

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,500

Open access books available

136,000

International authors and editors

170M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Metabolic Programming and Nutrition

*Poliana Guiomar de Almeida Brasiel  
and Sheila Cristina Potente Dutra Luquetti*

## Abstract

Epidemiological and experimental studies have and continue to offer valuable insight into the Developmental Origins of Health and Disease (DOHaD) hypothesis, which emphasizes the importance of early-life nutritional and environmental changes on the increased risk of metabolic diseases in later life. It is now known that non-communicable chronic diseases that were previously associated with lifestyle and genetics have their origins early in life. It is well established that early life environmental signals, including nutrition, set the stage for long-term health and disease risk—effects that span multiple generations. This relationship began still in the intrauterine period and extends throughout the critical period of development. Many types of nutritional challenges including caloric restriction, macronutrient excess, and micronutrient insufficiencies have been shown to induce early life adaptations that produce long-term dysfunction. Several pathways have been suggested to underpin these associations, including epigenetic reprogramming of germ cells. While the mechanisms still remain to be fully investigated, the relationship of nutrition factors in early life and metabolic diseases are clear. This chapter focuses on the role that the nutrition presents during critical periods of development and its repercussions into adulthood.

**Keywords:** metabolic programming, nutrition, epigenetics, developmental programming, obesity, microbiome

## 1. Introduction

In the development period, the fetus may be exposed to an altered risk of developing diseases in adulthood. In this regard, the hypothesis called Developmental Origins of Health and Disease (DOHaD) highlights the relationship between stimuli in the early stages of life and the subsequent development of the disease [1–3]. This model studies the adaptations that occur in the fetus in response to the intrauterine environment, leading to a permanent set of homeostatic systems to assist in immediate survival and improve success in an adverse postnatal environment. However, inappropriate interpretations or environmental changes can lead to an incompatibility between prenatal predictions and postnatal reality [4, 5].

Thus, these adaptations known as predictive adaptive responses can be disadvantageous in adulthood, resulting in an increased risk of diseases that can be transmitted to future generations. In this perspective, it was established that some nutritional changes early in life can lead to an increased risk for several diseases in adulthood [6, 7].

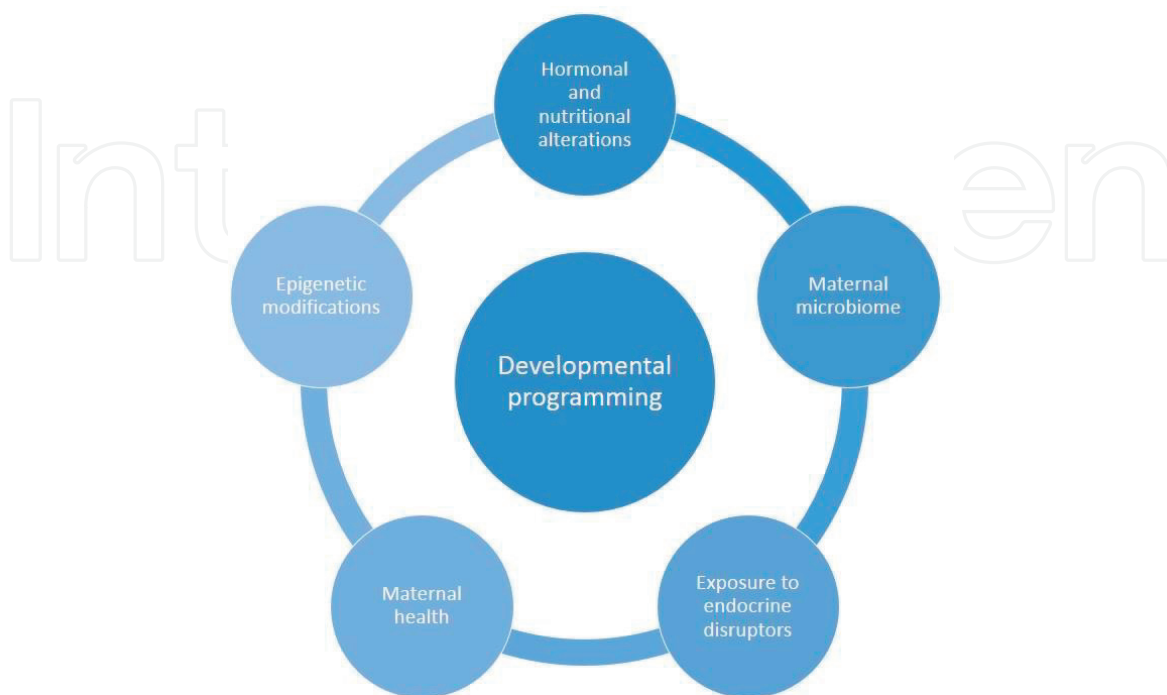
Various studies have shown an association between maternal malnutrition and exposure to hormones during critical periods of development, with metabolic changes, with an emphasis on chronic non-communicable diseases, thyroid disorders, among others [8, 9]. The mother's malnutrition characteristic is capable of interfering with the nutritional status of adult offspring. Maternal protein restriction during lactation led to low weight of the offspring at weaning. Caloric restriction resulted in greater weight gain and resistance to leptin in adult offspring [10].

Programming at a critical stage of development can lead to changes in tissues and organs, which extend throughout life; it may also present a latency period and manifest only in adult life. More studies are emerging to explain the possible mechanisms related to metabolic programming [11, 12].

The mechanisms involved are not entirely clear, but it is believed that there is a relationship between changes in the structural development of the organs and with persistent changes at the cellular level [13]:

- performance in epigenetic memory, with changes in the transcription process;
- alteration of the organ structure in vascularization, innervation, and juxtaposition, such as the position of hepatocytes, endothelial cells, and Kupffer cells, which during organogenesis can permanently modify metabolism;
- hyperplasia or hypertrophy;
- abnormal cell growth under specific metabolic conditions; and
- Metabolic differentiation process.

Molecular mechanisms suggested include acute or chronic changes in gene expression, through various avenues, where there is an epigenetic interrelation between certain genes, exposure to environmental factors, and biological events [5].



**Figure 1.** A complex network that affects adult health and disease, including hormonal and nutrition alterations, epigenetic modifications, microbiota, and the exposure to endocrine disruptors.

As the epigenetic regulation during development changes, the dynamic epigenome has an unstable nature, providing a response and adaptation to environmental pressures, including nutritional changes [2]. **Figure 1** presents the principal mechanisms linked to developmental programming.

There is still a lot to be understood, although epigenetics helps to reveal how exposure to environmental factors, in critical periods of development, leads to changes in adult life, it is necessary to understand the post-epigenetic changes involved in the various processes that lead to the emergence of diseases [13].

## **2. The early-life origins of obesity**

Obesity is defined by an excess of adipose tissue and occurs when an imbalance in the balance of energy exists [14]. The origin of obesity is a complex process that involves genetic and environmental factors and is often associated with the development of chronic complications, such as hyperglycemia, hypertriglyceridemia, low HDL levels, and hypertension. Individuals who have at least three of these criteria are clinically diagnosed as having metabolic syndrome, which increases the risk of developing metabolic diseases, such as type 2 diabetes and cardiovascular diseases [15, 16].

In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these, over 650 million were obese; 41 million children under the age of 5 were overweight or obese, as well as over 340 million children and adolescents aged 5–19 [14]. Recognizing its etiology is essential to face the global epidemic. This creates a challenge since the pathway to obesity in many individuals begins before birth; a predisposition to obesity can occur through epigenetic and other forms of early programming, and obesity and its metabolic consequences result from physiological changes set during fetal and early postnatal development [17–19].

It is known that a number of factors, including epigenetic signals, mitochondrial inheritance, milk composition, gut microbiota, and features of the maternal metabolic environment, such as insulin resistance, fatty acids, and inflammation, may cause developmental programming. In many cases, the effects of the prenatal perturbations are exacerbated by postnatal exposure to a high-calorie diet, accelerated postnatal growth, stress, or other factors [20–22].

The early-life origins of obesity are supported by a number of studies, which have shown that being exposed to inappropriately nutrition levels during critical periods of development (fetal and postnatal) is associated with increased risk of obesity, insulin resistance, and type 2 diabetes in child and adult life [23, 24]. The excessive or deficient nutritional status before birth alters the development of the fat cell, the adipocyte, and results in a permanent increase in the capacity to form new cells in adipose depots (adipogenesis) or to store lipid in existing adipocytes (lipogenesis) since the adipogenesis occurs primarily during late fetal and early postnatal life, and is highly sensitive to the nutritional environment at this time, in particular to the prevailing concentrations of insulin-like growth factors, glucose, insulin, and glucocorticoids [17, 25].

In addition, there are animal and human data that show that obese mothers are more likely to generate to an overweight baby and that these infants are at greater risk of obesity in later life. This “intergenerational cycle of obesity” already is a well-defined phenomenon, showing that maternal obesity, maternal diabetes, and an increase in nutrient supply to the developing fetus constitute major risk factors for obesity in postnatal life [26–28].

There is a greater propensity to develop altered energy metabolism in adult life, in particular, overweight and/or hyperphagia, after malnutrition during fetal

development. This predisposition to develop obesity is particularly clear in the offspring of calorie-restricted dams and is also exacerbated when animals are exposed to an obesogenic environment in adulthood. Mechanisms contained in the deregulation of food intake and energy balance, due to perinatal nutrition, could be related to hypothalamic alterations and a lower capacity to respond to insulin and leptin signaling [29]. One potential mechanism of developmental programming is through permanent structural alterations of different organs. Different stress exposures (oxidative, immune, and inflammatory stresses, as well as maternal-placental-fetal endocrine disturbances) during the prenatal development could reprogram the telomere biology system [30, 31].

### **3. Metabolic pathways and epigenetics**

During their lifetime, cells receive several external signals, like hormones, growth factors, cytokines, and other extracellular factors. This flow of metabolites, through complex metabolic networks, acts optimizing diverse epigenetic cofactors, thus relating nutrition and diet changes into cytoplasmic signaling and chromatin remodeling. Histone modifications—as DNA methylation, RNA interference, and non-coding RNA—inserted by the term epigenetics represent diverted ways by which cells control the expression of genes without any alteration in the underlying genetic material [32].

The produced metabolites remain the same for a given cell, but tissue function and nutrient availability will determine the metabolite requirements. In addition, metabolic challenges, such as calorie or oxygen restriction or even a high-fat diet, drive decisions about cell fate. Consistently, dramatic epigenetic changes have been associated with metabolic disorders, such as obesity, insulin resistance, type 2 diabetes, and cancer [32, 33].

The changes on the cellular and tissue level are followed by alterations in epigenetic regulation of gene expression. Epigenetic modifications refer to heritable changes in gene expression occurring without changes in DNA sequence. The epigenetic code is changed dramatically in the course of embryonic development to initiate varying patterns of gene expression in different developing tissues. This code consists of modifications of chromatin histones and DNA playing a central role in packing DNA by forming nucleosomes. Mechanisms of epigenetic regulation are DNA methylation at cytosine residues in promoter or enhancer gene regions, intragenic DNA methylation usually leading to transcriptional silencing, and posttranslational modifications of core histone proteins, such as acetylation usually resulting in transcriptional activation. Non-coding microRNAs which can govern gene activity at both transcriptional and posttranscriptional levels are one more recently discovered key component of epigenetic control. Another important factor is the microRNA expression that may be modulated by histone modifications or DNA methylation and vice versa, thereby causing feedback loops in epigenetic regulation [30, 34, 35].

The ability of the genotype to produce different phenotypes in response to different environments is termed “plasticity.” The time of maximal plasticity appears to be during development. Nonetheless, heritable phenotypic variation at a later stage is also possible because of the individual’s capability to respond to environmental conditions. Plasticity in developmental programming has evolved to provide the best chances of survival and reproductive success to the organism. When reflecting this theory to developmental data, adaptive growth and metabolic-related strategies for transition from one life history phase to the next and the timing of such transitions (inherent adaptive plasticity) have evolved [36, 37].



Adaptive plasticity enables a species to respond to an environmental change to survive and reproduce and may manifest itself as polyphenism or as a continuous variation in traits. In evolutionary terms, plastic and developmental responses in early life enable an organism to adjust its phenotype so that it can survive in the environment in which it will grow and reproduce. However, the adaptation is not always positive, and the outcome may be harmful and may result in teratogenesis, diseases, or death [36].

There are two types of adaptive responses (plasticity). The first type is the anticipatory or predictive adaptive responses, where the developing organism forecasts the future environment and then adjusts its phenotypic trajectory accordingly. The second type is the immediate adaptive responses that promote short-term maternal or fetal survival with some advantages in later life (developmental plasticity). These adaptive responses have a significant cost, and a cost-benefit analysis is performed to determine the true value of the adaptive response. The links between epigenetics, developmental programming, and plasticity in early growth and nutrition provide subsidies to understand aspects involved in child growth and development and their long-term impact [7, 36].

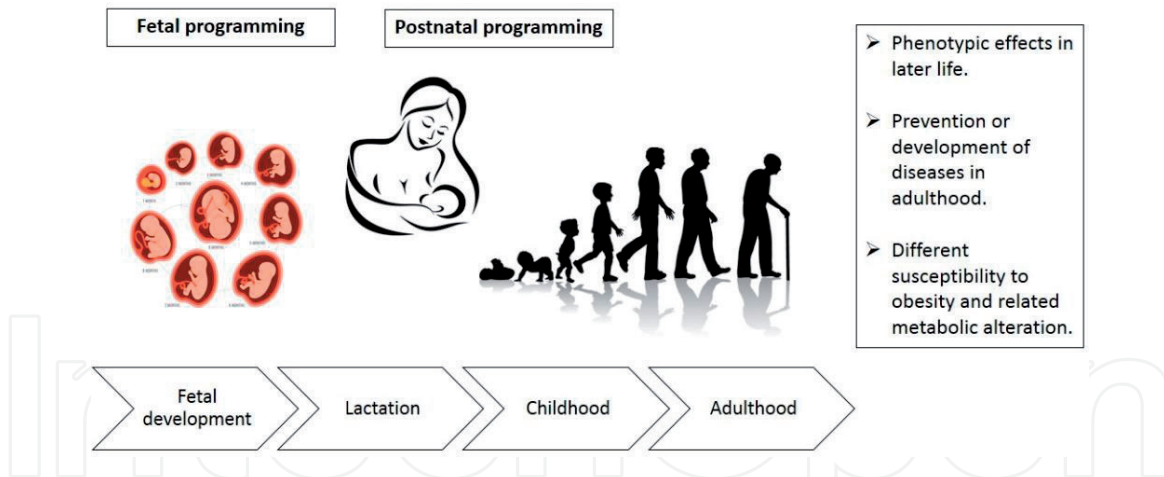
The nutrition is one of the most studied environmental epigenetic factors, and already associations have been observed between adverse prenatal nutritional conditions, postnatal health, and increased risk of disease. It is known that maternal and paternal diets influence metabolic phenotypes in offspring through epigenetic information transmission. Over molecular mechanisms with respect to the fetal origins of adult disease have been suggested including mitochondrial dysfunction and oxidative stress as among the earliest events described in offspring exposed to nutrient restriction. This in turn modifies the expression of critical genes and can affect health and longevity [38].

The foods contain nutrients and bioactive components that can modify epigenetic marks and alter the expression of genes. These compounds, including folate, vitamin B12, methionine, among others, can affect DNA methylation and histone, altering 1-carbon metabolism. The S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), metabolites of 1-carbon metabolism, can alter the methylation of DNA and histones. Thus, nutrients and bioactive components, as well as conditions that may affect the levels of AdoMet or AdoHcy in the tissue, have the ability to modify the methylation of DNA and histones [11, 39].

In a study developed by our research group, we identified that the maternal intake of soybeans in lactation changed the lipid content of breast milk and programmed offspring for a phenotype of the lower metabolic risk. The difference in fat content of breast milk and the higher isoflavones content of soy diet are possible imprinting factors that could program the offspring [18]. This is particularly important because it highlights the dual role of nutritional alterations, whether as reprogramming strategies to prevent disease or leading to adult disease [40].

The metabolic mechanism linked to the programming induced by the adverse intrauterine environment is not completely clear, but fetal metabolic programming has already been indicated to contribute to changes in tissue development, number of cells, neural circuits, and so on. Epigenetic programming plays an important role in the differentiation and development of embryonic, tissue, and stem cells. The changes induced by epigenetic modification in cell or tissue function can be transmitted from fetuses to adults and induce the development of the metabolic syndrome in adult offspring. There is a vulnerable “window” for epigenetic programming when germ cells, embryos, and fetuses are in development [11, 41].

**Figure 2** presents a scheme of developmental origins of health and disease. Epigenetic marks can be modulated by environmental factors, are heritable, perpetuate gene-expression changes that underlie programming, and may contribute to the onset of disease/health in later life.



**Figure 2.** Scheme demonstrative of developmental origins of health and disease, during prenatal and early postnatal life, involved in the susceptibility to obesity and metabolic changes.

#### 4. Microbiome and metabolic health

The genetic set of the microbiome provides extensive metabolic and immunological potential. Genetic and environmental factors influence microbiota composition and function, and these complex host-microbe interactions contribute to health and disease state. The gut microorganisms have a significant role in epithelial barrier function, fermentation of dietary fiber, synthesis of vitamins, regulation of the immune system, and defense against pathogens. This community has also been found to play some important roles in angiogenesis, brain development, and behavior [15, 42].

Given the various functions of microbiota, alterations in this community (dysbiosis) have been associated with a range of non-communicable diseases, including obesity, diabetes, inflammatory bowel disease, metabolic syndrome, cancer, asthma, allergy, non-alcoholic fatty liver disease (NAFLD), and even certain neuropsychiatric disorders [43–46].

The early-life microbiota presents a unique microbial communities consisting of numerous bacteria and viruses. A part of this microbiota already has identified by using different kinds of technologies including 16S rRNA sequencing. Over the last decades, the paradigm of a sterile condition *in utero* is shifting to the possibility of the prenatal maternal-fetal coexist with commensal and symbiotic microbes. Recent studies also support a prenatal microbial milieu through bacterial presentation in placenta, amniotic fluid, umbilical cord, and meconium. In addition, there are emerging reports of the prenatal microbial composition on fetal and postnatal development [47–49].

A maternal condition during pregnancy and postnatal period can provide a critical window for susceptibility to microbiome development through environmental factors such as mode of delivery and maternal diet. The delivery mode has a crucial function in the early gut microbiota composition. Infants by vaginally delivery have higher levels of intestinal *Bacteroides*, *Lactobacilli*, and *Bifidobacterium*, which are commonly present in vaginal route, whereas infants by cesarean section (C-section) have higher level of *Enterococcus*, and *Clostridium* from skin, oral, or hospital environment [47, 50].

The gestational age is another important influencer for gut microbiome development. It is reported that the gut microbiota of preterm infants has shown delayed colonization by limited microbial diversity and this risk of gut dysbiosis.

The gut microbiota composition of preterm infants has *Enterobacter*, *Enterococcus*, *Escherichia*, and *Klebsiella* predominantly and relatively low level of gammaproteobacteria than those in full-term infants [51, 52].

It is known that breastfeeding influences the infant microbiota. The microbiome may affect the DNA methylation through breast milk, which influences the gut microbiome composition. Breastfeeding is associated with greater *Bacteroides* and *Bifidobacterium*, which are folate producers, thereby affecting DNA methylation. Breast milk oligosaccharides alter core microbiome community that secretes short-chain fatty acid (SCFA). Therefore, the strain of *Bifidobacterium* and *Lactobacillus* by breastfeeding could make intestinal contents more acidic with SCFA, which modulate a defense mechanism against pathogens and have epigenetic effects [53–55].

The microbial metabolites such as B vitamins, short-chain fatty acids, polyphenols, and omega 3 polyunsaturated fatty acids are reported to influence epigenetic mechanisms. Maternal gut microbe metabolites can change the host cellular levels of important epigenetic modifiers like histone acetyl transferases (HATs), histone deacetylases (HDACs), DNA methyltransferases (DNMTs), and DNA demethylases. The microbial SCFAs from the fermentation of dietary fiber were shown to maintain the nervous and immune systems through epigenetic modification. These, acetate and butyrate are the most abundant in the intestinal tract and can be produced with acetyl-CoA which is universal acetyl group donor for histone acetylation [45, 47].

Different essential functions for human health develop correspondingly with gut microorganism increase, including vitamin biosynthesis, energy extraction from the diet, gut barrier function, and immune system maturation. The immune system of neonates is immature and requires the exposure of gut bacteria to develop properly. Depending on the health of the mother, maternal bacterial communities may already be imbalanced when passed on to the infant. In children, metabolic diseases, including obesity, insulin resistance, and NAFLD, along with other related immune-based diseases, are associated with modifications in infant gut bacterial composition; however, the mechanisms involved are not entirely clear [43, 56].

## 5. Conclusions

It is known that there is a close relationship between maternal obesity, diet consumption during pregnancy and lactation, and their impact on the microbiota of both mother and infant, including their links to early gut colonization and innate immunity in the infants that drive an increased risk for metabolic diseases.

For the most effective confrontation of metabolic diseases, which represent a great burden of global health, it is important to consider the issues involving early nutrition, metabolic programming, and epigenetics. Thus, the adoption of health policies during critical stages of development, including pregnancy, lactation, and puberty, is essential to achieve long-term consistent results.

## Conflict of interest

The authors declare no conflict of interest.



IntechOpen

IntechOpen

### **Author details**

Poliana Guiomar de Almeida Brasiel\* and Sheila Cristina Potente Dutra Luquetti  
Department of Nutrition, Federal University of Juiz de Fora, MG, Brazil

\*Address all correspondence to: [brasiel.poliana@gmail.com](mailto:brasiel.poliana@gmail.com)

### **IntechOpen**

---

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Barker D, Bull A, Osmond C, Simmonds S. Fetal and placental size and risk of hypertension in adult life. *BMJ*. 1990;**301**:259-262
- [2] Vickers MH. Early life nutrition, epigenetics and programming of later life disease. *Nutrients*. 2014;**6**:2165-2178
- [3] Barker D. Fetal origins of coronary heart disease. *BMJ*. 1995;**311**:171-174
- [4] Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of In utero and early-life conditions on adult health and disease. *The New England Journal of Medicine*. 2008;**359**(1):61-73
- [5] Laker RC, Wlodek ME, Connelly JJ, Yan Z. Epigenetic origins of metabolic disease: The impact of the maternal condition to the offspring epigenome and later health consequences. *Food Science and Human Wellness [Internet]*. Beijing Academy of Food Sciences. 2013;**2**(1): 1-11. DOI: 10.1016/j.fshw.2013.03.002
- [6] Fernandez-Twinn DS, Ozanne SE. Early life nutrition and metabolic programming. *Annals of the New York Academy of Sciences*. 2010;**1212**:78-96
- [7] Gluckman P, Hanson M, Spencer H. Predictive adaptive responses and human evolution. *Trends in Ecology & Evolution*. 2005;**20**(10):527-533
- [8] Passos M, da Fonte Ramos C, Dutra SP, de Moura EG. Transfer of iodine through the milk in protein-restricted lactating rats. *The Journal of Nutritional Biochemistry*. 2001;**12**(5):300-303
- [9] Lisboa P, Fagundes A, Denolato A, Oliveira E, Bonomo I, Alves S, et al. Neonatal low-protein diet changes deiodinase activities and pituitary TSH response to TRH in adult rats. *Experimental Biology and Medicine*. 2008;**233**(1):57-63
- [10] Passos M, Vicente L, Lisboa P, de Moura E. Absence of anorectic effect to acute peripheral leptin treatment in adult rats whose mothers were malnourished during lactation. *Hormone and Metabolic Research*. 2004;**36**(9):625-629
- [11] Zhu Z, Cao F, Li X. Epigenetic programming and fetal metabolic programming. *Front Endocrinol (Lausanne)*. 2019;**10**(764):1-15
- [12] Vieira AM, Brasiel PGA, Ferreira MS, Aguiar AS, Luquetti SCPD. Relationship between the consumption of soy and its derivatives during critical periods of development and in adulthood and endocrine-metabolic disorders. *Journal of Endocrinology and Metabolism*. 2017;**7**(5):135-140
- [13] Koletzko B, Symonds M, Olsen S, Programming PEN, Nutrition AE. Programming research: Where are we and where do we go from here? *The American Journal of Clinical Nutrition*. 2011;**94**:2036S-2043S
- [14] WHO. Obesity and Overweight. World Health Organization (WHO). 2020. Available from: <https://www.who.int/news-room/fact-sheets/detail/o>
- [15] Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas M. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Medicine [Internet]*. 2016;**8**:1-12. DOI: 10.1186/s13073-016-0303-2
- [16] Alberti K, Zimmet P, Shaw J, Group ETFC. The metabolic syndrome—A new worldwide definition. *Lancet*. 2005;**366**:1059-1062
- [17] Muhlhausler B, Smith SR. Early-life origins of metabolic dysfunction: Role of the adipocyte. *Trends in Endocrinology and Metabolism*. 2008;**20**:51-57

- [18] Vieira AM, de Almeida Brasiel PG, Ferreira MS, Mateus K, Figueiredo MS, Lisboa PC, et al. Maternal soybean diet during lactation alters breast milk composition and programs the lipid profile in adult male rat offspring. *Endocrine* [Internet]. 2018;**60**:272-281. DOI: 10.1007/s12020-018-1572-x
- [19] Rito AI, Buoncristiano M, Spinelli A, Salanave B, Kunešová M, Hejgaard T, et al. Association between characteristics at birth, breastfeeding and obesity in 22 countries: The WHO European Childhood Obesity Surveillance Initiative—COSI 2015/2017. *Obesity Facts*. 2019;**12**:226-243
- [20] Isganaitis E. Developmental programming of body composition: Update on evidence and mechanisms. *Current Diabetes Reports*. 2019;**19**(8):60
- [21] Jazwiec PA, Sloboda DM. Nutritional adversity, sex and reproduction: 30 years of DOHaD and what have we learned? *The Journal of Endocrinology*. 2019;**242**(1):T51-T68
- [22] Neri C, Edlow AG. Effects of maternal obesity on fetal programming: Molecular approaches. *Cold Spring Harbor Perspectives in Medicine*. 2016;**6**:1-21
- [23] Lukaszewski M, Eberlé D, Vieau D, Breton C. Nutritional manipulations in the perinatal period program adipose tissue in offspring. *American Journal of Physiology. Endocrinology and Metabolism*. 2013;**305**(10):E1195-E1207
- [24] Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: Causes and consequences for obesity in children and adults. *International Journal of Obesity*. 2006;**30**:S11-S17
- [25] Patel M, Srinivasan M. Metabolic programming in the immediate postnatal life. *Annals of Nutrition & Metabolism*. 2011;**58**:18-28
- [26] Morris MJ. Early life influences on obesity risk: Maternal overnutrition and programming of obesity. *Expert Review of Endocrinology and Metabolism*. 2009;**4**(6):625-637
- [27] Millership SJ, Van De Pette M, Withers DJ. Genomic imprinting and its effects on postnatal growth and adult metabolism. *Cellular and Molecular Life Sciences* [Internet]. 2019;**76**(20):4009-4021. DOI: 10.1007/s00018-019-03197-z
- [28] Montalvo-Martínez L, Maldonado-Ruiz R, Cárdenas-Tueme M, Reséndez-Pérez D, Camacho A. Maternal overnutrition programs central inflammation and addiction-like behavior in offspring. *BioMed Research International*. 2018;**2018**:8061389
- [29] Sominsky L, Jasoni CL, Twigg HR, Spencer SJ. Hormonal and nutritional regulation of postnatal hypothalamic development. *The Journal of Endocrinology*. 2018;**237**(2):R47-R64
- [30] Vaiserman AM. Birth weight predicts aging trajectory: A hypothesis. *Mechanisms of Ageing and Development* [Internet]. 2018;**173**:61-70. DOI: 10.1016/j.mad.2018.04.003
- [31] Thompson LP, Al-hasan Y. Impact of oxidative stress in fetal programming. *Journal of Pregnancy*. 2012;**2012**:1-8
- [32] Rabhi N, Hannou SA, Froguel P, Annicotte J-S. Cofactors as metabolic sensors driving cell adaptation in physiology and disease. *Front Endocrinol (Lausanne)*. 2017;**8**:1-8
- [33] Moody L, Wang H, Jung PM, Chen H, Pan Y. Maternal and post-weaning high-fat diets produce distinct DNA methylation patterns in hepatic metabolic pathways within specific genomic contexts. *International Journal of Molecular Sciences*. 2019;**20**(13):E3229
- [34] Bannister AJ, Kouzarides T. Regulation of chromatin by histone

- modifications. *Cell Research* [Internet]. 2011;21:381-395. DOI: 10.1038/cr.2011.22
- [35] Wei J, Huang K, Yang C, Kang C. Non-coding RNAs as regulators in epigenetics (review). *Oncology Reports*. 2017;37(1):3-9
- [36] Hochberg Z, Feil R, Constanica M, Fraga M, Junien C, Carel J, et al. Child health, developmental plasticity, and epigenetic programming. *Endocrine Reviews*. 2011;32:159-224
- [37] Chui C, Li Y, Maloney CA, Cropley JE, Suter CM. Epigenetic programming by maternal nutrition: Shaping future generations. *Epigenomics*. 2010;2(4):539-549
- [38] Tiffon C. The impact of nutrition and environmental epigenetics on human health and disease. *International Journal of Medical Sciences*. 2018;19(11):E3425
- [39] Choi S, Friso S. Epigenetics: A new bridge between nutrition. *Advances in Nutrition*. 2010;1:8-16
- [40] Hsu C-N, Tain Y-L. The good, the bad, and the ugly of pregnancy nutrients and developmental programming of adult disease. *Nutrients*. 2019;11(4):1-21
- [41] Marousez L, Lesage J, Eberl D. Epigenetics: Linking early postnatal nutrition to obesity programming? *Nutrición Hospitalaria*. 2019;11(12):2966
- [42] Stinson LF. Establishment of the early-life microbiome: A DOHaD perspective. *Journal of Developmental Origins of Health and Disease*. 2019:1-10
- [43] Mulligan CM, Friedman JE. Maternal modifiers of the infant gut microbiota—Metabolic consequences. *The Journal of Endocrinology*. 2017;235(1):R1-R12
- [44] Giorgetti G, Brandimarte G, Fabiocchi F, Ricci S, Flamini P, Sandri G, et al. Interactions between innate immunity, microbiota, and probiotics. *Journal of Immunology Research*. 2015:1-7
- [45] Li Y. Epigenetic mechanisms link maternal diets and gut microbiome to obesity in the offspring. *Frontiers in Genetics*. 2018;9:1-13
- [46] Stols-Gonçalves D, Tristão LS, Henneman P, Nieuwdorp M. Epigenetic markers and microbiota/metabolite-induced epigenetic modifications in the pathogenesis of obesity, metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease. *Current Diabetes Reports*. 2019;19(6):31
- [47] Lee H. The interaction between gut microbiome and nutrients on development of human disease through epigenetic mechanisms. *Genomics & Informatics*. 2019;17(3):e24
- [48] Smith-Brown P, Morrison M, Krause L, Davies PSW. Mothers secretor status affects development of childrens microbiota composition and function: A pilot study. *PLOS One*. 2016;11(9):e0161211
- [49] Calatayud M, Koren O, Collado MC. Maternal microbiome and metabolic health program microbiome development and health of the offspring. *Trends in Endocrinology and Metabolism* [Internet]. 2019;30(10):735-744. DOI: 10.1016/j.tem.2019.07.021
- [50] Zhou X, Du L, Shi R, Chen Z, Zhou Y, Li Z. Early-life food nutrition, microbiota maturation and immune development shape life-long health. *Critical Reviews in Food Science and Nutrition*. 2019;59:S30-S38
- [51] Milani C, Duranti S, Bottacini F, Casey E, Turrone F, Mahony J, et al. The first microbial colonizers of the



human gut: Composition, activities, and health implications of the infant gut microbiota. *Microbiology and Molecular Biology Reviews*. 2017;**81**(4):e00036-e00017

[52] Montoya-Williams D, Lemas DJ, Spiryda L, Patel K, Carney OO, Neu J, et al. The neonatal microbiome and its partial role in mediating the association between birth by cesarean section and adverse pediatric outcomes. *Neonatology*. 2018;**114**(2):103-111

[53] Ramos-Roman MA. Breast milk: A postnatal link between maternal life choices and the prevention of childhood obesity. *Clinical Therapeutics*. 2018;**40**(10):1655-1658

[54] Pannaraj PS, Li F, Cerini C, Bender JM, Yang S, Rollie A, et al. Association between breast Milk bacterial communities and establishment and development of the infant gut microbiome. *JAMA Pediatrics*. 2017;**171**(7):647-654

[55] Pauwels S, Symons L, Vanautgaerden E, Ghosh M, Duca RC, Bekaert B, et al. The influence of the duration of breastfeeding on the infant's metabolic epigenome. *Nutrients*. 2019;**11**(6):E1408

[56] Jasarevic E, Bale TL. Prenatal and postnatal contributions of the maternal microbiome on offspring programming. *Frontiers in Neuroendocrinology* [Internet]. 2019;**55**:100797. DOI: 10.1016/j.yfrne.2019.100797