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REVIEW

Update on the influence of fatty acids in epigenetic programming mechanisms

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Abstract

Purpose Parental nutrition can influence the early stages of offspring development, leading to fetal programming. During this critical period, fatty acids play an important role in the regulation of lipid metabolism, essential for the proper development of offspring. Epigenetic mechanisms seem to be involved in the changes in structure and function of several tissues due to poor nutrition, as long as deficient or excessive maternal exposure to saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA), and monounsaturated fatty acids (MUFA) seem to be able to alter offspring metabolism and influence long-term chronic diseases. This review addresses an update on the influence of SFA, PUFA, and/or MUFA in the epigenetic mechanisms on fetal programming.

Methods The literature search was performed in the database PubMed and original papers in the English language were selected, containing the effects of different types of fatty acids in epigenetic programming mechanisms of chronic diseases. The time limit was not set for a broader identification of papers published within the field.

Results SFA present in maternal high-fat diets (HFD) has been shown to cause epigenetic alterations in the liver, adipose tissue, heart, and brain, leading to changes in glucose, lipid, and cardiovascular metabolism of the offspring. Maternal consumption of MUFA oleic acid during pregnancy and lactation can be beneficial especially to lipid metabolism, as long as PUFA intake exerts positive outcomes on offspring neurodevelopment and epigenome reshape, preventing chronic diseases.

Conclusions The present data showed that maternal intake of different types of SFA, MUFA, and PUFA can influence the offspring programming of epigenetic machinery through histone modifications, DNA methylation, and miRNA regulation. More studies including both male and female offspring are needed in order to compare differences between sexes, as well as epigenetic studies in the offspring from male progenitors exposed to different types of fatty acids.

Keywords Fetal programming · Epigenetics · Saturated fatty acids · Monounsaturated fatty acids · Polyunsaturated fatty acids · Chronic diseases

Introduction

The influence of parental nutrition has been a wide debated theme over the years, especially nowadays, once new evidence of its impact on the health of the next generations has been emerging. According to the Developmental Origins of Health and Disease (DOHaD), the pattern of health and disease can be influenced in the early stages of offspring development — called fetal programming. At this point, cells and tissues are highly susceptible to respond to environmental conditions that generate adaptative responses, leading to profound changes in gene expression and therefore, changes in structure and function of several tissues and organs. These modifications can influence long-term chronic diseases in offspring adult life, such as cardiovascular disease, insulin resistance, obesity and hypertension, and/or the inheritance of risk factors across generations [1–3].

Evidence shows that epigenetics plays an important role in fetal programming caused by poor parental nutrition [4, 5]. Epigenetics consists of heritable changes in gene expression that do not alter DNA nucleotide sequence, such as covalent modifications in histone lysine residues, DNA methylation, and post-transcriptional changes. These epigenetic markers regulate gene expression through the silencing and activation of gene transcription. Gene

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silencing is mediated by DNA methylation, a process catalyzed by DNA methyltransferases (DNMTs). These enzymes add a methyl group to the 5-carbon position of cytosine residue within CpG dinucleotides, leading to the formation of 5-methylcytosine in DNA [6]. During cell replication, the DNA methylation is maintained by DNMT1 while DNMT3a and DNMT3b, are de novo DNMTs [6, 7].

DNA methylation relies on the methyl donor S-adenosyl-L-methionine from micronutrients such as betaine, choline, folate, vitamin B12, and other B vitamins [6]. DNA methylation recruits methyl CpG binding proteins (MeCP) and histone deacetylases (HDAC) that are capable of blocking RNA polymerase activity by condensing chromatin and inhibit the binding of transcription factors, preventing then, the initiation of gene expression [8].

DNA methylation and demethylation are dynamic and balanced cellular processes. Gene activation is mediated by modifications in histone tails through acetylation and methylation processes, that alter the state of chromatin and regulate the transcriptional activity of genes. The interaction between histones and DNA is altered by histone tails, influencing nucleosome interactions and chromatin folding [8]. When inactive, DNMTs induce the demethylation of the CpG sites, promoting gene expression, as well as the ten-eleven translocation methylcytosine dioxygenases (TETs) can induce DNA demethylation when oxidizing 5-methylcytosine to 5-hydroxy-methylcytosine [6]. At a post-transcriptional level, microRNAs (miRNAs) are a class of small non-coding RNA molecules able to control gene expression by binding to and regulating target protein-coding mRNAs [9].

During fetal and postnatal development, fatty acids are critical factors strongly associated with normal fetal and postnatal development. The regulation of lipid metabolism is essential for proper offspring development and as a consequence, deficient or excessive exposure to different types of fatty acids can influence fetal programming. Excessive maternal intake of saturated fatty acids (SFA) is likely to influence liver and adipose tissue function and is correlated to obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, and cancer. The polyunsaturated fatty acids (PUFAs) has been shown to benefit offspring development and epigenetic regulation with anti-inflammatory, antioxidant, and antiapoptotic effects, whereas monounsaturated fatty acids (MUFAs) play beneficial physiological roles by stimulating thermogenic capacity and changing liver metabolism, and seem to prevent cardiovascular disease in the offspring [10, 11].

In this sense, this review addresses an update on the influence of SFA, PUFA, and/or MUFA in the epigenetic mechanisms on fetal programming.

Methods

The literature search was performed in the database PubMed for all types of articles, being the publications to February, 2021. Original papers in the English language were selected, containing the effects of different types of fatty acids in epigenetic programming mechanisms of chronic diseases. The following keywords were used: saturated fatty acids, high-fat diet, monounsaturated fatty acid, oleic acid, unsaturated fatty acid, polyunsaturated fatty acids, programming, fetal programming, metabolic programming, fetal development, epigenetics, chronic diseases, and offspring. Time limit was not set for a broader identification of papers published within the field.

Saturated fatty acids

SFAs are long straight-chained fatty acids containing an even number of carbon atoms, with single carbon–carbon bonds, tend to be solid at room temperatures and are present in dietary source as triacylglycerols. They include lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0). They are derived from animal fats and plant oils and are found in milk, lard, meat, egg yolks, and also in palm, coconut, and palm kernel oils. Processed foods like dairy products, baked goods, fried foods and processed meat are also source of this type of fat and have a high saturated fat content. The increasing intake of high-fat diets (HFD) poses a great concern towards general health, once high dietary intake of SFA is related to the risk of cardiovascular disease, obesity, type 2 diabetes mellitus, and cancer [10, 12, 13].

The development of chronic diseases due to the content of SFA in HFD seems to be modulated by epigenetic processes. It has been shown that high fat intake can induce changes in the epigenome, and these changes can be transmitted through generations, programming the health of the next generation [14]. The intake of a HFD rich in SFA by mothers prior to and through gestation and lactation has been shown to induce epigenetic modifications in the offspring (Fig. 1).

The maternal consumption of HFD prior to conception and during gestation was shown to cause hyperacetylation at histone 3 at lysine 14 residues (H3K14) with an increasing trend of acetylation at histone 3 at lysine 9 residues (H3K9) and at histone 3 at lysine 18 residues (H3K18) in fetal hepatic tissue [15]. In this study, a decrease in expression of HDAC1 mRNA in fetal hepatic tissue of male offspring was also observed. These alterations could have led to changes observed in the expression or remodeling of genes involved in fatty acid catabolism and ketone body syntheses, such as glutamic pyruvate transaminase (alanine aminotransferase)

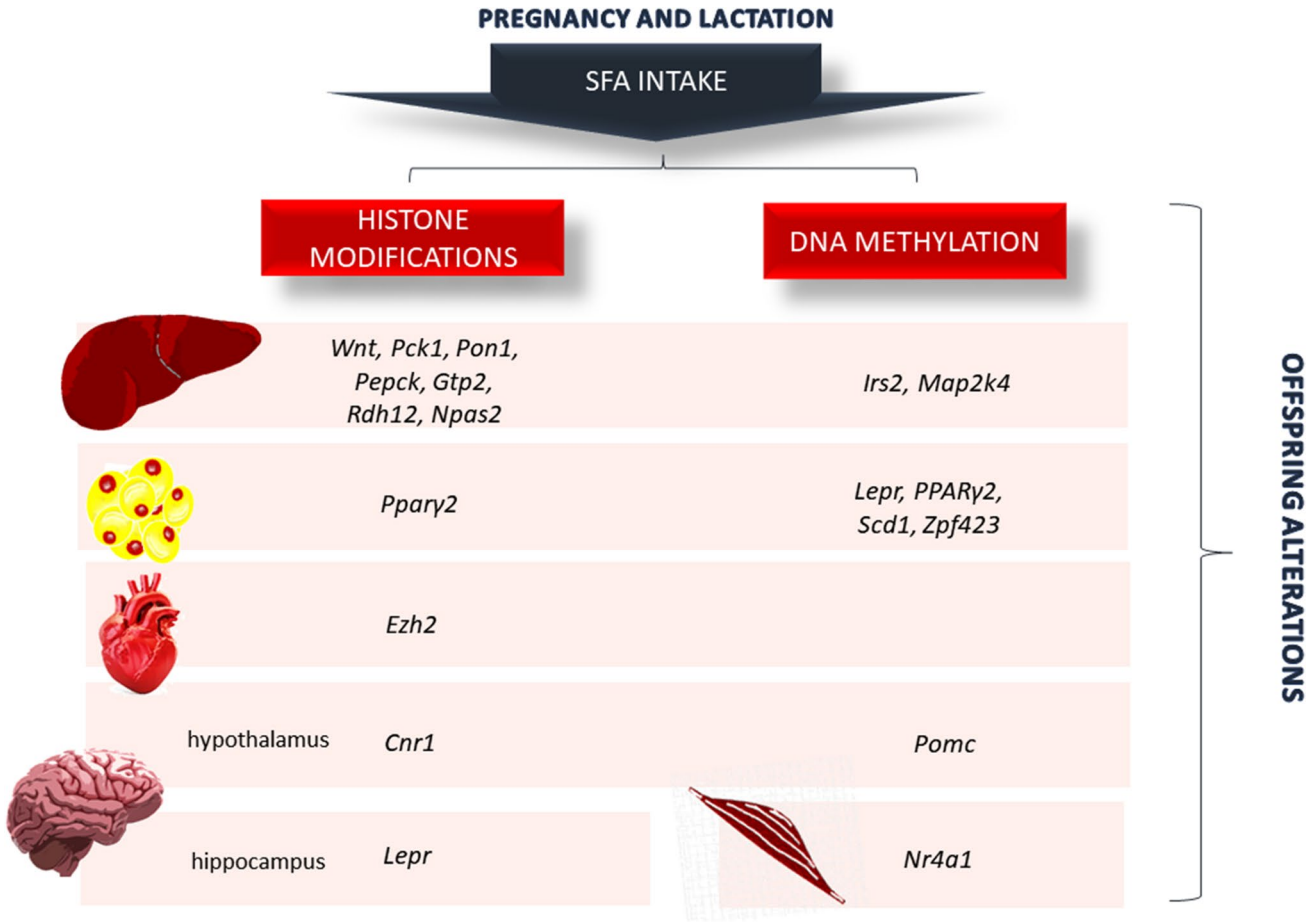

Fig. 1 Saturated fatty acids (SFA) intake during pregnancy and lactation modulate different tissues of offspring through epigenetic modifications. During the aforementioned period, SFAs can program the offspring's metabolism by modifying histones and DNA methylation pattern in tissues such as liver, heart, hypothalamus, hippocampus, skeletal muscle, and adipose tissue. In this sense, maternal SFA can lead offspring to a higher risk of developing chronic diseases. Phosphoenolpyruvate carboxykinase 1 (Pck1); paraoxonase 1 (Pon1); Glutamic pyruvate transaminase (alanine aminotransferase) 2 (Gtp2); Phosphoenolpyruvate carboxykinase (Pepck); Retinol dehydrogenase 12 (Rdh12); Neuronal PAS Domain Protein 2 (Npas2); Peroxisome proliferator-activated receptor γ 2 (Pparγ2); Zeste of homolog 2 (Ezh2); Leptin receptor (Lepr); Insulin receptor substrate 2 (Irs2), Mitogen-activated protein kinase kinase 4 (Map2k4), Stearoyl-CoA desaturase-1 (Scd1); Zinc finger protein 423 (Zfp423); proopiomelanocortin (Pomc); Cannabinoid receptor 1 (Cnr1); Nuclear Receptor Subfamily 4 Group A Member 1 (Nr4a1)

2, detoxification of lipid peroxidation products in response to oxidative stress (retinol dehydrogenase 12), as well as regulation of peripheral metabolism and satiety signals with circadian mechanisms (Neuronal PAS Domain Protein 2) [15]. HFD intake during gestation and regardless of maternal obesity and diabetes programs histone modifications in hepatic gluconeogenic phosphoenolpyruvate carboxykinase 1 gene in acetylated histone 3 (H3Ac), dimethylated histone 3 at lysine 4 residues (H3K4Me2), trimethylated histone 3 at lysine 9 residues (H3K9Me3) and trimethylated histone 3 at lysine 27 residues (H3K27Me3) of the 21-day-old male offspring and could lead to high glucose production and altered insulin sensitivity in adulthood [16]. Another study evaluated the male offspring at postnatal day 7 and showed a decrease in acetylated histone 4 (H4Ac) at the *Wnt1* promoter region and in H3Ac at the *Wnt1* coding region, inducing the suppression of the Wnt/β-catenin signaling pathway, which could potentially increase the risk of metabolic syndrome in these animals [17].

In a model of obesity in female rats fed a HFD, it was shown increased H4Ac and dimethylated histone H3(H3Me2) of the hepatic paraoxonase 1 gene in both male and female offspring on embryonic day 20, with increased H3K9Me3 at the promoter and coding region of female offspring [18]. The hepatic paraoxonase 1 encodes for enzymes of the paraoxonase family, playing a critical role in the oxidative balance system and these modifications could lead to altered oxidative balance in adult offspring, besides explaining the differences observed between the male and female response to oxidative stress [18]. In adult female

offspring from mothers fed a HFD during gestation, there were increased levels of H3K4Me2 at multiple regions of the hepatic phosphoenolpyruvate carboxykinase gene. H3Ac and H3K4Me3 were induced at the coding region with decreased H3K9Me3 at the promoter. Phosphoenolpyruvate carboxykinase gene controls critical signaling pathways regulating both glucose and fatty acid metabolism, contributing to the increased triglyceride synthesis, induced fatty acid synthase expression and NADH levels, possibly leading to increased fat deposition in a gender-specific manner [19].

Panchenko et al. showed that the epigenetic machinery gene expression, particularly the histone acetylation pathway of the placenta and fetuses at embryonic day 18.5, is highly sensitive to maternal obesity. Although preconceptional weight loss seems to be favorable to fetal growth, some effects of maternal obesity were maintained in offspring phenotype [20]. Maternal HFD intake prior to conception and during gestation and lactation led to DNA hypomethylation of Map2k4 and hypermethylation of insulin receptor substrate 2 in the liver of offspring exposed to HFD for 5 weeks. The hepatic insulin receptor substrate can be inhibited by activation of mitogen-activated protein kinases (MAPKs), causing inhibition of insulin activity. Accordingly, *Map2k4* gene expression and was increased insulin receptor substrate 2 gene expression was reduced, leading to glucose intolerance and insulin resistance, setting a predisposition to long-term diabetes [21].

The white adipose tissue, besides lipid storage, plays an important role in energy homeostasis control through the secretion of leptin. Hypomethylation of 9, 12, and 6 CpG leptin gene sites were observed in fetal, subcutaneous, and visceral adipose tissues of offspring from mothers fed a HFD throughout gestation and lactation, respectively. This study also showed that children born to mothers with high triglyceride levels presented leptin promoter hypomethylation in lymphocytes, so as rat offspring born to mother fed a HFD. That was correlated to the elevated blood pressure observed, showing leptin as a key biomarker and mediator of vascular dysfunction and hypertension. DNMT1 mRNA expression was reduced in subcutaneous adipose tissue, whereas the mRNA levels of TET1 were increased in fetal, subcutaneous, and visceral adipose tissues and in human lymphocytes from children born to mothers with high triglyceride levels [22].

Modification of epigenetic marks in early-life (postnatal day 12 and postnatal day 21) was shown to persist throughout life (9 months of age) in perirenal and inguinal white adipose tissue. There was a lower percentage of modifications of four CpG dinucleotides within the upstream enhancer of the leptin gene, decreased levels of 5-methylcytosine (5mC), H3K9Me3, 5-hydroxymethylcytosine (5hmC), and increased levels of H3K27Ac. Effects on leptin gene expression were observed in this adult obesity-prone offspring from mothers fed a HFD throughout gestation and lactation [23].

The peroxisome proliferator-activated receptor γ (PPARγ) has been shown to play a role in adipose tissue, and regulate processes involved in adipocyte function. 21 days old offspring from obese dams showed higher DNMT activity and global DNA methylation in inguinal white adipose tissue. When adults at 9 months of age, the offspring exhibited decreased *Pparγ* expression levels in adipose tissue, which was associated with CpG hypermethylation and depletion in H3Ac/H3K4Me3 in the *Pparγ*2 promoter. These sustained epigenetic marks link maternal obesity to a predisposition for later adiposity in the offspring [24].

Maternal HF feeding during suckling programs epididymal white adipose tissue expansion of adult offspring. It was shown that this expansion occurs in part by stearoyl-CoA desaturase-1 (*Scd1*) epigenetic reprogramming. The enzyme SDC1 uses fatty acids as substrates in triglyceride synthesis and the reduction of DNA methylation in *Scd1* promoter in a PPARγ-binding region was associated with upregulation of *Scd1* gene in adipose tissue [25]. The PPARγ is also related to the conversion of preadipocytes to adipocytes. The regulator zinc finger protein 423 promotes *Pparγ* expression and adipogenic differentiation, and maternal HFD intake has been shown to reduce DNA methylation in the zinc finger protein 423 promoter, increasing its expression and progenitor adipogenesis in offspring [26].

Maternal high saturated fat intake can also alter skeletal muscle function by inducing promoter hypomethylation of CpG-1408, which correlated with increased *Nr4a1* gene expression in offspring. Nr4a1 is the major isotype in skeletal muscle and plays a role in myofiber size and muscle mass besides the liver, by preventing hepatic steatosis [27]. In the cardiac tissue, maternal HFD intake prior to conception and during gestation in a diabetic model, was shown to induce a differential peak distribution on gene promoters at H3Ac, H3K4Me3, and H3K27Me3 in newborn offspring. 54% of the genes displayed the H3K4Me3 mark and many of these genes were associated with metabolic processes, particularly with positive regulation of cholesterol biosynthesis. These genes also overlapped with several trait loci for blood pressure, body weight, serum cholesterol and are linked to cardiac disease. Although synergy between prenatal exposure of a HFD and diabetes was not observed, the study shows the critical role of the prenatal environment affected by HFD, diabetes, or both in the cardiometabolic health of the offspring [28].

Maternal HFD intake also decreased H3K27Me3, monoubiquitination of histone H2A at lysine 119, DNA methylation levels, enhancer of zeste homolog 2 and DNMT3B expression in the cardiac tissue of male offspring at postnatal day 21. Enhancer zeste of homolog 2 stabilizes cardiac gene expression, mediating chromatin decompaction and pro-hypertrophic and pro-fibrotic genes in offspring from mothers exposed to HFD. The levels of the target genes involved

in cardiac pathogenesis, such as isl lim homeobox 1, six homeobox 1 and mads box transcription enhancer factor 2, polypeptide C (Mef2c) were increased in this study [29].

The brain tissue of the offspring can also be programmed by maternal HFD intake with leptin playing important roles such as in the maturation of neural circuitry and synaptogenesis. It was shown decreased H3K9Me3 at the leptin receptor promoter of the hippocampus of female offspring from obese mothers fed a HFD 10 weeks prior to conception. There were also increased expression of the leptin receptor and in vitro exposure of hippocampal neurons to interleucine-6 with decreased binding of H3K9Me3 at the leptin receptor promoter in female fetuses, suggesting that exposure to metabolic inflammatory molecules can impact epigenetic regulation of gene expression in the developing hippocampus [30]. Another study evaluated the effects of maternal HFD in brain tissue and showed that the maternal HFD intake 8 weeks prior to conception and throughout gestation increased histone acetylation and androgen receptor binding at *Cnr1* promoter in the hypothalamus of newborn male offspring. The *Cnr1* gene encodes the cannabinoid receptor CB1, which increases appetite, stimulates feeding and reward for palatable foods. High activation of the endocannabinoid system is related to leptin resistance, and down-regulated leptin signaling with up-regulated *Cnr1* mRNA levels in the hypothalamus of the newborn offspring was found. In the same study, there was increased plasma n6 to n3 fatty acid ratio in male offspring, which is an important risk factor for metabolic diseases and might indicate an over activation of endocannabinoid signaling [31].

In the hypothalamus, neuropeptides produced in the arcuate nucleus (ARC) regulate energy balance. The α-melanocyte-stimulating hormone, a product of pro-opiomelanocortin (POMC), plays a role in satiety and energy homeostasis. Hormonal signals, such as leptin, mediate POMC accessibility to the transcription mechanisms. In the offspring from HFD-fed dams prior to conception and during gestation and lactation, there was a negative correlation in 5hmC and a positive correlation in its derivative 5mC with body weight. POMC expression in obese offspring was determined by an increase in CpG methylation at the *Pomc* promoter, enabling the bind of methyl-binding domain 1 to 5mC. *Pomc* mRNA expression was reduced by the methyl-binding domain 1 in order to promote H3K9Me2, leading to an open chromatin structure and increased response of *Pomc* to energy-storage signals. These results suggest an epigenetic regulatory mechanism that influences the predisposition to obesity traits [32].

Male offspring from mothers fed a HFD prior to and throughout gestation and lactation exhibited hypermethylation at the enhancer region (nPE1 and nPE2) in the ARC POMC gene and at the promoter sequence mediating leptin effects at postnatal day 21. There was persistent hypermethylation at the POMC promoter region in the offspring when adult, which retained the increased body weight from weaning. Therefore, maternal overnutrition predisposes the offspring to metabolic disorders later through programming of long-term epigenetic alterations in the offspring's hypothalamic *Pomc* promoter [33]. The ARC of male offspring from mothers fed a HFD prior to and during gestation and lactation had significantly decreased DNMT1, energy sensors, and feeding-related neuropeptides at 1 day of age. These alterations could impact neuroprogenitor cell proliferation and differentiation. At 6 months of age, the offspring exhibited increased energy sensors and decreased histone deacetylases SIRT1 and HDAC1. The altered energy sensors and epigenetic responses that modulate gene expression and adult neuronal differentiation could contribute to hyperphagia and obesity in HF male offspring [34].

miRNAs also play a role in offspring programming. Cardiac expression of eight miRNAs was altered in offspring from obese mothers when the offspring was subjected to high SFA diet during life, suggesting that miRNAs are involved in the response of cardiac function to poor nutrition. Eight cardiac miRNAs expression were altered in offspring from obese mothers when challenged with HFD. However, postnatal exposure to HFD alone induced changes in the expression of 33 miRNA in offspring of lean and 46 miRNA in offspring of obese mothers, which suggests that maternal obesity may have some negative consequences for the cardiovascular health of the offspring; however, individual's lifestyle choices determine heart health outcomes. [35].

Siddeek et al. [36] showed the role of miRNA biogenesis in long-term cardiac health, where a miRNA subset that regulates transforming growth factor-beta (TGFβ)-mediated remodeling was downregulated. Apparently, DiGeorge critical region 8 expression, which is involved in miRNA biogenesis, plays a role in the alterations of the miRNA profile and the TGFβ-mediated remodeling [36]. Another class of non-coding RNA are the tRNA-derived small RNAs (tsRNAs), and have been shown to be involved in the transgenerational transmission of obesogenic phenotypes, such as marked adiposity, insulin insensitivity, and altered circulating metabolic parameters via the paternal lineage. Male offspring born to mothers that were exposed to HFD rich in SFA had increased expression of sperm tsRNAs as well as the male offspring born to these fathers [37]. Transgenerational transmission of obesogenic traits could also be demonstrated in imprinted genes. In the third generation from mothers fed on a HFD, females presented increased body size and paternally expressed genes in the liver, which demonstrates there is a stable germline-based transgenerational mode of inheritance [38].

Therefore, the maternal intake of HFD rich in SFA can influence the programming of epigenetic mechanisms in offspring, leading to alterations in the function of several

tissues, mainly in the hepatic, adipose, cardiac, and brain tissue, and consequently to increased risk for the development of metabolic diseases.

Polyunsaturated fatty acids

PUFAs contain two or more double bonds in the molecule. The α-linolenic acid (ALA; 18:3n-3) and linoleic acid (LA; 18:2n-6) PUFAs are essential dietary fatty acids, they cannot be synthesized despite the lack of enzymes in humans. These are substrates for desaturases and elongates enzymes for the production of long-chain PUFAs (LC-PUFAs)—eicosapentaenoic acid (EPA; 20:5n-3), docosapentaenoic acid (DPA; 22:5n-3), and docosahexaenoic acid (DHA; 22:6n-3) are derived from ALA, and arachidonic acid (AA; 20:4n-6) is derived from LA [39]. The adequate n-6/n-3 ratio is important to avoid the negative influence of excess n-6, which can inhibit the synthesis and incorporation of DHA and EPA in tissues.

The primary source of n-3 PUFA during early life is from placental transfer and maternal milk, due to the limited capacity of the fetus and neonate to synthesize DHA from ALA, hence the maternal intake of n-3 PUFA will determine the offspring brain development. DHA is the most prevalent FA in cellular membrane and phospholipid in the brain—it has anti-inflammatory, antioxidant, and antiapoptotic effects, which are crucial for adequate neurodevelopment [40].

Maternal erythrocytes (a medium-term assessment of n-3 PUFA consumption) containing low and high levels of n-3 PUFAs showed different DNA methylation sites and regions, and four different methylated genes: MSTN, IFNA13, ATP8B3, and GABBR2. These genes belonged to pathways that could affect the offspring's metabolic programming, due to their relation to the onset of insulin resistance and adiposity, innate immune response, fatty acid transfer across cell membranes, and addiction paths of the central nervous system [41].

Maternal supplementation of n-3 PUFA during pregnancy and lactation in mice impacted irreversibly its concentration in the offspring's brain in adulthood through epigenetic alterations, such as the decrease of the methylation in the brain-derived neurotrophic factor — which is responsible for long-term neurogenesis and for maintaining the neuronal populations and connections [40]. Moreover, maternal n-3 supplementation during pregnancy affects DNA methylated regions of offspring at birth persisting to childhood. At birth it was found 21 differentially methylated regions, 17/21 showed lower methylation levels in the differentially methylated region's group. The differentially methylated regions identified were located at genes ESYT3, SLC12A6, CCK, RAETIL, LTB, SLC12A6, TRAK1, LPHN3, and RFPL2, which functions are related to lipid metabolism, appetite regulation, immune function, and neurodevelopment function. At 5 years, 10 differentially methylated regions were identified, all lower methylated [42].

On the other hand, maternal high n-6 PUFA consumption (characteristic of "western" diets) during pregnancy is related to offspring impaired neurodevelopment, with anxiety and depression behavior later in life. The n-6 PUFA is represented by AA that is a precursor to eicosanoids and is linked to the repression of regulatory transcription factors, such as signal transducer and activator of transcription 3 (STAT3), myeloblastosis oncogene, and CCAAT/enhancer-bind protein β. In addition, the n-6 PUFA exposure affects fetal cortical architecture and induces gene repression by hypermethylation in CpG islands in the brains [43].

The type and the amount of fat consumed by the mother have a great impact on offspring's health. The PUFAs ARA and DHA were lower in the offspring's liver from dams-fed HF (diets based on fish oil or butter) compared to adequate fat intake. Maternal fat intake (even diet PUFA-enriched) during pregnancy and lactation were found negatively correlated to FADS2 mRNA expression in offspring liver and were found altered methylation of specific CpG in FADS2 promoter in adult offspring. These repercussions on offspring can be related to future capacity to synthesize EPA and DHA, mainly in female offspring — impacting their ability to synthesize long-chain PUFA in their pregnancy [44]. In a study with gilthead sea bream [45], the parental high FADS2 expression associated with the parental fish oil diet favoring higher growth and programming the DNA methylation — in specific positions: CpG2 and CpG3 — on the promoter region of FADS2 in the offspring.

Fads1 and Fads2 mRNAs expression was altered in the aorta of offspring at 77 days of age. Fads 1 mRNA was higher and Fads2 was lower in offspring from dams fed 21% fat compared to 7% fat diets, regardless of the type of fatty acids consumed from 2 weeks before conception until lactation period, showing altered methylation of CpG -394, -84, and -76 Fads promoter. The 20:4 n-6 proportion in aorta total lipids were different accordantly type of fat. In male offspring, there were lower 20:4 n-6 from dams fed 7% hydrogenated or butter diets, compared to PUFAs-riched diets, it is likely due to competition for the enzymes essential in the n-3 and n-6 metabolism. Maternal fat intake could induce dysregulation of Fads 1 and Fads 2 gene expression in offspring aorta, impacting on the 20:4 n-6, which is required for vasoconstriction in the offspring [46]. In this sense, the type and amount of fat consumed by the mother can affect the offspring's risk to develop cardiovascular diseases.

Fish oil is one of the main PUFAs sources, its consumption during pregnancy and lactation seems to protect the offspring against allergies, proinflammatory status and is beneficial to adiposity [47, 48]. It is associated with immunological changes in cord blood, persisting to childhood and

adolescence. Prenatal and neonatal exposure to n-3 PUFA (by maternal fish oil supplementation) modulate offspring metabolism, impacting glucose tolerance and insulin sensitivity, as well as modulate epigenetic factor for brown tissue development in mice — decreasing HDAC1 activity with an increase in acetylation and decreasing tri-methylation (me3) at H3K27 site and increasing acetylation at H3K9 [49].

At the post-translational level, fish oil supplementation modulates brown adipose tissue development in the mice offspring, by increased miR-30b, miR-193b, and miR-365 expression [49]. Long noncoding RNA (lncRNA) is a key epigenetic mechanism in breast cancer development. Li et al. [50] have found 53 lncRNA upregulated and 45 downregulated in offspring mammary glands by maternal n-3 PUFA, being the target genes related to p53 signaling pathway and apoptosis (upregulated lncRNAs) and MAPK, Jak-STAT, estrogen, and NF-kB signaling pathways (downregulated lncRNAs). In this sense, exposure to maternal n-3 PUFAs (EPA, DPA, and DHA) is detrimental to decrease the n-6/n-3 ratio in offspring and altering lncRNA expression decreasing the risk of mammary cancer later in life.

Maternal n-3 PUFA intake has a direct impact on offspring neurodevelopment and can reshape the offspring epigenome preventing chronic diseases. Adequate balance in n-6 and n-3 intake during pregnancy and lactation seems to be essential for offspring health throughout life (Fig. 2). The DHA and EPA supplementation during pregnancy and lactation could be a strategy to guarantee their adequacy, therefore providing the offspring healthy metabolic programming.

Monounsaturated fatty acids

MUFAs have a single double bond in the fatty acid that can occur in different positions [51]. The main source of exogenous MUFAs is vegetable oils — mainly olive oil, nuts, red meat, and milk products [52]. The endogenous MUFA can be synthesized by the enzyme stearoyl-coenzyme A desaturase-1 (SCD1) — highly expressed in liver and adipose tissues — by adding a double bond to a saturated fatty acid: SFA palmitate (16:0) and stearate (18:0), which are converted to palmitoleate (16:1) and oleate (18:1 n-9), respectively [53].

It is known that MUFAs have beneficial effects in preventing metabolic diseases. Oleic acid is the main representative of MUFA, which can improve insulin sensitivity through anti-inflammatory mechanisms [11]. Also, studies suggest MUFAs effects on markers associated with CVD, such as serum lipids and lipoproteins, and may affect vascular function markers, postprandial vascular function, and energy intake and metabolism [54].

A recent study [55] found beneficial effects in 21-day-old offspring from diabetic dams olive oil supplemented. It was observed reduced pro-oxidant markers in the offspring's heart, and the supplementation prevented the increase of

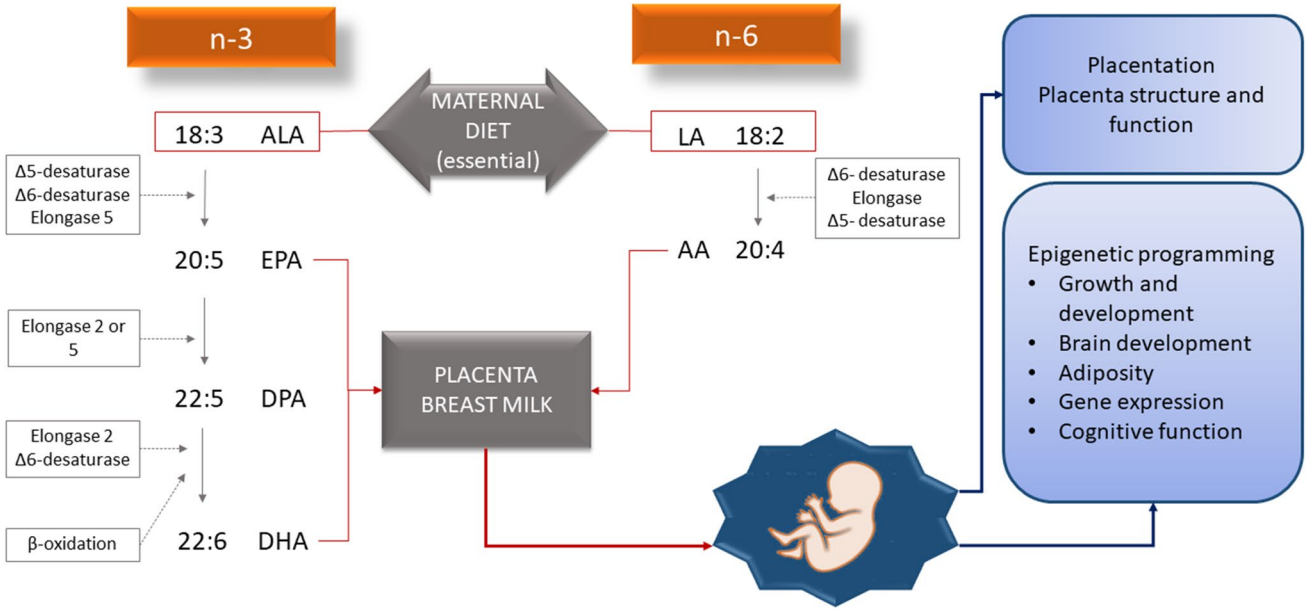

Fig. 2 Maternal intake of PUFAs and offspring outcomes. The essential fatty acids ALA and LA undergo processes of desaturation and elongation to become LC-PUFA, such as EPA, DPA, DHA (n-3), and AA (n-6). Through the placenta and/or breast milk the offspring receive LC-PUFAs, which participate in different processes by epigenetic programming, since placentation until adequate metabolism preventing diseases. Polyunsaturated fatty acids (PUFA); Linoleic acid (LA); α-linolenic acid (ALA); Eicosapentaenoic acid (EPA); Docosapentaenoic acid (DPA); docosahexaenoic acid (DHA); Arachidonic acid (AA); Long-chain polyunsaturated fatty acids (LC-PUFAs)

apoptotic cells and the deposition of extracellular matrix components. In this sense, maternal supplementation of olive oil could prevent offspring programming of cardiovascular disease. Moreover, other results from the same group [56] showed that maternal supplementation of olive oil is sex-specific, it can prevent hypertriglyceridemia and in female fetal offspring a reduced liver concentration of triglycerides, cholesterol, and free fatty acids. In male offspring, this diet can affect fetal liver metabolism, preventing the increased lipid content, the higher expression of sterol regulatory binding protein – 1 gene expression in the liver, and the increased of PPARδ and PPARγ levels in the liver. Finally, it was found a reduced expression of lipid oxidation enzymes in livers of male and female fetuses [56]. Olive oil supplementation during pregnancy seems to be positive, since the changes observed may be beneficial to lipid metabolism throughout offspring's life.

Supplementation of olive oil can reshape developmental programming possibly through an epigenetic mechanism. A maternal diet composed of fish and olive oil, which are the main source of oleic acid, is associated with histone acetylation levels of immune cells in the placenta. The placenta is an organ that mediates the maternal effects on epigenetic programming in offspring [57]. Moreover, Casas-Agustench et al. [58] demonstrated offspring's hepatic fatty acid profile at birth reflects the maternal diet fatty acids composition. Dams were fed with different types of fatty acids in the first 12 days of pregnancy, being found altered miRNAs expression in the offspring's liver (at birth and 12 months old) accordingly to maternal diet, the miR-383–5p — related to the insulin pathway — was decreased in the adult liver offspring from dams fed olive oil.

Govindarajah et al. [59] found the expression of DNMT3a and methyl-CpG binding domain protein 1 in offspring mammary glands from HFD based on olive oil not significantly higher compared to the control group. However, there was higher expression of Btn1a1 — a potential biomarker in breast cancer, altered by HFD in metastatic breast cancer — with no or less effect in mammary tumorigenesis in the offspring from dams fed HFD based in olive oil, compared to HFD based in butter and safflower. Although HFD during pregnancy can increase the susceptibility of more aggressive mammary tumors in female offspring, the type of diet and the timing of exposure to it are crucial to reprogram the development of decedents' mammary glands, thus these results elucidate the diet-dependence in the risk of breast cancer development.

Maternal consumption of oleic acid during pregnancy and lactation — a diet based on olive oil — seems to epigenetically program the offspring through different levels,

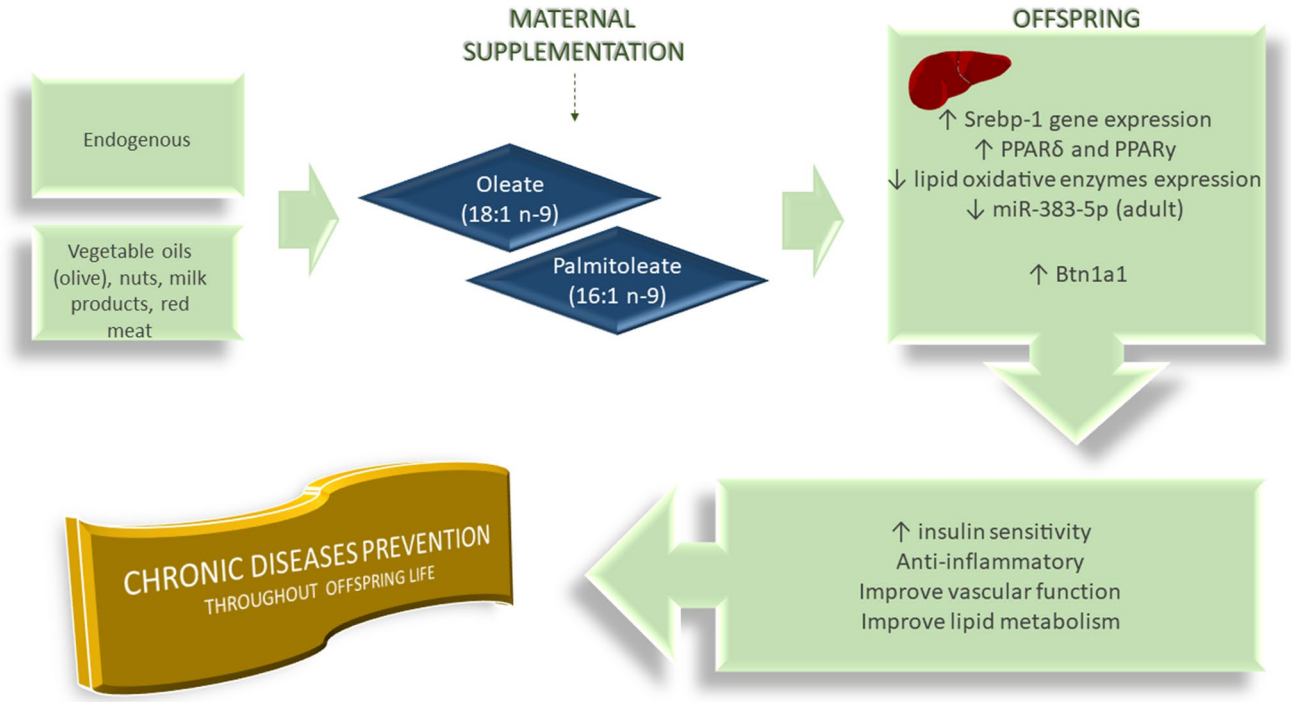

Fig. 3 Maternal intake or endogenous production of n-9 MUFAs can reshape epigenetically the offspring metabolism preventing chronic diseases. Maternal intake — including supplementation — during pregnancy and lactation can improve lipid metabolism and modify biomarkers in fetal and adult offspring. Monounsaturated fatty acids (MUFAs); sterol regulatory binding protein – 1 (Srebp-1); Peroxisome proliferator-activated receptor γ (PPARγ); Peroxisome proliferator-activated receptor δ (PPARδ)

with DNA modifications, histone modifications, and in post-transcriptional level in diverse tissue targets, with implications related mainly to lipid metabolism (Fig. 3).

Conclusion

Several reports have shown that maternal intake of different types of fatty acids -namely saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids PUFA — can influence the offspring programming of epigenetic machinery through histone modifications, DNA methylation, and miRNA regulation, as well as methyltransferases and deacetylases activity. Saturated fatty acids present in high-fat diets could lead to deleterious changes in the function of several tissues, such as hepatic, adipose, cardiac, and brain tissue, and consequently to alteration in glucose, lipid, and cardiovascular metabolism. Maternal consumption of monounsaturated fatty acids oleic acid during pregnancy and lactation is implicated especially in offspring lipid metabolism, as long as polyunsaturated fatty acids intake exert beneficial impacts on offspring neurodevelopment besides reshape the offspring epigenome preventing chronic diseases. More studies are needed including both male and female offspring and the comparison between sexes, since some studies pointed out marked differences in epigenetic changes according to the sex [30, 31, 38]. Moreover, epigenetic studies in the offspring from male progenitors exposed to different types of fatty acids are also needed, since evidence points towards modifications in parental sperm quality with consequences to the metabolic health of the offspring [60]. In this sense, this review points towards mechanisms involved in fetal health programming, which may incorporate the basis for public health politics for the prevention of obesity and associated diseases.

Abbreviations SFAs: Saturated fatty acids; PUFAs: Polyunsaturated fatty acids; MUFAs: Monounsaturated fatty acids; HFD: High fat diets; DOHaD: Developmental Origins of Health and Disease; DNMT: DNA methyltransferases; MeCP: Methyl CpG binding proteins; HDAC: Histone deacetylases; TETs: Ten-eleven translocation methylcytosine dioxygenases; miRNAs: MicroRNAs; H3K14: Histone 3 lysine 14; H3K9: 3 Lysine 9 residues; H3K18: Histone 3 lysine 18 residues; H3Ac: Acetylated histone 3; H4Ac: Acetylated histone 4; H3K4Me2: Dimethylated histone 3 lysine 4 residues; H3K9Me3: Trimethylated histone 3 lysine 9 residues; H3K27Me3: Trimethylated histone 3 lysine 27 residues; H3Me2: Dimethylated histone H3; H3K4Me3: Trimethylated histone H3 lysine 4; PPARγ2: Peroxisome proliferator-activated receptor γ 2; MAPKs: Mitogen-activated protein kinases; SCD1: Stearoyl-CoA desaturase-1; ARC: Arcuate nucleus; POMC: Pro-opiomelanocortin; 5hmC: 5-Hydroxymethylcytosine; TGFβ: Growth factor-beta; tsRNAs: Small RNAs; ALA: α-Linolenic acid; LA: Linoleic acid; AA: Arachidonic acid; LC-PUFAs: Long-chain polyunsaturated fatty acids; EPA: Eicosapentaenoic acid; DPA: Docosapentaenoic acid; DHA: Docosahexaenoic acid; STAT3: Signal transducer and activator of transcription 3

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Code availability Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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References

1. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ, Hanson MA, Forrester T, Gluckman PD, Godfrey KM. Origins of lifetime health around the time of conception: causes and consequences. Lancet. 2018;391:1842–52. https://doi.org/10.1016/S0140-6736(18)30312-X.
2. Radford EJ. Exploring the extent and scope of epigenetic inheritance. Nat Rev Endocrinol. 2018;14:345–55. https://doi.org/10.1038/s41574-018-0005-5.
3. Jazwiec PA, Sloboda DM. Nutritional adversity, sex and reproduction: 30 years of DOHaD and what have we learned? J Endocrinol. 2019;242:T51–68. https://doi.org/10.1530/JOE-19-0048.
4. Reid MA, Dai Z, Locasale JW. The impact of cellular metabolism on chromatin dynamics and epigenetics. Nat Cell Biol. 2017;19:1298–306. https://doi.org/10.1038/ncb3629.
5. Safi-Stibler S, Gabory A. Epigenetics and the developmental origins of health and disease: parental environment signalling to the epigenome, critical time windows and sculpting the adult phenotype. Semin Cell Dev Biol. 2020;97:172–80. https://doi.org/10.1016/j.semcdb.2019.09.008.
6. Mahmoud AM, Ali MM. Methyl donor micronutrients that modify DNA methylation and cancer outcome. Nutrients. 2019;11.https://doi.org/10.3390/nu11030608.
7. Lyko F. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. Nat Rev Genet. 2018;19:81–92. https://doi.org/10.1038/nrg.2017.80.
8. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nat Rev Genet. 2016;17:487–500. https://doi.org/10.1038/nrg.2016.59.
9. Landrier J-F, Derghal A, Mounien L. MicroRNAs in obesity and related metabolic disorders. Cells. 2019;8.https://doi.org/10.3390/cells8080859.

10. Mennitti LV, Oliveira JL, Morais CA, Estadella D, Oyama LM, Oller do Nascimento CM, Pisani LP, . Type of fatty acids in maternal diets during pregnancy and/or lactation and metabolic consequences of the offspring. J Nutr Biochem. 2015;26:99–111. https://doi.org/10.1016/j.jnutbio.2014.10.001.
11. Castrejón-Téllez V, Villegas-Romero M, Pérez-Torres I, Zarco G, Rubio-Ruiz ME, Carreón-Torres E, Díaz-Díaz E, Grimaldo OE, Guarner-Lans V. Effect of sucrose ingestion at the end of a critical window that increases hypertension susceptibility on peripheral mechanisms regulating blood pressure in rats. Role of Sirtuins 1 and 3. Nutrients. 2019;11. https://doi.org/10.3390/nu11020309.
12. Mensink RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva: World Health Organization; 2016.
13. Astrup A, Bertram HCS, Bonjour J-P, de Groot LCP, de Oliveira Otto MC, Feeney EL, Garg ML, Givens I, Kok FJ, Krauss RM, Lamarche B, Lecerf J-M, Legrand P, McKinley M, Micha R, Michalski M-C, Mozaffarian D, Soedamah-Muthu SS. WHO draft guidelines on dietary saturated and trans fatty acids: time for a new approach? BMJ. 2019;366:l4137. https://doi.org/10.1136/bmj.l4137.
14. Parrillo L, Spinelli R, Nicolò A, Longo M, Mirra P, Raciti GA, Miele C, Beguinot F. Nutritional factors, DNA methylation, and risk of type 2 diabetes and obesity: perspectives and challenges. Int J Mol Sci. 2019;20.https://doi.org/10.3390/ijms20122983.
15. Aagaard-Tillery KM, Grove K, Bishop J, Ke X, Fu Q, McKnight R, Lane RH. Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. J Mol Endocrinol. 2008;41:91–102. https://doi.org/10.1677/JME-08-0025.
16. Strakovsky RS, Zhang X, Zhou D, Pan Y-X. Gestational high fat diet programs hepatic phosphoenolpyruvate carboxykinase gene expression and histone modification in neonatal offspring rats. J Physiol. 2011;589:2707–17. https://doi.org/10.1113/jphysiol.2010.203950.
17. Yang K, Cai W, Xu J, Shi W. Maternal high-fat diet programs Wnt genes through histone modification in the liver of neonatal rats. J Mol Endocrinol. 2012;49:107–14. https://doi.org/10.1530/JME-12-0046.
18. Strakovsky RS, Zhang X, Zhou D, Pan Y-X. The regulation of hepatic Pon1 by a maternal high-fat diet is gender specific and may occur through promoter histone modifications in neonatal rats. J Nutr Biochem. 2014;25:170–6. https://doi.org/10.1016/j.jnutbio.2013.09.016.
19. Zhou D, Wang H, Cui H, Chen H, Pan Y-X. Early-life exposure to high-fat diet may predispose rats to gender-specific hepatic fat accumulation by programming Pepck expression. J Nutr Biochem. 2015;26:433–40. https://doi.org/10.1016/j.jnutbio.2014.10.009.
20. Panchenko PE, Voisin S, Jouin M, Jouneau L, Prézelin A, Lecoutre S, Breton C, Jammes H, Junien C, Gabory A. Expression of epigenetic machinery genes is sensitive to maternal obesity and weight loss in relation to fetal growth in mice. Clin Epigenetics. 2016;8:22. https://doi.org/10.1186/s13148-016-0188-3.
21. Zhang Q, Xiao X, Zheng J, Li M, Yu M, Ping F, Wang T, Wang X. A maternal high-fat diet induces DNA methylation changes that contribute to glucose intolerance in offspring. Front Endocrinol (Lausanne). 2019;10:871. https://doi.org/10.3389/fendo.2019.00871.
22. Lin X-H, Gao L, Tian S, Klausen C, Guo M-X, Gao Q, Liu M-E, Wang H, Wu D-D, Zhou C-L, Yang J, Meng Y, Liu Y, Xu G-F, Tan Y-J, Ullah K, Zhu Y-M, Fraser WD, Sheng J-Z, Leung PCK, Muglia LJ, Wu Y-T, Huang H-F. Maternal high-fat-diet exposure is associated with elevated blood pressure and sustained increased leptin levels through epigenetic memory in offspring. Sci Rep. 2021;11:316. https://doi.org/10.1038/s41598-020-79604-4.
23. Lecoutre S, Oger F, Pourpe C, Butruille L, Marousez L, Dickes-Coopman A, Laborie C, Guinez C, Lesage J, Vieau D, Junien C, Eberlé D, Gabory A, Eeckhoute J, Breton C. Maternal obesity programs increased leptin gene expression in rat male offspring via epigenetic modifications in a depot-specific manner. Mol Metab. 2017;6:922–30. https://doi.org/10.1016/j.molmet.2017.05.010.
24. Lecoutre S, Pourpe C, Butruille L, Marousez L, Laborie C, Guinez C, Lesage J, Vieau D, Eeckhoute J, Gabory A, Oger F, Eberle´ D, Breton C, . Reduced PPARγ2 expression in adipose tissue of male rat offspring from obese dams is associated with epigenetic modifications. FASEB J. 2018;32:2768–78. https://doi.org/10.1096/fj.201700997R.
25. Butruille L, Marousez L, Pourpe C, Oger F, Lecoutre S, Catheline D, Görs S, Metges CC, Guinez C, Laborie C, Deruelle P, Eeckhoute J, Breton C, Legrand P, Lesage J, Eberlé D. Maternal high-fat diet during suckling programs visceral adiposity and epigenetic regulation of adipose tissue stearoyl-CoA desaturase-1 in offspring. Int J Obes. 2019;43:2381–93. https://doi.org/10.1038/s41366-018-0310-z.
26. Liang X, Yang Q, Fu X, Rogers CJ, Wang B, Pan H, Zhu M-J, Nathanielsz PW, Du M. Maternal obesity epigenetically alters visceral fat progenitor cell properties in male offspring mice. J Physiol. 2016;594:4453–66. https://doi.org/10.1113/JP272123.
27. Kasch J, Kanzleiter I, Saussenthaler S, Schürmann A, Keijer J, van Schothorst E, Klaus S, Schumann S. Insulin sensitivity linked skeletal muscle Nr4a1 DNA methylation is programmed by the maternal diet and modulated by voluntary exercise in mice. J Nutr Biochem. 2018;57:86–92. https://doi.org/10.1016/j.jnutbio.2018.03.015.
28 Upadhyaya B, Larsen T, Barwari S, Louwagie EJ, Baack M, Dey M. Prenatal exposure to a maternal high-fat diet affects histone modification of cardiometabolic genes in newborn rats. Nutrients. 2017;9(4):407. https://doi.org/10.3390/nu9040407.
29 Blin G, Liand M, Mauduit C, Chehade H, Benahmed M, Simeoni U, Siddeek B. Maternal exposure to high-fat diet induces long-term derepressive chromatin marks in the heart. Nutrients. 2020;12(1):181. https://doi.org/10.3390/nu12010181.
30. Glendining KA, Higgins MBA, Fisher LC, Jasoni CL. Maternal obesity modulates sexually dimorphic epigenetic regulation and expression of leptin receptor in offspring hippocampus. Brain Behav Immun. 2020;88:151–60. https://doi.org/10.1016/j.bbi.2020.03.006.
31. Almeida MM, Dias-Rocha CP, Reis-Gomes CF, Wang H, Atella GC, Cordeiro A, Pazos-Moura CC, Joss-Moore L, Trevenzoli IH. Maternal high-fat diet impairs leptin signaling and up-regulates type-1 cannabinoid receptor with sex-specific epigenetic changes in the hypothalamus of newborn rats. Psychoneuroendocrinology. 2019;103:306–15. https://doi.org/10.1016/j.psyneuen.2019.02.004.
32. Marco A, Kisliouk T, Tabachnik T, Weller A, Meiri N. DNA CpG methylation (5-methylcytosine) and its derivative (5-hydroxymethylcytosine) alter histone posttranslational modifications at the pomc promoter, affecting the impact of perinatal diet on leanness and obesity of the offspring. Diabetes. 2016;65:2258 LP – 2267. https://doi.org/10.2337/db15-1608.
33. Gali Ramamoorthy T, Allen T-J, Davies A, Harno E, Sefton C, Murgatroyd C, White A. Maternal overnutrition programs epigenetic changes in the regulatory regions of hypothalamic Pomc in the offspring of rats. Int J Obes. 2018;42:1431–44. https://doi.org/10.1038/s41366-018-0094-1.
34. Desai M, Han G, Ross MG. Programmed hyperphagia in offspring of obese dams: altered expression of hypothalamic nutrient sensors, neurogenic factors and epigenetic modulators. Appetite. 2016;99:193–9. https://doi.org/10.1016/j.appet.2016.01.023.
35. Wing-Lun E, Eaton SA, Hur SSJ, Aiken A, Young PE, Buckland ME, Li CCY, Cropley JE, Suter CM. Nutrition has a pervasive

impact on cardiac microRNA expression in isogenic mice. Epigenetics. 2016;11:475–81. https://doi.org/10.1080/15592294.2016.1190895.
36. Siddeek B, Mauduit C, Chehade H, Blin G, Liand M, Chindamo M, Benahmed M, Simeoni U. Long-term impact of maternal high-fat diet on offspring cardiac health: role of micro-RNA biogenesis. Cell Death Discov. 2019;5:71. https://doi.org/10.1038/s41420-019-0153-y.
37. Sarker G, Sun W, Rosenkranz D, Pelczar P, Opitz L, Efthymiou V, Wolfrum C, Peleg-Raibstein D. Maternal overnutrition programs hedonic and metabolic phenotypes across generations through sperm tsRNAs. Proc Natl Acad Sci. 2019;116:10547 LP – 10556. https://doi.org/10.1073/pnas.1820810116.
38. Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. Endocrinology. 2011;152:2228–36. https://doi.org/10.1210/en.2010-1461.
39. Gonzalez-Soto M, Mutch DM. Diet regulation of long-chain PUFA synthesis: role of macronutrients, micronutrients, and polyphenols on Δ-5/Δ-6 desaturases and elongases 2/5. Adv Nutr. 2020. https://doi.org/10.1093/advances/nmaa142.
40. Fan C, Fu H, Dong H, Lu Y, Lu Y, Qi K. Maternal n-3 polyunsaturated fatty acid deprivation during pregnancy and lactation affects neurogenesis and apoptosis in adult offspring: associated with DNA methylation of brain-derived neurotrophic factor transcripts. Nutr Res. 2016;36:1013–21. https://doi.org/10.1016/j.nutres.2016.06.005.
41. Bianchi M, Alisi A, Fabrizi M, Vallone C, Ravà L, Giannico R, Vernocchi P, Signore F, Manco M. Maternal intake of n-3 polyunsaturated fatty acids during pregnancy is associated with differential methylation profiles in cord blood white cells. Front Genet. 2019;10:1050. https://doi.org/10.3389/fgene.2019.01050.
42. van Dijk SJ, Zhou J, Peters TJ, Buckley M, Sutcliffe B, Oytam Y, Gibson RA, McPhee A, Yelland LN, Makrides M, Molloy PL, Muhlhausler BS. Effect of prenatal DHA supplementation on the infant epigenome: results from a randomized controlled trial. Clin Epigenetics. 2016;8:114. https://doi.org/10.1186/s13148-016-0281-7.
43. Cinquina V, Calvigioni D, Farlik M, Halbritter F, Fife-Gernedl V, Shirran SL, Fuszard MA, Botting CH, Poullet P, Piscitelli F, Máté Z, Szabó G, Yanagawa Y, Kasper S, Di Marzo V, Mackie K, McBain CJ, Bock C, Keimpema E, Harkany T. Life-long epigenetic programming of cortical architecture by maternal 'Western' diet during pregnancy. Mol Psychiatry. 2020;25:22–36. https://doi.org/10.1038/s41380-019-0580-4.
44. Hoile SP, Irvine NA, Kelsall CJ, Sibbons C, Feunteun A, Collister A, Torrens C, Calder PC, Hanson MA, Lillycrop KA, Burdge GC. Maternal fat intake in rats alters 20:4n–6 and 22:6n–3 status and the epigenetic regulation of Fads2 in offspring liver. J Nutr Biochem. 2013;24:1213–20. https://doi.org/10.1016/j.jnutbio.2012.09.005.
45. Turkmen S, Perera E, Zamorano MJ, Simó-Mirabet P, Xu H, Pérez-Sánchez J, Izquierdo M. Effects of dietary lipid composition and fatty acid desaturase 2 expression in broodstock gilthead sea bream on lipid metabolism-related genes and methylation of the fads2 Gene promoter in their offspring. Int J Mol Sci. 2019;20.https://doi.org/10.3390/ijms20246250.
46. Kelsall CJ, Hoile SP, Irvine NA, Masoodi M, Torrens C, Lillycrop KA, Calder PC, Clough GF, Hanson MA, Burdge GC. Vascular dysfunction induced in offspring by maternal dietary fat involves altered arterial polyunsaturated fatty acid biosynthesis. PLoS One. 2012;7:e34492. https://doi.org/10.1371/journal.pone.0034492.
47. Mennitti LV, Oyama LM, Santamarina AB, do Nascimento CM da PO, Pisani LP, . Early exposure to distinct sources of lipids affects differently the development and hepatic inflammatory profiles of 21-day-old rat offspring. J Inflamm Res. 2018;11:11–24. https://doi.org/10.2147/JIR.S152326.
48. Miles EA, Calder PC. Can early omega-3 fatty acid exposure reduce risk of childhood allergic disease? Nutrients. 2017;9.https://doi.org/10.3390/nu9070784.
49. Fan R, Toney AM, Jang Y, Ro S-H, Chung S. Maternal n-3 PUFA supplementation promotes fetal brown adipose tissue development through epigenetic modifications in C57BL/6 mice. Biochim Biophys Acta Mol Cell Biol Lipids. 2018;1863:1488–97. https://doi.org/10.1016/j.bbalip.2018.09.008.
50. Li J, Li K, Gao J, Guo X, Lu M, Li Z, Li D. Endogenously synthesized n-3 polyunsaturated fatty acids in pregnant fat-1 mice decreases mammary cancer risk of female offspring by regulating expression of long noncoding RNAs. Mol Nutr Food Res. 2019;63: e1801150. https://doi.org/10.1002/mnfr.201801150.
51. Alonso A, Ruiz-Gutierrez V, Martínez-González MA. Monounsaturated fatty acids, olive oil and blood pressure: epidemiological, clinical and experimental evidence. Public Health Nutr. 2006;9:251–7. https://doi.org/10.1079/phn2005836.
52. Raisanen S, Hogue CJR, Laine K, Kramer MR, Gissler M, Heinonen S. A population-based study of the effect of pregnancy history on risk of stillbirth. Int J Gynaecol Obstet. 2018;140:73–80. https://doi.org/10.1002/ijgo.12342.
53. Mika A, Sikorska-Wiśniewska M, Małgorzewicz S, Stepnowski P, Dębska-Ślizień A, Śledziński T, Chmielewski M. Potential contribution of monounsaturated fatty acids to cardiovascular risk in chronic kidney disease. Pol Arch Intern Med. 2018;128:755–63. https://doi.org/10.20452/pamw.4376.
54. Joris PJ, Mensink RP. Role of cis-monounsaturated fatty acids in the prevention of coronary heart disease. Curr Atheroscler Rep. 2016;18:38. https://doi.org/10.1007/s11883-016-0597-y.
55. Roberti SL, Higa R, Sato H, Gomez Ribot D, Capobianco E, Jawerbaum A. Olive oil supplementation prevents extracellular matrix deposition and reduces prooxidant markers and apoptosis in the offspring´s heart of diabetic rats. Reprod Toxicol. 2020;95:137–47. https://doi.org/10.1016/j.reprotox.2020.05.002.
56. Fornes D, Gomez Ribot D, Heinecke F, Roberti SL, Capobianco E, Jawerbaum A. Maternal diets enriched in olive oil regulate lipid metabolism and levels of PPARs and their coactivators in the fetal liver in a rat model of gestational diabetes mellitus. J Nutr Biochem. 2020;78:108334. https://doi.org/10.1016/j.jnutbio.2019.108334.
57. Acevedo N, Frumento P, Harb H, Alashkar Alhamwe B, Johansson C, Eick L, Alm J, Renz H, Scheynius A, Potaczek DP. Histone acetylation of immune regulatory genes in human placenta in association with maternal intake of olive oil and fish consumption. Int J Mol Sci. 2019;20.https://doi.org/10.3390/ijms20051060.
58. Casas-Agustench P, Fernandes FS, Tavares do Carmo MG, Visioli F, Herrera E, Dávalos A. Consumption of distinct dietary lipids during early pregnancy differentially modulates the expression of microRNAs in mothers and offspring. PLoS One. 2015;10:e0117858. https://doi.org/10.1371/journal.pone.0117858.
59. Govindarajah V, Leung Y-K, Ying J, Gear R, Bornschein RL, Medvedovic M, Ho S-M. In utero exposure of rats to high-fat diets perturbs gene expression profiles and cancer susceptibility of prepubertal mammary glands. J Nutr Biochem. 2016;29:73–82. https://doi.org/10.1016/j.jnutbio.2015.11.003.
60. Lane M, Zander-Fox DL, Robker RL, McPherson NO. Peri-conception parental obesity, reproductive health, and transgenerational impacts. Trends Endocrinol Metab. 2015;26:84–90. https://doi.org/10.1016/j.tem.2014.11.005.