocating resources, prioritizing brain development at the expense of liver or muscle growth and by altering hormonal axes like insulin-IGF signaling to be "thrifty"<sup>46</sup>. While such adaptations can be beneficial for short-term survival, they become maladaptive if the postnatal environment is nutritionally abundant, often leading to a mismatch that predisposes to obesity, type 2 diabetes and cardiovascular disease.

The Dutch Famine studies remain the hallmark example. Prenatal exposure to severe caloric restriction, especially during early gestation, was associated with higher rates of obesity, hypertension and hyperlipidemia in the adult offspring<sup>47</sup>. Epigenetic analyses of these individuals support that persistent DNA methylation changes at metabolic genes, like IGF2, are present<sup>5</sup>. Other famine or cohort studies, such as those from China's Great Leap Forward famine, have similarly found links between early gestational undernutrition and adult disease, often with sex-specific effects and intergenerational consequences<sup>48</sup>.

On the other end of the spectrum, maternal overnutrition and obesity can also program the offspring for future disease. Pregnancies complicated by maternal obesity or excessive gestational weight gain increase the risk of the child developing obesity and metabolic syndrome<sup>49</sup>. Part of this risk is conveyed by the postnatal environment, such as an obesogenic diet or lifestyle in the family, but studies controlling for postnatal factors still find an independent effect of the intrauterine environment.

Maternal hyperglycemia or diabetes similarly elevates risk for childhood obesity and glucose intolerance<sup>50</sup>. The mechanisms proposed include fetal hyperinsulinemia, due to high maternal glucose crossing the placenta and epigenetic modifications in the fetus' developing appetite and energy expenditure regulators. A review of 46 studies published between 2008 and 2013 found no consistent link between global DNA methylation and obesity but identified several obesity-related methylation changes, mainly in blood cells. Some methylation patterns at birth were linked to later obesity and small, specific changes were seen in weight loss interventions. Call attention to the potential for modifying unfavorable epigenetic profiles through prenatal and lifestyle interventions<sup>51</sup>.

Maternal nutrition plays a dual role in the developmental programming of hypertension. Poor maternal diet can predispose offspring to high blood pressure, while targeted nutritional

interventions during pregnancy and breastfeeding may help reverse this risk. A review article outlines evidence from human and animal studies, explores underlying mechanisms and highlights nutritional strategies that may prevent hypertension from early life stages, potentially reducing its global burden<sup>52</sup>.

The concept of programming extends crucially beyond nutrition alone. It is the integration of nutrition with other factors, like stress, toxin exposures and the microbiome, that defines the early environment. The gut microbiota is increasingly viewed as an agent of early-life programming.

Microbiota studies link gut bacterial shifts, like the Firmicutes/Bacteroidetes ratio and Prevotella abundance, to diseases mostly in adults; however, early-life gut microbiota differs and is key to disease development. Changes seen after disease onset may result from, not cause, illness. Most research focuses on bacteria types, but metabolic functions are crucial to understanding disease and finding early biomarkers. Large studies tracking infants' microbiota and metabolism during the first year, a critical window, are needed to enable early interventions that promote lifelong gut health and disease prevention<sup>44</sup>. Germ-free animal studies demonstrate a range of developmental abnormalities, many of which can be "rescued" by introducing microbes early in life. Microbial colonization in mammals influences host physiology, including immunity and nutrition. A study shows that gut microbiota also affects brain development and adult behavior. Germ-free mice exhibit increased motor activity and reduced anxiety compared to normal mice, linked to changes in brain gene expression related to neural signaling and synaptic function. Early exposure to microbiota normalizes these behaviors and brain protein levels. Gut microbes, thus, initiate signals that shape neural circuits controlling movement and anxiety<sup>53</sup>. Microbial metabolites such as butyrate can enter the host circulation and act as epigenetic modulators<sup>54</sup>.

The interplay of maternal nutrition and microbiota is particularly evident in programming of the immune and metabolic systems. A maternal Western diet, for example, can promote a pro-inflammatory milieu, which might skew fetal immune programming. The core gut microbiota influences disease development by altering metabolic pathways through epigenetic changes. In a study of 8 pregnant women grouped by dominant gut bacteria, Bacteroidetes, Firmicutes, Proteobacteria, DNA methylation patterns were linked to bacterial predominance. Firmicutes dominance was notably associated with gene methylation related to cardiovascular disease risk, lipid metabolism, obesity and inflammation<sup>55</sup>.

Postnatal influences are also vital. The concept of the "first 1000 days" emphasizes how postnatal nutrition and environment interact with prenatal exposures. Breastfeeding is crucial, especially in low- and middle-income countries, where only 37% of infants under 6 months are exclusively breastfed. Longer breastfeeding protects against infections, malocclusion and may improve intelligence while reducing overweight and diabetes. It lowers breast cancer deaths by 20,000 annually and could prevent 823,000 child deaths under 5 each year. Benefits apply worldwide, regardless of income<sup>56</sup>. Rapid catch-up growth after intrauterine growth restriction has been linked to metabolic risk<sup>57</sup>. Breastfeeding versus formula feeding, timing of introducing solid foods and weaning diet composition all have programming effects<sup>58</sup>. Environmental factors during early develop-

ment influence the risk of chronic noncommunicable diseases later in life, a concept known as the DOHaD. This risk arises mainly from adaptive developmental plasticity rather than early pathological damage. Both adaptive and nonadaptive developmental processes, including epigenetic mechanisms, can affect disease risk, sometimes across generations.

Understanding these pathways has important implications for preventing NCDs like type 2 diabetes and cardiovascular disease, supporting a lifecourse approach in public health and social policy<sup>59</sup>.

Early-life programming is a multifaceted process involving nutrition, microbiota and epigenetics, determining lifelong health trajectories. Recognizing this, public health strategies increasingly focus on optimizing the maternal and infant environment

## 6. Immune Development: Shaping Tolerance and Immunity through Nutrition and Microbes

The neonatal period is foundational and decisive for both metabolic and immune system development. The infant's immune system is immature at birth and must learn to distinguish between harmless substances and potential threats. Nutrition and the microbiota play crucial roles in educating the immune system during this time.

The "hygiene hypothesis" suggests that reduced microbial exposure in early life, due to factors like ultra-sanitary environments, antibiotic overuse, formula feeding or Cesarean delivery, may skew the immune system towards allergic or auto-immune responses<sup>60-63</sup>. This is because certain immune cells, such as regulatory T-cells, Tregs, require microbial stimulation to develop properly. Without adequate microbial cues, infants may develop weaker regulatory networks and a bias toward Th2 allergy-associated responses<sup>64</sup>.

Breast milk contains immunomodulatory components that influence immune development. For instance, Immunoglobulin A (IgA) helps shape the gut immune environment and cytokines like transforming growth factor-beta (TGF- $\beta$ ) and interleukin-10 (IL-10) promote tolerance<sup>65</sup>. Breastfeeding is associated with a lower risk of infections in infancy and may protect against immune-mediated diseases like eczema and wheezing<sup>58</sup>. This protective effect is partly due to the promotion of a gut microbiota rich in bifidobacteria and the provision of immune factors that encourage a non-inflammatory milieu in the infant gut. Formula-fed infants, in contrast, often have different gut microbiota compositions, which may contribute to a higher incidence of allergic outcomes. Formula lacks HMOs and contains different proteins and fats that can influence gut flora and gut immune interactions; however, modern formulas often include some prebiotics or probiotics to partially emulate these effects.

The composition of the infant gut microbiome itself has been correlated with allergy risk. Infants who develop allergic sensitizations or eczema often show lower levels of commensal *Lactobacillus* and *Bifidobacterium* and higher proportions of potentially pro-inflammatory organisms in early infancy<sup>66</sup>. A diverse, well-balanced microbiota seems to promote the expansion of regulatory immune cells, whereas dysbiosis may fail to provide those signals.

In the case of cow's milk allergic (CMA) infants, dysbiosis is

often exhibited, characterized by decreased abundances of *Bifidobacterium* spp. and increased abundances of *Lachnospiraceae* spp. Feeding CMA infants a formula supplemented with the probiotic *Lactobacillus rhamnosus* GG along with extensively hydrolyzed casein formula has been shown to accelerate tolerance acquisition to milk<sup>15</sup>. Studies on the developmental origin of health and disease show that early nutrition influences epigenetic mechanisms, affecting adult susceptibility to chronic diseases like metabolic syndrome, diabetes, obesity and cardiovascular conditions. Both maternal under- and over-nutrition impact gene expression related to metabolism. Early postnatal nutrition also shapes gut microbiota, which is crucial for immune and overall health development. Probiotics may help restore gut balance and prevent chronic immune diseases, potentially through epigenetic effects mediated by short-chain fatty acids (SCFAs)<sup>67</sup>. The hygiene hypothesis partly explains the rise in allergies, asthma and autoimmune diseases, but recent research shows diet and bacterial metabolites also play key roles in immune regulation. These metabolites activate specific receptors on immune and gut cells, promoting anti-inflammatory effects. Lack of healthy foods reduces beneficial metabolites, potentially contributing to inflammatory diseases common in Western countries. This review explores the links between diet, metabolites, immune pathways and inflammation<sup>68</sup>.

Epidemiological evidence supports that certain maternal diets correlate with lower allergic outcomes in children. Conversely, maternal diets high in pro-inflammatory nutrients, such as excessive omega-6 fatty acids or junk food diets, might increase the propensity for infant immune dysfunction. A low-fiber/high-fat maternal diet, along with other environmental factors like Cesarean section and antibiotic use, can induce gut dysbiosis in the child and is associated with a higher incidence of food allergy. Large-scale biodiversity loss and changes in social behavior are impacting human microbial ecology, contributing to the global rise in inflammatory diseases like early-life allergies. Proper colonization of microbes, especially in the gut, is crucial for immune development. Underlining the potential of probiotics, prebiotics and synbiotics for prevention. Randomized trials and new World Allergy Organization guidelines support their use in certain cases, though evidence quality is low and more research is needed; meanwhile, addressing diet and lifestyle factors causing dysbiosis is equally important<sup>69</sup>.

A study analyzed gut microbiota from two Japanese birth cohorts and identified six distinct enterotypes in children and mothers. At 1 month old, infants with Bifidobacterium-dominant enterotypes-especially those with high fecal propionate-had significantly lower risks of food sensitization (FS) and food allergy (FA), compared to Bacteroides- and Klebsiella-dominant types. Findings suggest early-life gut microbiota, particularly enterotype composition, influences the development of FS and FA<sup>70</sup>.

Another facet of early immune development is autoimmunity prevention. There is interest in whether early microbiota composition affects the risk for autoimmune diseases like type 1 diabetes or celiac disease. Studies have noted differences in the gut microbes of infants who later developed type 1 diabetes, although causal links remain under investigation.

Type 1 Diabetes (T1D) is an autoimmune disease influenced by genetics, environment and the gut microbiome. A study

of infant gut microbiomes analyzed 10,913 metagenomes from stool samples of 783 children and found that microbial functions, especially those producing short-chain fatty acids, may protect against T1D, though specific microbial species varied widely. Breastfeeding shaped certain beneficial gut bacteria. Underlining function in early T1D development<sup>71</sup>. Maternal factors, including diet and microbiome, likely also play a role in modulating fetal immune education to self-antigens.

Premature infants, who often have altered microbiota due to hospital interventions and immaturity, are prone to serious immune-mediated complications like necrotizing enterocolitis (NEC). This condition is strongly tied to an imbalance in gut bacteria and an excessive inflammatory response in the gut. Nutritional practices such as using maternal breast milk or donor human milk for preemies, instead of formula, significantly lower NEC incidence, indicating the critical role of appropriate nutrition and microbiota in maintaining immune homeostasis during early life. A study on *Bifidobacterium longum* subsp. *infantis* in an experimental necrotizing enterocolitis model showed it altered inflammation, innate immune response and gut microbiota, indicating potential protective effects against NEC<sup>72</sup>.

Early-life immune development is orchestrated by a dialogue between diet, microbiota and maturing immune cells. Maternal and infant nutrition provide necessary substrates and signals, while the colonizing microbiota provides critical training for distinguishing friend from foe. The outcome of this dialogue can tilt the balance toward healthy immune tolerance or toward hypersensitivity and dysregulation. Strategies to nurture a tolerance-prone immune trajectory include ensuring infants have exposure to beneficial microbes and an adequate supply of immune-supportive nutrients. The reduction in allergy and other immune disorders seen with such practices aligns with our growing scientific understanding that microbiota and nutrition in early life are as important to immune education as textbooks are to human education.

## 7. Conclusion

Maternal nutrition and the early-life microbiota together create an ecosystem that guides the developmental fate of the child. Nutrigenetics adds a further layer, reminding us that genetic individuality can modulate these effects. The evidence reviewed here indicates that the foundations of lifelong health are, to a significant extent, built in the womb and early infancy. Through epigenetic markings established during these periods, a mother's diet can turn certain fetal genes on or off, influencing processes from metabolism to neurodevelopment. The microbes passed from mother to child and the nutrients that feed those microbes, simultaneously, help train the child's immune system and shape nutrient processing. Early-life programming is not a singular pathway but a symphony of interactions among genes, epigenetic mechanisms, diet and microorganisms.

From a public health and clinical perspective, the implications are far-reaching. Interventions in the perinatal window can yield long-term benefits, such as optimizing maternal diet with sufficient micronutrients like folate, iron, iodine and others, balanced macro-nutrients and fiber to support a healthy microbiome could reduce the risk of adult-onset diseases in the offspring. Encouraging practices like exclusive breastfeeding for the first six months can impart both optimal nutrition and beneficial microbes to the infant, mitigating genetic risks

and enhancing immune protection. There is also the potential for personalized nutrition guidance, leveraging knowledge of nutrigenetic profiles, such as advising carriers of certain polymorphisms to adjust nutrient intake, to further tailor early-life interventions. Microbiome-based therapies, probiotics, prebiotics or even maternal microbiota transplantation in certain cases, are being further explored to prevent or treat conditions like infant colic, eczema or malnutrition by steering the gut ecosystem toward a healthy state.

Ongoing research is unraveling the detailed mechanisms by which nutrigenetic and microbiota-related factors exert their influence. The burgeoning field of metabolomics, for instance, is identifying specific metabolites (many microbially derived) in maternal and cord blood that correlate with infant growth and neurodevelopment. Epigenome-wide association studies in birth cohorts are, likewise, linking specific DNA methylation changes at birth with later health indicators, providing biomarkers of early nutritional exposures. While many questions remain, such as the exact timing and duration of interventions needed to achieve certain outcomes, the consensus is that prevention of disease can begin far earlier than was traditionally appreciated.

The importance of nutrigenetics and microbiota in early life cannot be overstated. They represent intertwined threads in the complex tapestry of developmental biology. Maternal and early infant nutrition, interacting with genetic and microbial factors, set the stage for either a trajectory of resilience or one of vulnerability. By advancing our understanding and integrating insights from human epidemiology and animal models, we are better equipped to design early-life interventions that ensure children not only survive but thrive. The long-term vision is a future where incidence of non-communicable diseases is reduced because we successfully nourished and guided the next generation's genomes and microbiomes from the very start.

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