

## Nutrition and Cardiovascular Diseases: Programming and Reprogramming

Emiliana Barbosa Marques,<sup>1</sup> Karyne Pollo de Souza,<sup>2</sup> Thaís Alvim-Silva,<sup>3</sup> Ivis Levy Fernandes Martins,<sup>4</sup> Samuel Pedro,<sup>5</sup> Christianne Bretas Vieira Scaramello<sup>6</sup>

Universidade Federal Fluminense, Instituto Biomédico, Niterói, RJ - Brazil

### Abstract

The Developmental Origin of Health and Disease (DOHaD) is an area of science dedicated to studying the processes by which insults during critical periods of mammals development leading to physiological changes result in diseases throughout life. Studies point to a complex interaction between nutritional status in early life and cardiovascular system homeostasis in which maternal malnutrition during gestation and/or lactation, as well as early weaning, are associated with development of cardiovascular diseases in adulthood. In this context, epigenetic changes, such as DNA methylation, histone acetylation, and change in microRNA expression have been considered molecular bases of cellular plasticity, which can also be gender-dependent. Experimental studies have demonstrated that interventions encompassing the consumption of functional food/bioactive compounds, as well as energetic and nutrients adjustments on the diet, may attenuate or even prevent consequences associated with plasticity of development, improving cardiovascular health. This review aimed to gather and discuss the findings within this context, published over the last ten years.

### Introduction

Cardiovascular diseases (CVDs) are the main cause of death worldwide and belongs to the group of chronic non-communicable diseases (NCDs).

### Keywords

Cardiovascular Diseases; Nutrition; Pregnancy; Lactation; Functional Food; Epigenomics.

According to the World Health Organization (WHO), approximately 17.9 million people died of CVD in 2016, nearly 31% of the total number of deaths in the world.<sup>1</sup> In Brazil, where the scenario is similar, these diseases are responsible for the highest mortality rates in the same year.<sup>2</sup> This health public problem results in high costs with treatments and hospitalizations by Brazilian Unified Health System (SUS in Portuguese), in addition to indirect economic impact caused by reduction on productivity and sick absence.<sup>3</sup>

For years, it was believed that CVDs were determined by genetic factors and lifestyle. However, evidences has shown that, in the majority of cases, CVDs in adulthood may be related to the process of cellular plasticity due to nutritional insults during pregnancy and/or lactation.<sup>4</sup> Experimental studies have proven that mother's nutritional status during the critical periods of development, such as gestation and lactation, as well as early weaning, may favor NCDs programming throughout life.<sup>5</sup> These studies encompass a new area of science called *Developmental Origin of Health and Disease* (DOHaD) introduced by David Barker, which investigate the programming of diseases with fetal origins.<sup>5-7</sup>

Currently, it is well-known that the programming of the cardiovascular system can also occur directly in critical stages of life.<sup>4</sup> Recent studies have illustrated that the differentiation and proliferation of cardiac cells are not entirely complete at birth, continuing in the immediate post-natal period. DNA synthesis of these cells still takes place during the first two weeks of life in rodents and, in human beings, in the first 20 years, making the mammals' hearts vulnerable to insults during intrauterine development as well as during lactation period.<sup>8,9</sup> Moreover, embryonic and immediate post-natal development periods are stages of life characterized by rapid growth and organs and

**Mailing Address: Emiliana Marques**

Rua Professor Hernani Pires de Melo, 110. Postal Code: 24220-900, Niterói, RJ – Brazil  
E-mail: milibmarques@hotmail.com

systems maturation. Thus, the lack or excess of nutrients during these periods favors adaptations that look for guarantee of survival in an adverse environment.<sup>10</sup> The direct impact upon gene expression, stimulating or inhibiting factors that control the cell cycle, mitosis rates, maturity, and cell death alter homeostasis, characterizing the adaptive process of many species.<sup>7</sup> In this context, epigenetic changes, such as DNA methylation, histone acetylation, and change in the microRNA expression have been considered molecular bases of cell plasticity.<sup>11</sup>

Diets that are inadequate in macro and micronutrients have been identified as an important stimulator of epigenetic processes, especially DNA methylation.<sup>12</sup> Studies in animal models have demonstrated that maternal malnutrition during the critical periods of development affects the DNA methylation of specific genes, changing the phenotype of the offspring and contributing to the programming of diseases, including cardiometabolic diseases.<sup>7,13</sup> By contrast, nutritional interventions in these same periods could favor the reprogramming of diseases through similar mechanisms.<sup>6,14</sup> Interventions with bioactive

compounds from functional foods may attenuate or even reprogram the physiological changes related to cell plasticity (Figure 1).<sup>15</sup>

Although evidence shows that the sex is an important variable, for various reasons this variable is ignored in many studies conducted primarily with individuals of the male sex. The literature points out differences in gender, regarding the progression, response, and treatment of CVDs, in such a way that studies conducted only with men can lead to incorrect diagnoses and inappropriate therapies.<sup>16</sup> Thus, it is important to consider that disease development may be influenced by sex, as well as be passed down through generations.<sup>18</sup> This review aimed to gather the findings about programming and reprogramming of CVDs associated with malnutrition during gestation and/or lactation, as well as about interventions with functional foods/bioactive compounds, addressing whenever possible, sexual dimorphism and physiologic changes passed down through generations. Since epidemiological studies often fail to answer many questions related to developmental plasticity, this review focused in rodents studies.

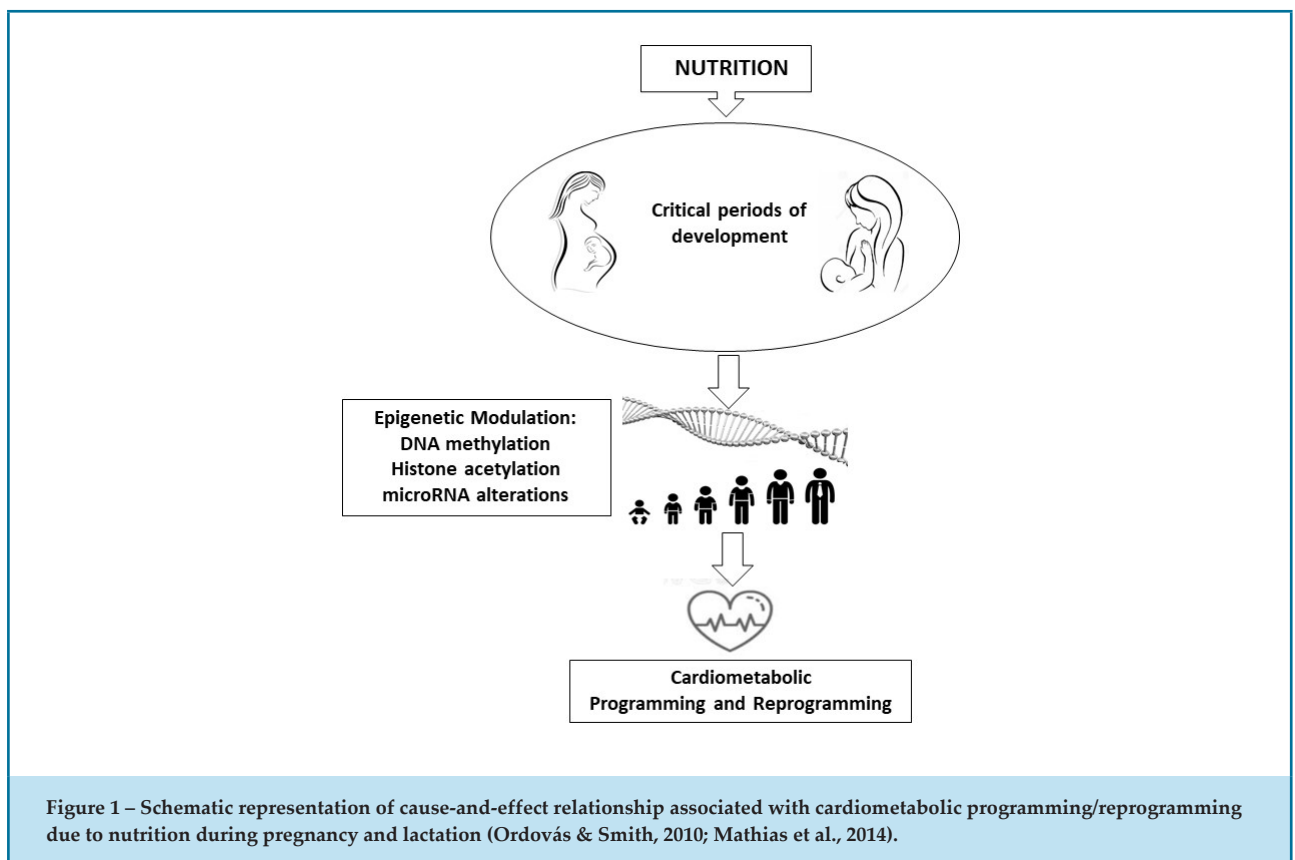


Figure 1 – Schematic representation of cause-and-effect relationship associated with cardiometabolic programming/reprogramming due to nutrition during pregnancy and lactation (Ordovás & Smith, 2010; Mathias et al., 2014).

## Methods

To conduct this review, a bibliography study was carried out in January 2020 by 05 (five) separate researchers, with a subsequent group discussion. The studies were selected by accessing the Pubmed/MEDLINE and Scielo databases. The terms used in this research sought to gather studies involving cardiometabolic programming/development plasticity, including different animal models (rodents) of maternal malnutrition during gestation and/or lactation, including early weaning, as well as studies involving interventions with functional foods and/or isolated bioactive compounds. This study searched for articles that presented outcomes associated with the risk of development and CVDs, as well as those which had been published over the last ten years. Studies in languages other than Portuguese or English, through the reading of titles and abstracts, were excluded. Finally, some articles were also excluded upon reading the full text.

## Results

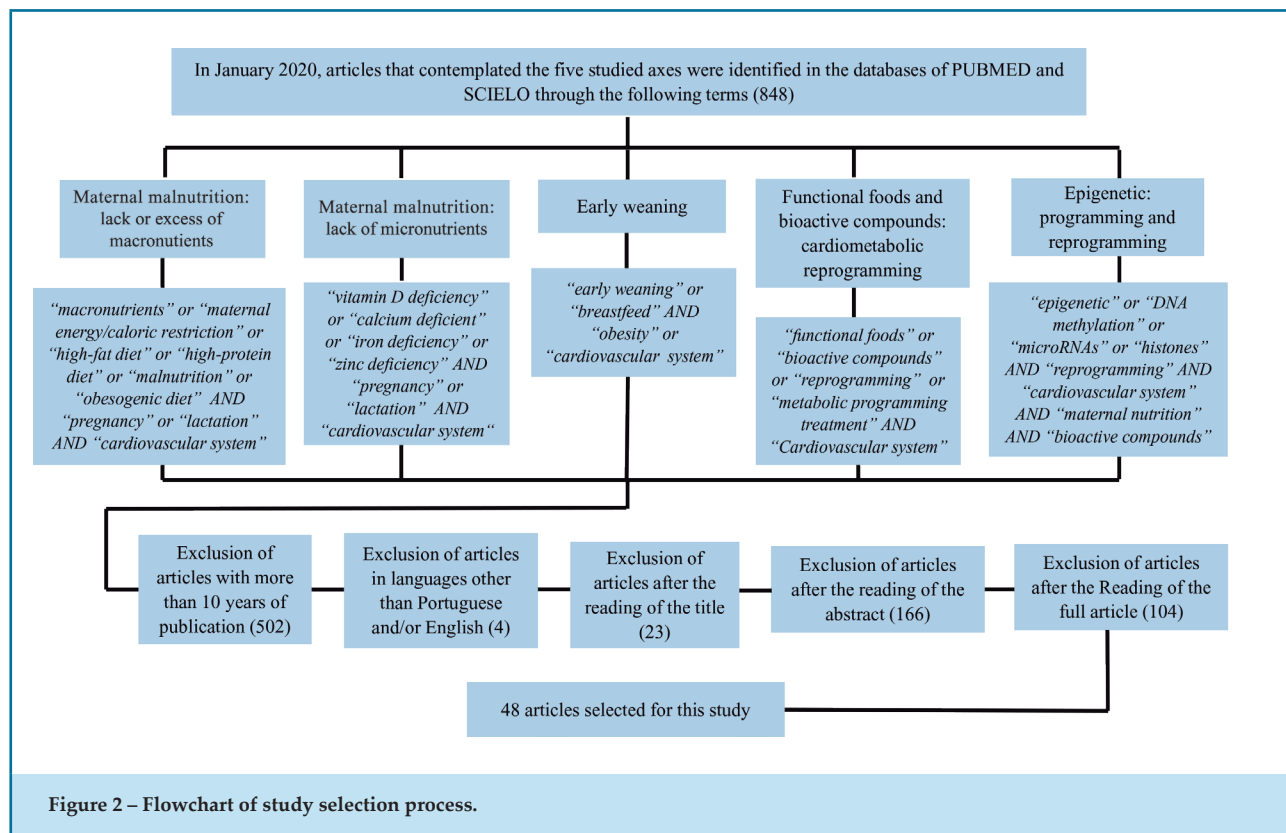
Figure 2 illustrates the literature selection process. In total, 848 results were found, of which 799 articles

were excluded due to the criteria mentioned above. Therefore, 48 articles were selected as they presented a direct connection to the object of this study.

### Maternal malnutrition: lack or excess of macronutrients

The study including the Dutch Famine, which occurred during World War II, represents a historical milestone for studies involving the origin of diseases related to malnutrition in the early life. This work demonstrated that maternal malnutrition during gestation disrupts the metabolism of the descendants in the long run, resulting in hyperglycemia, a greater incidence of CVD, blood clotting disorders, as well as an increase in the capacity of response to stress and obesity.<sup>19</sup>

According to the WHO,<sup>20</sup> malnutrition refers to the deficiencies, excesses, or imbalances in the energy and/or nutrient intake. The inadequate consumption of macronutrients during the critical periods of development has been related to cardiometabolic diseases in one's offspring.<sup>21</sup> Malnutrition during the intrauterine life associated with maternal food restrictions contributes to a worse performance and a premature phenotype of cardiac aging in adult offspring. Similarly, nutritional



excesses in the early life, associated with maternal obesity can induce the involvement of the descendants' cardiac function over the long term. These exposures alter one's cardiac metabolism and the microRNAs involved in each development stage of the heart and seem to play a crucial role in the unfavorable programming of CVDs.<sup>22</sup>

Thus, diets that are restrictive in macronutrients and/or obesogenic diets, characterized by the excess of calories, sugars, and lipids, can lead to malnutrition and, if consumed by the mother during gestation and/or lactation, can be equally capable of programming the offspring for cardiometabolic diseases.<sup>23</sup> Maternal malnutrition (F0 generation) programs its direct descendants (F1 generation), and it is capable of programming its subsequent generations (F2, F3, for example).<sup>24</sup> Table 1 shows studies, including animal models, which evaluate the consequences, over the long term, of the excess or restriction of macronutrients during these critical periods.

### Maternal malnutrition: lack of micronutrients

The same way as macronutrients, the micronutrients are also essential to biological activity.<sup>35</sup> Their deficiencies affect many pregnant women and are considered a growing health problem that encompasses nearly 2 billion people worldwide. This condition is also known as hidden hunger, and includes deficiencies of iron, calcium, iodine, folate, and zinc, as well as other lesser-known micronutrients, such as selenium, chromium, and vanadium.<sup>36,37</sup>

The consumption of micronutrients varies widely during gestation and among populations. Women from underdeveloped countries are more exposed to malnutrition during gestation, and the nutritional demands of this period can accentuate the deficiencies of these nutrients, with severe consequences for the health of the mother and the baby. It is currently estimated that 15-20% of these women suffer from lack of iron, 15% from lack of vitamin A, and 25% from lack of zinc.<sup>35</sup> Micronutrient supplements diminish the risk of low birth weight, small size for the gestational age, and stillbirths due to malnutrition, thus justifying this intervention during pre-natal follow-up. The positive effects of a proper maternal diet regarding micronutrients can persist into childhood, but data is scarce concerning possible benefits in the long run.<sup>35</sup> Table 2 summarizes the main findings resulting from the need for micronutrients in animal models during critical periods of development.

### Early weaning

Breast milk is the ideal food for a newborn's nutrition. In general, human milk is 87% water, 7% lactose, 3.8% fat and 1% protein; however, its composition varies during lactation, adapting to the changes needed for the child's growth.<sup>46,47</sup> Supplementation with infant formula is recommended only for the cases in which exclusive breastfeeding is impossible, unsustainable, or inadequate. In most cases, cow's milk or soy milk is used as a base, complemented with ingredients produced by genetic engineering, which most closely resembles breast milk. Even though the industry's intention is to imitate human milk as closely as possible, the use of infant formulas should only be considered after having depleted all alternative possibilities of breastfeeding.<sup>47,48</sup>

Adequate breastfeeding is essential for the survival, health, and growth of children; it preserves the mother's health and contributes to the development of human capital. Strong evidence of this can be found in studies with humans that show the existence of a proportionally inverse relationship between the duration of breastfeeding and the risk of obesity, hypertension, dyslipidemia, and type II diabetes mellitus in adulthood.<sup>49</sup> Based on this, since 1990, international agencies specialized in health adopted the Innocenti Declaration, recommending exclusive breastfeeding until six months of age.<sup>50</sup> However, the WHO analyzed the duration of breastfeeding in 108 countries and found that only 32% of the children received only breast milk in the first semester of life. One of the determining factors of early weaning seems to be the socioeconomic aspect.<sup>51</sup> Some studies discuss that in high-income countries, the socioeconomic status seems to be positively associated with the duration of breastfeeding. Others believe that breastfeeding became less common in high-income countries during the 20<sup>th</sup> century and that similar standards have been observed in women with a high educational level, from urban environments, and who have a higher purchasing power in middle and low-income countries.<sup>50,51</sup> Although breastfeeding is cited as the reason for women to leave the workplace, evidence suggests that the majority remain in their jobs and choose to use breast milk substitutes or interrupt breastfeeding.<sup>50</sup>

Table 3 presents studies including animal models that evaluate the consequences of early weaning over the long term.

**Table 1 – Studies in animal models, including maternal malnutrition resulting from a lack or excess macronutrients and its outcome in offspring**

Reference	Model of malnutrition (F0 generation)	Species	Post-natal moment of evaluation, generation, and evaluated sex	Main outcomes in the offspring
24	Maternal energy restriction: gestation	Wistar Rats	16 weeks (F1, F2, and F3 generation) Male	↑ Blood pressure ↓ Vasodilator response to acetylcholine Damage to the production of nitric oxide in the F1, F2, and F3 generations
25	Protein restriction: gestation	Wistar Rats	70 days (F1 generation) Male	Induction of cardiac fibrosis markers Damage to myocardial function ↓ Ejection and shortening fractions ↑ Ventricular diameter
26	Protein restriction: gestation /lactation	Wistar Rats	90 days (F1 generation) Male	↑ Cardiovascular sympathetic tone ↑ Blood pressure
27	Protein restriction: gestation /lactation	Wistar Rats	70-90 days (F1 generation) Male	Disruption of glutamatergic signaling in the nucleus of the solitary tract ↑ Blood pressure
28	Protein restriction: gestation	Albino Rats	24 weeks (F1 generation) Male	Positive regulation of nitric oxide synthase Cell apoptosis ↓ Number of cardiomyocytes ↑ Interstitial Fibrosis
29	Hyperlipidic Maternal Diet: gestation /lactation	Sprague Dawley Rats	60 days (F1 generation) Male	↑ Blood pressure ↓ Cardiac baroreflex function ↑ Response to angiotensin II and pro-inflammatory cytokines through the positive regulation of the cerebral renin-angiotensin system Oxidative and inflammatory stress
30	Hyperlipidic Maternal Diet: gestation /lactation	Sprague Dawley Rats	Neonatal (F1 generation) Male and Female	Damage in the glycolytic and respiratory capacity ↑ Lipid peroxidation and mitochondrial dysfunction Cardiac dysfunction
31	Hyperlipidic Maternal Diet: gestation	Sprague Dawley Rats	3 months (F1 generation) Male and Female	Gender-dependent cardiac hypertrophy ↑ Susceptibility of the heart to the ischemia/reperfusion lesion in male rats ↓ Connection of the glucocorticoid receptors to their response elements in the angiotensin II receptor ↓ Glucocorticoid receptors in the heart of male rats
32	Pre-gestational Maternal Obesity: gestation/lactation	Mice C57BL/6	3, 5, 8, and 12 weeks (F1 generation) Male	Cardiac hypertrophy Cardiac dysfunction Dominance of the sympathetic activity in the heart
33	Obesogenic Maternal Diet: lactation	Mice C57BL/6	8 weeks (F1 generation) Male	Hypertension Cardiac dysfunction Hypertrophy ↑ Cardiomyocyte area Cardiac remodeling
34	Obesogenic Maternal Diet: gestation/ lactation	Sprague Dawley Rats	12 weeks (F1 generation) Male	Modulation of the angiogenetic activity in endothelial cells ↓ Vasorelaxant response Poor revascularization ↑ Tissue fibrosis

**Table 2 – Studies in animal models including the maternal malnutrition resulting from a lack of micronutrients and its outcome in offspring.**

Reference	Model of malnutrition (F0 generation)	Species	Post-natal moment of evaluation and evaluated sex (F1 generation)	Main outcome in offspring
38	Maternal diet deficient in Iron: 2 weeks after mating and in the perinatal period	Sprague Dawley Rats	6 months Male and Female	↓ Production of nitric oxide
39	Maternal diet deficient in Zinc: gestation/lactation	Wistar Rats	60 days Male	↑ Blood pressure Vascular dysfunction Damage to the renal function
40	Maternal diet deficient in Zinc: gestation/lactation	Wistar Rats	6 and 81 days Male and Female	↓ Nitric oxide synthase in the aorta ↑ Oxidative stress ↑ Deposition of collagen in the tunica media ↓ Activity of endothelial nitric oxide synthase ↑ Systolic blood pressure in male rats
41	Maternal diet deficient in Zinc: gestation/lactation	Wistar Rats	81 days Male and Female	Activation of apoptotic and inflammatory processes ↓ Growth factor expression TGF-β1 ↓ Activity of nitric oxide synthase in the cardiac tissue
42	Maternal diet deficient in vitamin D: 4 weeks before mating and during gestation/lactation	Sprague Dawley Rats	3 and 30 days Male and Female	↑ Volume of left ventricle Hyperplasia and hypertrophy of cardiomyocytes ↑ Proportion of mononuclear cardiomyocytes
43	Maternal diet deficient in vitamin D: 6 weeks before mating and during gestation/lactation	Sprague Dawley Rats	8 weeks Male and Female	↑ Systolic blood pressure ↓ Vascular complacency
44	Maternal diet deficient in vitamin D: 10 weeks before mating and during gestation	Sprague Dawley Rats	12 weeks Male and Female	↑ Systolic blood pressure Involvement of endothelium relaxation
45	Maternal diet deficient in Calcium: gestation/lactation	Wistar Rats	180 days Male and Female	↑ Serum glucose and insulin in male rats ↑ HOMA-IR Index in male rats ↓ Systolic blood pressure in female rats ↓ Heart rate in female rats

### Functional foods and bioactive compounds: cardiometabolic reprogramming

Specialists highlight a balanced, healthy, and varied diet as the best way to prevent chronic diseases. These recommendations are based on existing associations between the consumption of foods, such as fruits, vegetables, and whole grains, and the prevention of CNCD. In fact, epidemiological studies show an inverse association between the prevalence of these diseases and

the consumption of these foods. As a result, the so-called “functional foods” emerged, which provide benefits to the health of those who eat them.<sup>56</sup>

Brazilian law sets forth the legal definition of functional foods: “foods or ingredients that, in addition to their basic nutritional functions, when consumed as part of the usual diet, produce metabolic effects and/or physiological and/or benefits to health, which should be safe for consumption without medical prescription”.<sup>57</sup> These foods contain

**Table 3 – Studies in animal models including early weaning and its outcomes in offspring.**

Reference	Protocol for early weaning (F0 generation)	Species	Post-natal moment of evaluation and evaluated sex (F1 generation)	Main outcome in offspring
52	Physical barrier: Bandages on the mother on post-natal day 18	Wistar Rats	21 and 180 days Male	Metabolic syndrome ↑ adiposity dyslipidemia resistance to insulin resistance to leptin
53	Physical barrier: Bandages on the mother or pharmacological barrier: administration of bromocriptine (0.5 mg/kg ip twice daily) on post-natal day 18	Wistar Rats	90, 120, 150, and 180 days Male	Hyperphagia, ↑ visceral fat and bone mass ↑ plasmatic levels of leptin and vitamin D
54	Maternal separation: 3h/day of the post-natal days 3 to 12	Sprague Dawley Rats	55-66 days Male and Female	↑ cardiac response to hypoxia Instability of the cardiorespiratory response
55	Physical barrier: Bandages on the mother or pharmacological barrier: administration of bromocriptine (0.5 mg/kg ip twice daily) on post-natal day 18	Wistar Rats	180 days Female	Weight gain ↑ adiposity hyperleptinemia ↓ estrogen

components, called “bioactive compounds”, defined as “nutrients or non-nutrients normally eaten as a component of some other food, producing metabolic or physiological action in the body.”<sup>58</sup>

Studies point out that diets rich in bioactive compounds can reduce the risk of CVD. For instance, anthocyanins present in red fruits; resveratrol, phenolic compound found in grapes; catechins, found in large quantities in green tea; phytosterols, present in vegetable oils; isoflavones, found in soy beans; Omega-3 fatty acids observed in linseed, chia, and fish; probiotics present in dairy products; prebiotics found in vegetables, fruits, and whole grain, oleaginous, and leguminous cereals; among others.<sup>56,59-61</sup> Evidence still suggests that intestinal dysbiosis plays an important role in the pathogenesis of these diseases, in which, bioactive compounds may act in the modulation of the microbiota in order to favor a healthy bacterial population.<sup>61</sup>

The literature proposes that these compounds can unleash epigenetic changes that have accumulated throughout life, involved in the pathogenesis of

diseases related to age.<sup>61</sup> Based on DOHaD theory, it is reasonable to assume that the early life could also constitute a temporal window to begin dietetic interventions focused on the prevention of diseases. The knowledge about the consequences of the early exposure to bioactive compounds is still limited. Table 4 presents experimental studies that investigated whether or not these compounds would be able to prevent both the development of cardiometabolic diseases associated with malnutrition in critical periods, as well as attenuate the injuries caused by it.

### Epigenetics: programming and reprogramming

As the epigenetic changes are modulated by environmental exposure, epigenetics is considered the interface between genetics and the environment. Thus, these changes have been highlighted as molecular mechanisms that are subjacent to the process that associates malnutrition in critical periods of development and cardiometabolic programming. In addition, given the capacity of response of the epigenetic markers to

**Table 4- Studies including the effects of bioactive compounds in the prevention or reprogramming of cardiometabolic diseases programmed in the offspring in different animal models of malnutrition in the beginning of life.**

Reference	Model of malnutrition (F0 generation)	Species	Functional food/ bioactive compound	Intervention: F0 or F1 generation Post-natal moment of evaluation and evaluated sex	Main outcomes in offspring
62	Overnutrition: Reduction in the litter during lactation	Wistar Rats	Yerba mate tea ( <i>Ilex paraguariensis</i> )	F1: treatment by gavage with yerba mate solution (1g/kg/2mL of water) between post-natal days 150 and 180 Male	Reversion of hypothalamic resistance to insulin Normalization of enzyme activity in the liver ↓ Lipid peroxidation ↓ Level of steatosis and of hepatic triglycerides
63, 64	Early weaning: physical barrier	Wistar Rats	Calcium carbonate	F1: diet supplemented with calcium carbonate (10g/kg of feed) between post-natal days 120 and 180 Male	Mitigated hyperphagia ↓ Overweight and adiposity ↓ Inflammatory state ↓ Resistance to vitamin D in adipocytes
65	Early weaning: physical barrier	Wistar Rats	Resveratrol	F1: treatment by gavage with resveratrol solution (30mg/kg in a 0.5% p/v solution of methylcellulose) between post-natal days 150 and 180 Male	↓ Overweight ↓ Feed intake ↓ Hypertrophy of adipocytes ↓ Serum leptin ↓ Glycemia ↓ Resistance to leptin and insulin ↑ Adiponectine
66	Hyperlipidic maternal diet: gestation/lactation	Wistar Rats	Grape seed extract rich in Procyanidin	F0: treatment by gavage with the extract (25mg/kg): gestation/lactation F1: evaluated on post-natal day 30 Male	↑ White adipose tissue ↑ Monocyte chemoattractant protein-1 (MCP-1) ↓ Plasmatic levels of glycerol
67	Hyperlipidic maternal diet: lactation	Wistar Rats	Grape skin extract ( <i>Vitis vinifera L.</i> )	F0: treatment by gavage with the extract (200mg/kg): lactation F1: evaluated on post-natal days 90 and 150 Male	Reversion of resistance to insulin ↓ Systolic blood pressure ↓ Adiposity ↓ Plasmatic triglycerides ↓ Glycemia ↓ Oxidative stress
68	Maternal diabetes induced by diet or administration of streptozocine (35mg/kg)	Wistar Rats	Linseed flour and oil	F0: feed supplemented with linseed flour (25%) or linseed oil (7%): gestation/lactation F1: evaluated on post-natal day 100 Male	Unaltered biochemical parameters Hindered aortic remodeling



69	Maternal hyperlipidic diet: gestation/lactation	Sprague Dawley	Prebiotic: Long chain inulin or Probiotic: <i>Lactobacillus casei</i>	F0: treatment with Inulin (5% p/p) or <i>Lactobacillus casei</i> (2×108 UFC/day), concomitant to hyperlipidic diet F1: evaluated after 16 weeks Male	Hindered increase in blood pressure ↑ Beneficial bacteria
70	Maternal diet with high fructose content (60%): gestation/lactation	Sprague Dawley	Resveratrol	F1: diet similar to maternal + resveratrol (50 mg/L) until post-natal day 90 Male	↓ Blood pressure ↓ Renal oxidative stress Positive modulation of the intestinal microbiota
71	Supplementation of fructose in the mother's water (100 g/L): gestation	Wistar Rats	Melinjo seed extract ( <i>Gnetum gnemon</i> )	F0: diet supplemented with 0.1% Melinjo: lactation F1: evaluated in day 17 after weaning Female	↑ Protein kinase expression activated by phosphorylated adenosine monophosphato (AMPK) and of endothelial nitric oxide synthase in the kidneys ↓ Systolic blood pressure
72	Maternal hypoprotein diet: gestation	Wistar Rats	Green tea extract	F0: diet supplemented with 0.12% or 0.24% of green tea extract: lactation F1: evaluated after weaning Female	Higher dose of green tea extract: ↓ Infiltration of macrophages and areas of fibrosis in the cardiac tissue Restored the serum concentration of insulin
73	Maternal hypoprotein diet: gestation.	Wistar Rats	Adzuki beans ( <i>Vigna angularis</i> )	F0: received a normoprotein diet supplemented with Adzuki beans: lactation F1: evaluated at 3 and 23 weeks of age Male	↓ Body weight ↓ Hepatic levels of triglycerides ↑ Phosphorylation of AMPK (liver and skeletal muscle) and Acetyl coenzyme Carboxylase (skeletal muscle).

food factors, one can speak of “epigenetic foods”, a type of functional food containing bioactive compounds capable of modulating the microRNA expression, DNA methylation, or histone modifications.<sup>74</sup>

Epigenetic modifications have been observed in cardiac pathologies. Analyses of newborns mice or healthy and heart failure (HF) adult mice cardiomyocytes DNA, showed an important role in DNA methylation in the modulation of many aspects of the cardiac biology, including in the development of the disease.<sup>75</sup> By contrast, the role of histones in the cardiovascular biology, as well as the role of histone deacetylase (HDAC) enzymes, as therapeutic targets of heart diseases, has been well defined.<sup>76</sup> Treatment using an *in vivo* HDAC inhibitor attenuated the cardiac hypertrophy and fibrosis<sup>77</sup> in hearts of rodents exposed to hypertrophic stimuli. Moreover, the microRNAs can regulate multiple cell functions

involved in atherosclerosis, such as oxidative stress, cholesterol metabolism, and endothelial dysfunction.<sup>78</sup>

Analyses of DNA methylation in the entire genome of siblings of the same sex in the cohort of the Dutch Famine study revealed a pattern of differentially methylated regions, associated with malnutrition.<sup>79</sup> Experimental studies that analyzed offsprings of mothers submitted to protein restrictions during gestation observed a reduction in the supply of methyl groups stemming from glycine, hypomethylation of the hepatic receptor of the glucocorticoids, altered histone methylation, and an increase in the DNA methylation in hepatocytes.<sup>21</sup> Consistent with these findings, the mother's energy restriction during gestation led to DNA hypomethylation in the hepatic tissue of the offspring, resulting in an increase in the gene expression involved in the oxidation of fatty acids and the reduction of genes involved in the lipid

synthesis.<sup>21</sup> By contrast, the excessive consumption of carbohydrates by the mother during gestation changes the DNA methylation, leading to changes in the gene expression responsible for adipogenesis in the white adipose tissue, in turn programming obesity in the offspring.<sup>21</sup> Finally, Strakovsky et al.<sup>80</sup> showed that, upon modifying the histone acetylation, a maternal hyperlipidic diet contributed to changing the expression of antioxidant enzymes in newborns.

Many micronutrients are essential for a wide range of metabolic processes, including methylation and transamination reactions.<sup>81</sup> These processes involve many enzymes with methyltransferase activity, in addition to co-factors, such as choline, methionine, zinc, and vitamins B6, B12, and B9, acting as methyl donors. B9 is a donor of one-carbon for DNA methylation and synthesis; its role is crucial during the early post-natal development, when rapid growth and cell proliferation take place. The B12 deficiency can result in global hypomethylation, since, together with the B9, it is involved in methionine synthesis and S-adenosyl methionine, necessary donors for the maintenance of DNA methylation patterns.<sup>81,82</sup> Due to its role in DNA methylation, zinc can exert a key influence upon the epigenome. Its deficiency during the intrauterine and post-natal life can contribute to change the methylation processes, which can lead to the development of chronic diseases and increase cardiovascular risks.<sup>82</sup>

There is evidence that sustains the notion that breast milk influences the DNA methylation and that this food contains microRNAs involved in the regulation of the gene expression at the post-transcriptional level. This study raised the hypothesis that the microbioma mediates the effects of this compound in this process, given that breastfeeding can modulate the composition of the intestinal microbiota and that this influences the DNA methylation.<sup>83</sup> One study, which compared rats submitted to early weaning, who were fed a formula rich in carbohydrates, and rats fed only with breast milk, showed lower levels of mRNA of the Nyp gene (which codifies the Y neuropeptide – orexigenic peptide) and of histone acetylation, as well as higher levels of mRNA of the Pomc gene (anorexigenic peptide) in the rats that received breast milk, possibly associated with high levels of histone acetylation in this group. Both of the genes are involved in many physiological processes, mainly energy homeostasis.<sup>83</sup>

As regards the bioactive compounds, *in vitro* and *in vivo* studies have demonstrated that these perform their protector effects in the chronic diseases by means of different mechanisms involving nutrigenomics. Anthocyanins have been associated with histone modifications, DNA methylation, and microRNA expression. Other bioactive compounds, such as isoflavones, curcumin, and resveratrol can regulate the activity of HDAC enzymes and histone acetyltransferase (HAT) and, consequently, modulate the histone acetylation. The benefits to one's health are attributed to these epigenetic mechanisms.<sup>15,61</sup>

DNA methylation has also been associated with the catechins present in green tea. The epigallocatechin-3-gallate (EGCG) can inhibit the DNMT enzyme (DNA methyltransferase) through indirect mechanisms or through the reduction of its expression, in addition to modulating epigenetic processes at the level of histone modifications. Moreover, studies have also suggested that butyrate, a short chain fatty acid formed in the colon through prebiotic fermentation by bacteria, seems to inhibit the HDAC activity, corroborating with a possible interaction between the epigenome and the microbioma.<sup>15,61</sup>

## Discussion

The DOHaD theory search to fill in the blanks in the knowledge of how nutritional experiences in crucial stages of early life can impact one's health in the long term.<sup>6, 10</sup> Both, programming and reprogramming of diseases, seem to occur through epigenetic mechanisms that show how the nutritional environment, whether adequate or not, can affect the functioning of genes, influencing the phenotype<sup>15</sup> However, epidemiological studies in involving human beings present some limitations that make a definitive conclusion difficult, not only due to the long interval of time between the cause (malnutrition in early life) and the effect (CVD in adulthood), but also due to the difficulty to obtain precise nutritional data in both qualitative and quantitative terms. These questions highlight the relevance of studies including animal models, especially small animals, such as rodents, which have a short lifecycle, which in turn makes the control of nutritional aspects feasible.<sup>7,84</sup> Even including distinct species, with different body sizes in the maturity rate and in other life history aspects, the literature suggests that the use of animal models

in studies involving development plasticity are appropriate for the study of similar effects in humans, though the strength of this association can vary with the study's design,<sup>85</sup> corroborating the relevance of studies with a translational approach.

Studies have demonstrated that, in addition to the adaption of energy and micro-macronutrients in one's diet, bioactive compounds also modulate effectors of the cardioprotector genes. Nevertheless, one major challenge includes a better definition of the regulator adaptive aspects of the cardiac epigenome, considering various feeding patterns in a complete meal. Trials that evaluate the conventional consumption of foods are different from those that involve pharmacos and present innumerable variables, including not only the adherence to the diet, but also the lifestyle, the nutrient-nutrient, pharmaco-nutrient, or comorbidity-nutrient interactions. The challenge in terms of food components, concentrations, processing, solubility in water/lipids and stability, bioconversion, metabolites, interactions, and time of ingestion, focused on the variety of epigenetic agents, requires a detailed evaluation in the context of cardiovascular health. Circulating epigenetic markers do not always reflect epigenetic effects of diet at the tissue/cell level in healthy individuals and patients in different stages of the disease. Tools involving sequencing and bioinformatics, for example, can minimize the limitations of these studies in defining the cause-effect relationships and the composition of ingredients, as well as the level of ideal intake. Despite the scarcity of beneficial results from clinical trials, approaches based on health teams can be useful for the comprehension of the interindividual response to a cardioprotector diet in the presence of common genetic variants and a similar microenvironment, as well as its point of intersection with the epigenome, to personalize the results.<sup>86</sup>

### Final considerations

The development of public policies that favor the adequate nutrition of mothers in gestational and breastfeeding periods, as well as exclusive breastfeeding up to six months of age, seem to constitute important strategies to reduce the incidence of cardiometabolic diseases in the population, diminishing direct and indirect expenses in health care.

Although it is challenging to obtain consistent findings in clinical studies with bioactive compounds, the introduction of functional foods in one's diet can constitute an additional strategy to mitigate the deleterious effects observed in the long run, resulting from malnutrition in early life. Epigenetic mechanisms, which can be gender dependent, represent the key to developmental plasticity and are involved in both programming and reprogramming of the cardiovascular system.

### Author contributions

Conception and design of the research: Marques EB, Scaramello CVB. Acquisition of data: Marques EB, de Souza KP, Alvim-Silva T, Martins ILF, Pedro SS, Scaramello CVB. Analysis and interpretation of the data: Marques EB, de Souza KP, Alvim-Silva T, Martins ILF, Pedro SS, Scaramello CVB. Obtaining financing: Scaramello CVB. Writing of the manuscript: Marques EB, de Souza KP, Alvim-Silva T, Martins ILF, Pedro SS, Scaramello CVB. Critical revision of the manuscript for intellectual content: Marques EB, de Souza KP, Alvim-Silva T, Scaramello CVB.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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