Effects of fructose consumption during pregnancy in murine models (Review)

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Abstract. After standardizing methods for industrial fructose production, this sugar has been intensively used as a food additive. The growing use of this sugar in food has coincided with increased metabolic disorders in recent decades, and it remains a widely used sweetener. The high ingestion of fructose has contributed to the increasing prevalence of numerous chronic health conditions. Fructose intake and its impact during pregnancy and lactation have drawn the attention of researchers. In the present review, the latest information on the effects of maternal diets rich in fructose on rat or mouse offspring was compiled. The findings suggest a generalized negative response to excess fructose, such as alterations in mitochondrial function, neuroinflammation, oxidative stress, reproductive health, placental and intrauterine effects, epigenetics, transcriptomics modifications and cognitive function impairment. This demonstrates that chronic maternal fructose consumption could deteriorate the offspring's health.

Contents

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1. Introduction

Fructose, a naturally occurring monosaccharide and isomer of glucose, is commonly found in fruit and honey. Unlike glucose, which is metabolized primarily to produce ATP, fructose follows a different metabolic pathway, being processed primarily in the liver to produce elevated serum levels of glucose, triglycerides and total cholesterol (1). Owing to its low cost and potent sweetening capacity, fructose has become a widely used sweetener in beverages globally, especially following the development of cost-effective synthesis methods in the 1970s. This advancement has resulted in a significant increase in both fructose production and consumption (2-4).

It has been found that a diet high in fructose can result in metabolic disorders, which in turn can trigger pathologies such as obesity, cardiovascular diseases, type 2 diabetes and cognitive dysfunction. Although these conditions usually manifest during adulthood, it has been suggested that they can also appear due to an adverse intrauterine environment (5,6). Developmental programming where maternal nutrition influences the health of offspring suggests that excessive fructose consumption during gestation and lactation affects neonatal development, causing metabolic diseases and cognitive impairment. Studies in animal models, especially in rodents, show that a maternal diet rich in fructose (MDRF) during pregnancy and lactation can negatively affect brain function, reduce cognitive abilities, cause inflammatory responses and provoke multiple metabolic disorders in the offspring (4).

Murine models are highly suitable for investigating the effects of high fructose intake during pregnancy and lactation. Fructose consumption is known to promote lipogenesis and elevate triglyceride levels, which can lead to hepatic insulin resistance-an effect similar to that observed in humans (2,7). Studying these models allows researchers to improve understanding of the potential consequences in humans and develop effective prevention and intervention strategies (5,6,8). While recent and comprehensive studies have examined the effects of fructose consumption during pregnancy in both humans and animal models, each focuses on a specific mechanism, such as mitochondrial dysfunction (9), epigenetic modifications (10), fertility issues (11), or cognitive impairment (12). The present review is novel in that it integrates these diverse perspectives,

exploring the cellular, molecular and functional effects of fructose consumption in a comprehensive manner. In the present review, the available literature on the effect of fructose consumption during gestation and lactation on offspring development using murine models was discussed.

2. Methodology

PRISMA guidelines were followed in the present review. A search was performed using the ScienceDirect (https://www.sciencedirect.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/), Oxford Academic (https://academic.oup.com/) and Scopus (https://www.scopus.com/home.uri) databases. The MeSH (Medical Subject Headings) terms 'pregnancy', 'Rats', 'Mice', 'Fructose' and 'Brain' were combined to form the search matrix '(pregnancy) AND ((Rats) OR (Mice)) AND (Fructose) AND (Brain)'. A total of 64 articles were found using the different databases.

Inclusion criteria. Studies included in the present review fulfil the following criteria: fructose had to be used as animal feed and administered during gestation +/- lactation.

Exclusion criteria. Studies in which fructose was administered only during lactation were excluded, as well as those where the term 'fructose' appeared only as part of a component or term of the experimental model or in the frame of references.

A total of 64 studies were retrieved from the databases. After applying the inclusion and exclusion criteria, 29 articles were retained. This included 28 research articles and 1 review article. Studies involved only the use of animal models, specifically rats and mice, articles published in 1993 (1), 2011 (1), 2014 (2), 2015 (1), 2016 (3), 2017 (1), 2018 (4), 2019 (2), 2020 (5), 2021 (3), 2022 (2), 2023 (3) and 2024 (1) were obtained. A total of 3 articles were taken into account by snowball capture about experimental animal models: 'Metabolic effects of fructose', 'Dietary fructose-induced gut dysbiosis promotes mouse hippocampal neuroinflammation: A benefit of short-chain fatty acids', and 'A high-fructose diet induces hippocampal insulin resistance and exacerbates memory deficits in male Sprague-Dawley rats', this to expand on the concept of some key terms in the development of this review, and 12 articles per snowball about preclinical studies that contrast studies in animal models; finishing with a total of 44 studies included as shown in Fig. 1.

3. Discussion

Mitochondrial function, neuroinflammation and its relation to oxidative stress. Neuroinflammation, the inflammation of the nervous system, involves the activation of microglia and astrocytes, release of cytokines and chemokines, production of reactive oxygen species (ROS) and often the infiltration of peripheral leukocytes into the central nervous system (4). A diet rich in processed sugars and fats has been reported to be associated with neuroinflammatory effects (13). Fructose consumption has been shown to increase the expression of proinflammatory cytokines in some brain regions, interfering with the function of some tissues. In addition, due to oxidative stress and brain mitochondrial dysfunction, fructose consumption during gestation and lactation may program susceptibility to cardio-metabolic disease in females and fetal hypertension by affecting sympathetic nervous system activity in the rostral ventrolateral medulla (14). It has been found that maternal and post-weaning exposure to high-fructose corn syrup can increase the expression of proinflammatory proteins in the hippocampus of the offspring, suggesting a synergistic effect on neuroinflammation and the development of brain dysfunction (5).

These findings indicate that fructose not only induces neuroinflammation but also brain mitochondrial dysfunction and a sex-dependent response to fructose and the involvement of mechanisms such as DNA methylation in the generation of oxidative stress in offspring as supported by several studies (5,6,8,14-20). Fructose consumption interferes with key molecular systems required for mitochondrial biogenesis, particularly the peroxisome proliferator-activated receptor gamma coactivator-1 alpha and Cytochrome c oxidase subunit II. This disruption suggests that mitochondrial dysfunction may be an early consequence of fructose exposure in the brain (21).

On the other hand, diet during gestation and early life can have lasting effects on offspring, influencing brain and metabolic function in adulthood by modifying the capacities of astrocytes (6). Multiple studies have shown that fructose exposure during gestation affects mitochondrial function in offspring, which may trigger metabolic changes associated with brain aging (5,6,9,14,19,22). Furthermore, the relationship between MDRF and mitochondrial dysfunction in the hippocampus could contribute to neuropsychiatric disorders and cognitive dysfunction. This also affects glycolysis and oxidative phosphorylation in astrocyte mitochondria, highlighting the importance of metabolic regulatory mechanisms in brain development. These findings underscore the complex interplay between maternal diet, brain function and hippocampal vulnerability, highlighting the need for further research of these processes and to improve understanding of their implications in long-life health (5,6,14,19,22). In this context, fructose reprograms cellular metabolic pathways to favor glutaminolysis and oxidative metabolism, which are required to support increased inflammatory cytokine production in both lipopolysaccharide (LPS)-treated human monocytes and mouse macrophages. A fructose-dependent increase in mechanistic target of rapamycin complex 1 activity drives the translation of pro-inflammatory cytokines in response to LPS. LPS-stimulated monocytes treated with fructose rely heavily on oxidative metabolism and have reduced flexibility in response to both glycolytic and mitochondrial inhibition, suggesting glycolysis and oxidative metabolism are inextricably coupled in these cells. The physiological implications of fructose exposure are demonstrated in a model of LPS-induced systemic inflammation, with mice exposed to fructose having increased levels of circulating IL-1β after the LPS challenge (23). Recently, associations have been reported between nutritional deficiencies, particularly excessive sugar consumption, and an increased risk of pre-eclampsia, potentially mediated by oxidative stress, inflammation, maternal endothelial dysfunction and blood pressure dysregulation in its pathophysiology (24). Additionally, preclinical models have been widely used to establish a causal relationship between

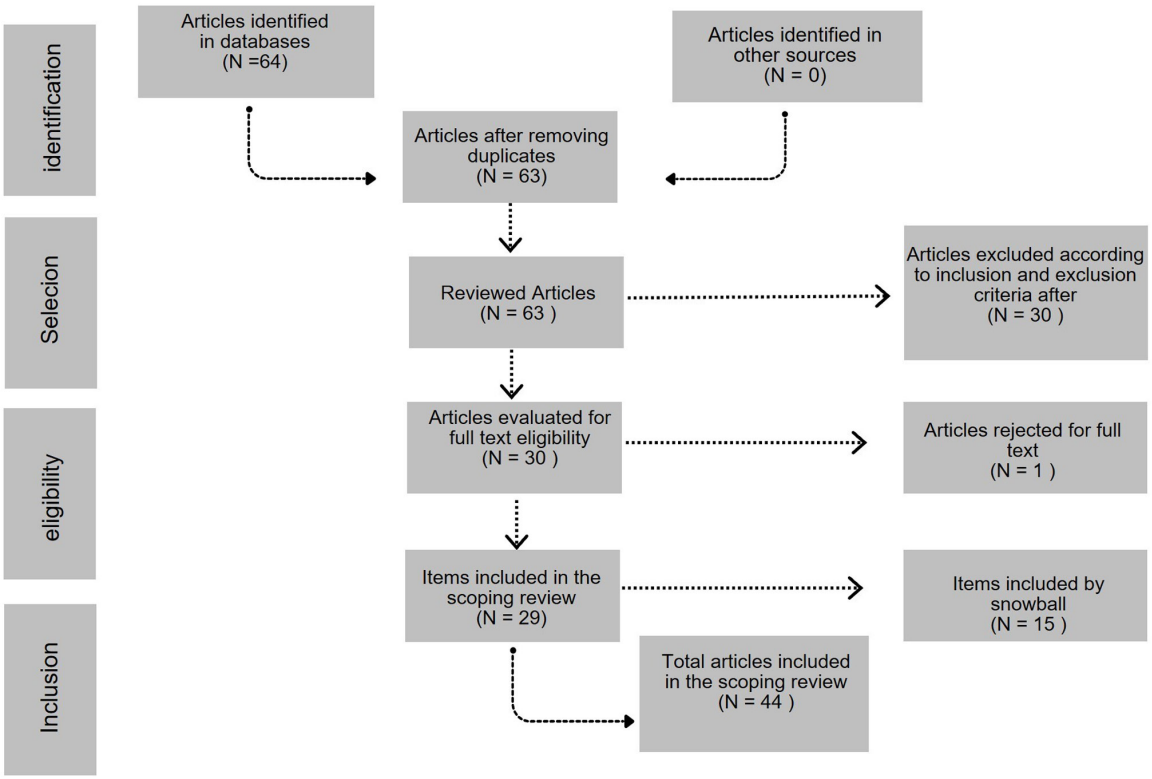

Figure 1. Algorithm for the literature review: Diagram of the article selection process for preparing the scoping review.

mitochondrial dysfunction, oxidative stress and memory deficits. Studies have indicated that cognitive impairment, induced by various conditions, including pharmacological, genetic, toxic and nutritional factors, is associated with reduced complex I activity, decreased mitochondrial membrane potential, elevated ROS production, lower antioxidant enzyme expression and increased lipid peroxidation (25).

Sustained consumption of high amounts of fructose also affects mothers by generating oxidative stress that can cause DNA damage. A study conducted in Brazil by Magenis *et al* (18) investigated whether fructose consumption during pregnancy affects genomic stability in female mice. The results showed more significant DNA damage in females receiving fructose during gestation and lactation. These results agree with previous studies in the literature stating that maternal fructose consumption could have adverse effects on both mother and offspring (18). The effects of high fructose intake on several physiological and molecular processes associated with oxidative stress in murine models are summarized in Fig. 2A and Table I.

Reproductive health, placental and intrauterine effect of maternal fructose consumption. Maternal nutrition during early life can significantly affect the postnatal phenotype of offspring. Undernutrition and hypercaloric maternal overnutrition can create an adverse environment, leading to a fundamental impact on fetal development and subsequent disease in adulthood, highlighting the importance of nutritional programming (26).

The placenta is an active intermediary between the maternal blood circulation and the fetus, thus playing a crucial role in fetal protection and nutritional programming (3,11). Liu *et al* (3) suggested that maternal consumption of fructose during pregnancy and lactation may lead to adverse outcomes in offspring, including insulin resistance, fatty liver, adipose tissue dysfunction, reduced adiponectin levels, dyslipidemia and alterations in endocrine function. Liu *et al* (3) found that pregnant rats consuming 10% fructose had a low fetus/placenta weight ratio, which is representative of the placental insufficiency observed in the fructose group; the same pregnant rats developed placentas with a weight of 0.53±0.12 g, whereas that control rats had placentas weighing of 0.74±0.08 g. These findings indicate that the placenta responds to alterations in maternal nutritional status and plays a crucial role in programming the fetal environment *in utero* through adaptive modifications in its structure and function. Reduced placental weight and a low fetus-to-placenta ratio may contribute to the asymmetric fetal growth restriction (AFGR) observed in the fructose group. Additionally, a significant decrease in maternal serum placental growth factor (PLGF), accompanied by an increase in soluble fms-like tyrosine kinase-1 (sFlt-1) concentrations and an elevated sFlt-1/PLGF ratio in the fructose group has been reported, further emphasizing placental insufficiency (3).

Fructose can be transported across the placenta and be present in fetal circulation, resulting in increased uric acid (UA) synthesis in both the liver and placenta. It is proposed that placentally produced UA may mediate the effects of fructose by promoting endothelial dysfunction and inefficient placentation. This dual role of UA is attributed to its ability to function as an extracellular antioxidant while inducing oxidative stress within cells (3). This oxidative stress could be

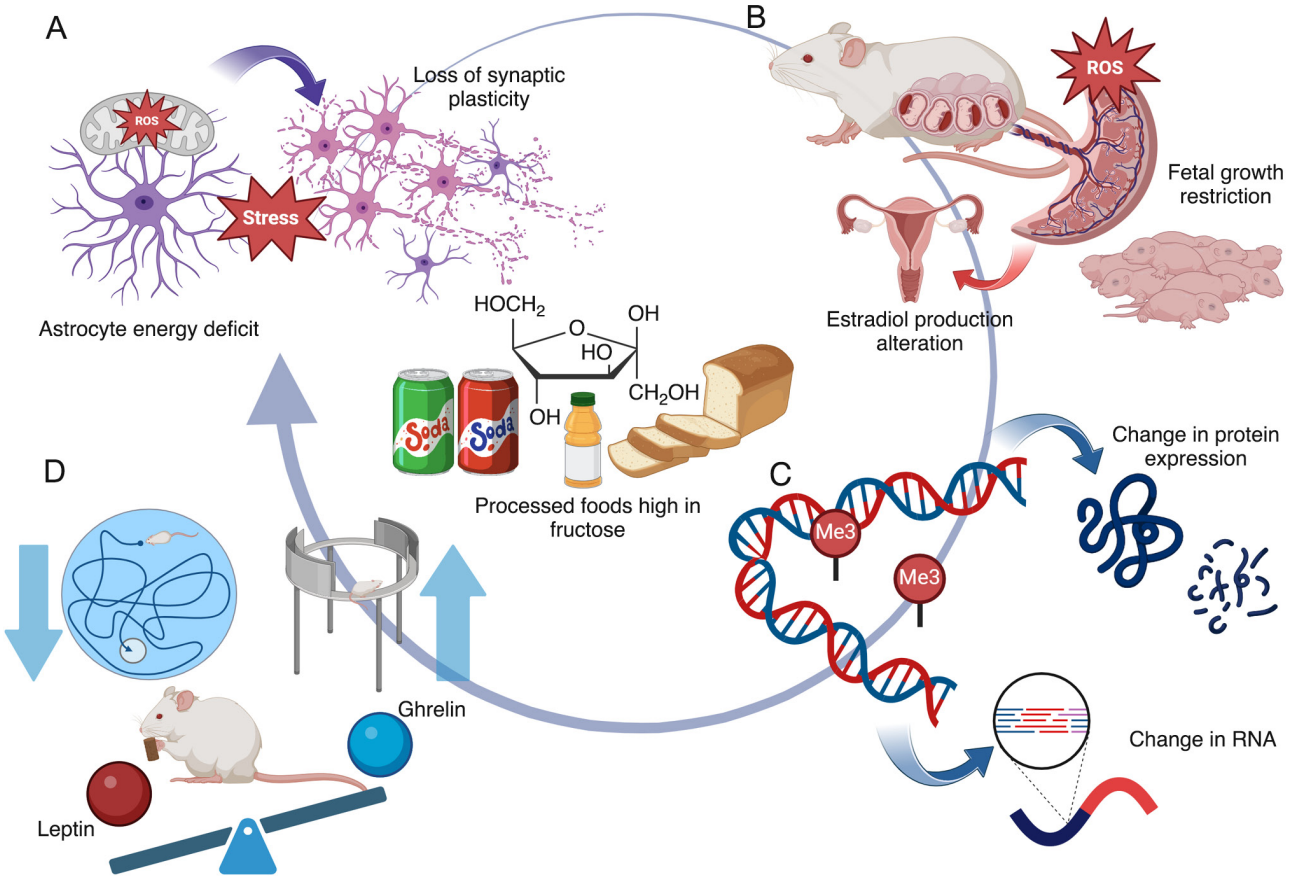

Figure 2. Main effects of fructose consumption during pregnancy. (A) Association of fructose consumption with neuroinflammation, mitochondrial dysfunction and genomic damage due to oxidative stress. (B) Influence of fructose consumption on the reproductive health of mothers in murine models and transgenerational effects on fetal development. (C) Effect of a fructose-rich diet during gestation at the molecular level. (D) Exposure to a maternal fructose-rich diet during pregnancy and lactation. ROS, reactive oxygen species.

the general underlying mechanism linking altered placental function to fetal programming since overproduction of ROS can lead to massive cellular damage, changing the course of pregnancy and generating a cascading effect leading to the genesis of *in utero* programming of adult diseases (3).

Vickers *et al* (26) observed that maternal fructose intake significantly elevated circulating plasma fructose and leptin levels in female fetuses, and reduced female placental weights-an effect absent in male fetuses. Based on these findings, they hypothesized a sex-specific effect on placental fructose sensitivity and/or transfer. This effect may be mediated by specific fructose transporters such as glucose transporter 5 or through alterations in placental growth and function influenced by fructose's impact on growth factors such as insulin-like growth factor and placental transporters. This hypothesis is feasible since other early-life influences have been shown to have sex-specific effects on the placenta, leading to changes in placental vascularity and growth (26).

The differential effects of fructose on sex are linked to the gene expression of various metabolic enzymes. Studies indicate that in male neonates, key enzymes involved in hepatic beta-oxidation, such as carnitine palmitoyl-transferase 1A and acetyl-coA acetyltransferase, are suppressed following fructose exposure. This suppression is associated with increased mRNA levels of sterol regulatory element-binding protein 1c, suggesting that hepatic fatty acid oxidation is diminished in favor of lipogenesis. By contrast, a distinct response is observed in females, characterized by an increase in mRNA levels of the gene encoding adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK). AMPK, a central metabolic regulator, enhances cellular energy levels by inhibiting anabolic pathways, such as fatty acid synthesis, while stimulating catabolic pathways that promote energy production, including fatty acid oxidation and glucose transport (27).

Other studies have pointed out that high fructose consumption during pregnancy can trigger oxidative stress in the placenta, generating AFGR and contributing to early pregnancy failure and fetal malformations due to placental insufficiency and elevated UA synthesis, which promotes endothelial dysfunction and placental insufficiency, increasing the risk of disease in the offspring (3,26).

A study by Vickers *et al* (26), which measured the impact of maternal fructose consumption on the placenta, fetal development and offspring growth, showed that this diet significantly increases circulating plasma fructose and leptin levels. This appetite-related peptide helps manage satiety through the hypothalamic system, which could induce decreased appetite. This change was accompanied by a decrease in placental weight of 41±9 mg (26,28). However, these changes were only observed in female offspring; the researchers noted no changes in placental weight in males, an increase in leptin, or an increase in leptin concentration

Table I. Summary of the main findings of the articles included in the scoping review.

First author/s, year	Main findings	(Refs.)
Mitochondrial function, neuroinflammation and its relation to oxidative stress		
Spagnuolo *et al*, 2020	Excess fructose was linked to obesity, dyslipidemia, and insulin resistance. The diet also promoted neuroinflammation, oxidative stress, mitochondrial dysfunction, and alterations in insulin signaling.	(4)
Chao *et al*, 2020	The maternal fructose rich diet during pregnancy and lactation caused fetal programming in rats, inducing deficient expression of receptor proteins, tissue oxidative stress, sympathetic activation, and nutrient-sensing signals are closely related to adult hypertension of fetal origin.	(14)
Yamazaki *et al*, 2023	Maternal and post-weaning consumption of a diet consisting of 20% fructose had a negative synergistic effect on the expression of pro-inflammatory cytokines in the hippocampus. In the postnatal, higher expression of tumor necrosis factor alpha was observed in the group with prenatal and postnatal high-fructose corn syrup intake, suggesting a synergistic detrimental impact.	(5)
Wu *et al*, 2019	The fructose rich diet (60%) suppressed glycolytic capacity, mitochondrial respiration and electron transport chain. It also affected mitochondrial DNA copies and mitochondrial transcription factors affecting brain metabolism.	(6)
Mizuno *et al*, 2021	The study suggests that a diet of 20% fructose for dams may decrease catalase (Cat) transcript levels in the offspring's hippocampus by altering DNA methylation, resulting in higher levels of oxidative stress.	(8)
Smith *et al*, 2022	Epigenetic modifications in mitochondrial genes are proposed as a potential contributing factor to these alterations, although their precise role remains to be fully elucidated.	(9)
Mortensen *et al*, 2014	Chronic maternal consumption of a diet with 485 g of fructose through pregnancy and lactation affects brain metabolism, cognitive function in adults and lower body weight in the offspring after weaning.	(15)
Liu *et al*, 2020	A maternal diet with 60% fructose diet triggered neuroinflammation in the hippocampus of 3-month-old female offspring. Pioglitazone treatment reversed these effects, suggesting a potential therapeutic use to treat the hippocampal impairment induced by a chronic fructose consumption.	(16)
Chao *et al*, 2022	β-biotic supplementation in young offspring may protect against the development of hypertension in adulthood in those exposed to a maternal diet 60% rich in fructose. The β-biotic helped to reduce oxidative stress and neuroinflammation.	(17)
Magenis *et al*, 2020	Chronic consumption of fructose (10 and 20%) during pregnancy and lactation causes DNA damage and negatively impacts intake, body weight, lipid profile and fasting blood glucose.	(18)
Yamada *et al*, 2019	Maternal exposure to a 20% fructose diet in rats induced detrimental effects on mitochondrial physiology and oxidative stress in offspring through epigenetic mechanisms.	(19)
Bukhari *et al*, 2018	Coexistence of inflammation derived from a maternal high-fructose diet (60%) and neonatal treatment with lipopolysaccharides affected anxiety-like behaviors and proinflammatory cytokine levels at multiple life stages of rodents.	(22)
Wang *et al*, 2022	FOXP1 syndrome is associated with neurological deficits. In Foxp1 +/- mice, mitochondrial dysfunction and oxidative stress are observed, which could explain the cognitive and motor impairment.	(25)
Kinshella *et al*, 2022	Foods high in added sugar, such as sugary drinks, were associated with increased risk of pre-eclampsia incidence.	(24)
Jones *et al*, 2021	Dietary fructose reprograms monocyte and macrophage metabolism, increasing inflammation through mechanistic target of rapamycin complex 1 and reducing metabolic flexibility. In mice, its consumption intensifies the systemic inflammatory response.	(23)
Jiménez-Maldonado *et al*, 2018	The high consumption of fructose during a week had no effect over the liver/body weight ratio, weight gain, glucose tolerance and insulin sensitivity, but I could reduce several aspects of hippocampal plasticity.	(21)
Reproductive health and placental and intrauterine effect of maternal fructose consumption		
Vickers *et al*, 2011	Female fetuses, unlike male fetuses, had smaller placentas, with high levels of leptin, fructose and glucose. Maternal exposure to a diet with 20% of caloric intake from fructose differentially affects placental, fetal and neonatal development in females.	(26)

Table I. Continued.

First author/s, year	Main findings	(Refs.)
Liu *et al*, 2021	High fructose consumption (10%) during pregnancy in rats caused placental insufficiency and fetal growth restriction, with reduced fetal and placental weight, increased oxidative stress and altered gene expression.	(3)
Kearns and Reynolds, 2024	The impact of non-nutritive sweetener consumption in cognitives and animal models suggests that it affects maternal metabolic health and offspring development. This review examines maternal sweetener intake and its effects on fertility and maternal health.	(11)
Koski *et al*, 1993	A maternal diet low in carbohydrates with adequate energy intake reduced fetal brain weight and affected composition, and altered neurotransmitter synthesis. Glucose and fructose presented similar results across different distributions.	(29)
Munetsuna *et al*, 2018	Offspring of dams fed fructose (20%) showed reduced steroidogenesis, lower estradiol, and downregulation of estrogen and progesterone receptors, indicating altered ovarian physiology.	(30)
Clayton *et al*, 2015	Maternal fructose intake alters fatty acid metabolism in mothers and offspring in an age- and sex-specific manner, affecting biological clock genes. In addition, it could impair the hepatic immune response by suppressing the inflammasome in mothers and male neonates.	(27)
Epigenetic and transcriptomic modifications in the offspring		
Zou *et al*, 2023	A maternal high-fructose diet (13 and 40%) altered hippocampal lncRNAs and target genes in offspring, which affected brain development and increased dopaminergic receptor expression, leading to anxious behaviors and suggesting a link between lncRNAs and emotional regulation.	(32)
Zou *et al*, 2023	Maternal fructose to diets supplied with 13 and 40% fructose impaired conditioning and associative memory, caused low levels of synaptic proteins, and alterations in gene edition mechanisms.	(31)
Wu *et al*, 2024	A maternal diet high in fructose (60%) impaired hippocampal memory, caused microbiota dysbiosis, and reduced butyrate levels in the offspring. These effects were partly reversed by fructo- oligosaccharides and butyrate, which restored protein expression, bioenergetics, and mitochondrial function.	(33)
Zou *et al*, 2022	Maternal intake of diets with 13 and 40% fructose contents affected learning and memory by inhibiting a pathway responsible for regulating processes such as tissue regeneration and differentiation of stem cells and cell proliferation. The diet also altered the expression of genes, which can cause changes in the development of the nervous system.	(35)
Chao *et al*, 2016	This study used next-generation sequencing to analyze transcriptome expression in male offspring exposed to a maternal high-fructose (60%) diet, revealing long-lasting changes in gene expression and metabolic syndrome phenotypes in adulthood.	(34)
Mukai *et al*, 2014	Excessive maternal fructose intake (10%) during gestation altered the expression of cellular energy sensors in the liver, hypothalamus and glucose-6-phosphatase activity, especially in female offspring, suggesting long-lasting metabolic effects and an increased risk of metabolic syndrome.	(36)
Koo *et al*, 2021	Offspring exposed to diets supplied with 20% fructose through maternal consumption had higher body weight, fatty liver, poorer glucose tolerance, and elevated levels of serum markers and blood pressure.	(1)
Ohashi *et al*, 2015	Maternal fructose intake (20%) increased mRNA levels of steroidogenic enzymes in the hippocampus of offspring, potentially affecting neuro-steroidogenesis and neuron survival.	(37)
Wu *et al*, 2016	Offspring of mothers fed high fructose (60%) showed impaired spatial learning and memory, reduced hippocampal BDNF, and increased nuclear histone deacetylase 4; however, post-weaning environmental stimulation for four weeks reversed these cognitive deficits and molecular changes.	(39)
Mizuno *et al*, 2017	Maternal consumption of a diet supplied with 20% fructose differentially affected the expression of steroidogenesis-related genes in the hippocampus of offspring with different effects through pregnancy and lactation.	(38)

Table I. Continued.

First author/s, year	Main findings	(Refs.)
Yamazaki *et al*, 2018	Excessive and early maternal exposure to fructose (20%) generated an increase in DNA methylation in the BDNF promoter region, which persisted until the rat's maturity and was related to hippocampal dysfunction.	(2)
Bokor *et al*, 2024	The study analyzes how maternal fructose intake during gestation and lactation can influence DNA methylation in offspring, affecting their metabolism and risk of obesity, highlighting the role of epigenetic changes in fetal programming.	(10)
Brain characterization and cognitive function		
Saad *et al*, 2016	The study found that exposure to fructose during pregnancy differentially affected the brain development of offspring: in males there was a reduction in the size of brain structures and an increase in neuronal cells, and in females only an increase in neuronal cells was observed. These findings suggest that maternal metabolic dysregulation induced by fructose (10%) may alter fetal brain development.	(42)
Gillespie *et al*, 2024	Maternal diet rich in fructose alters the expression of lncRNAs and their target genes in the hippocampus of the offspring, affecting key physiological functions, especially those related to brain development. A relationship was found between these changes in lncRNAs and anxiety-like behaviors in the offspring, suggesting an impact on emotional regulation and neurodevelopment.	(12)
Kisioglu and Nergiz-Unal, 2020	High-fructose diets led to increased body fat intake and altered appetite regulation with lower leptin, higher ghrelin, and higher cluster of differentiation 36 levels, suggesting that maternal fructose contributes to obesity programming.	(28)
Erbas *et al*, 2018	Significant differences appeared in behavioral tests, histological alterations in the hippocampus and differences in brain biochemical markers between controls and fructose-exposed groups, suggesting a link between maternal metabolic stress due to prolonged intake of a diet with 30% fructose and neurological development disorders in offspring.	(43)
Rivell and Mattson, 2019	It suggests that interventions that improve metabolic health may ameliorate developmental neuronal network abnormalities and consequent behavioral manifestations in autism spectrum disorders.	(44)
Crichton *et al*, 2016	Frequent consumption of sugary soft drinks is associated with poorer cognitive performance, especially in individuals with type 2 diabetes, while diet soft drinks showed no such effect. Additional studies are needed to understand the underlying mechanisms.	(40)
Ye *et al*, 2011	Greater intakes of total sugars, added sugars and sugar-sweetened beverages, but not of sugar-sweetened solid foods, were significantly associated with lower Mini-Mental State Examination scores, higher sugar intake appears to be associated with lower cognitive function, but longitudinal studies are needed to clarify the direction of causality.	(41)

BDNF, brain-derived neurotrophic factor; lncRNAs, long non-coding RNAs; FOXP1, forkhead box protein P1.

observed in the mothers. Several studies (3,26,29) have identified adverse placental and intrauterine effects. This could be related to the transfer of leptin to the placenta or the alteration of placental leptin production in female fetuses exposed to fructose (26).

On the other hand, a study by Munetsuna *et al* (30) revealed that chronic fructose consumption during pregnancy and lactation has a transgenerational effect on offspring. Maternal fructose consumption impacts ovarian estradiol synthesis in the offspring. The impact of maternal fructose on ovarian estradiol synthesis in the offspring was evaluated by performing a quantitative PCR. It was found that some steroidogenic enzymes, such as estradiol, were attenuated in fructose-exposed offspring. These findings suggest that excessive maternal fructose consumption might cause dysregulated ovarian function in the offspring throughout their lives. It was suggested that fructose-induced endoplasmic reticulum (ER) stress might represent one of the mechanisms by which estradiol synthesis is altered in the offspring. Based on this, it was hypothesized that the offspring may ingest fructose through fetal circulation and lactation, providing an environment in which there is abundant fructose *in utero*, which could

produce fructose-induced ER stress in the offspring, leading to attenuated transcription of steroidogenic genes (30).

Although a fructose-rich diet may adversely affect offspring health and development in murine models, fructose is a valuable energy substrate. It has been observed that changes in carbohydrate levels in the maternal diet during pregnancy can affect glycogen levels in fetal brains and brain function. Additionally, it has been reported that the absence of glucose and fructose in the maternal diet can result in lower fetal brain weight than carbohydrate-rich diets. Correlations between fetal brain glycogen and amniotic fluid glucose levels demonstrate that low-carbohydrate diets reduce amniotic fluid glucose in pregnant rats, leading to deficits in the weight of specific organs after fructose deprivation (29). These findings indicate that carbohydrate deprivation in the maternal diet may negatively affect fetal brain development. While fructose is a common component of daily foods, excessive intake, particularly during pregnancy, can harm intrauterine health and offspring development. However, eliminating sugars from the diet may also pose health risks, highlighting the importance of careful dietary management during pregnancy (Fig. 2B and Table I).

Epigenetic and transcriptomic modifications in the offspring. The harmful effects of a maternal fructose-rich diet on biological processes relevant to brain development at the tissue level have been discussed in the previous section. This section examines the molecular changes induced by fructose-rich diets and their impact at the organo-genic level. Zou *et al* (31) found that chronic fructose consumption can influence numerous biological processes related to brain development by altering transcriptional expression and disrupting essential RNA editing processes, leading to adverse effects on the nervous system of offspring (31,32). Wu *et al* (6) further highlighted that such diets impair synaptic plasticity, hippocampal neurogenesis and spatial memory. Moreover, neuro-steroids are particularly sensitive to maternal fructose intake. This suggests that maternal malnutrition during pregnancy and early organ development stages can result in fetal programming, altering the structure and function of the offspring's systems-a concept known as Barker's hypothesis (5). These findings emphasize the need to understand the molecular effects of high-fructose diets on brain and metabolic development in offspring (6).

After sequencing whole RNA using the Full-Length Nanopore RNA Sequencing method, researchers aimed to predict long non-coding RNA (lncRNA) chains, which, despite not encoding proteins, can influence metabolic processes, such as neuroreceptor signaling (as indicated by Zou *et al* (31,32). Additionally, lncRNAs regulate gene expression in pathways involved in embryonic development. MDRF has been shown to not only alter lncRNA expression but also affect messenger RNA sequences, poly-A chains and splice sites, potentially predisposing individuals to diseases such as non-alcoholic fatty liver disease or cancer (31,32). Furthermore, other studies suggest that altered DNA methylation following fructose ingestion may explain changes in gene expression, adding another layer to fetal programming mechanisms that shape offspring phenotype (23,32,33). Supporting this, techniques such as western blotting, immunofluorescence and gene silencing have revealed that MDRF during gestation suppresses plasma butyrate levels and hippocampal G-protein-coupled receptor 43 expression in offspring (Wu *et al*, 2024). Butyrate, which plays a crucial role in epigenetic regulation and mitochondrial biogenesis, is affected by the upregulation of histone deacetylase 4 (HDAC4) in hippocampal astrocytes following MDRF during gestation. These changes suggest transgenerational epigenetic effects on brain function (33).

Chao *et al* (34) found that maternal diet containing 13-40% fructose negatively impacted offspring's learning and memory abilities compared with a control group. Their study identified 369 differentially expressed transcripts (DETs) in the offspring of mothers consuming a 13% fructose diet and 501 DETs in those exposed to a 40% fructose diet. The effect of a MDRF on transcriptome expression in the brain, heart, kidney and urinary bladder of male offspring of Sprague-Dawley rats have been reported using next-generation sequencing technology (34). Chao *et al* (34) identified ErbB receptor feedback inhibitor 1 and connective tissue growth factor as the only two differentially expressed genes (DEGs) in the analyzed organs. According to the researchers, these genes may contribute to metabolic dysfunction in adulthood, supporting the hypothesis of prenatal metabolic programming. These results highlight the importance of future epigenetic research to determine whether these changes are mediated by DNA methylation or histone modifications, further reinforcing the hypothesis that maternal diet has long-term transgenerational effects.

These findings suggest that maternal fructose intake during gestation and lactation can impair learning and memory in offspring and alter brain function at the transcriptome level (35). Zou *et al* (35,30) investigated DETs and DEGs by constructing cDNA libraries from RNA extracted from the hippocampus of MDRF-exposed rats. The extracted RNA was sequenced, and the transcriptome analysis was conducted using Counts Per Million to identify differences in DETs and DEGs among groups. Their results revealed significant transcriptomic differences between rats fed a fructose-rich diet and those on chow and water-based diets. Some of the DET-associated functions included terms related to 'neuron migration' and 'brain development' (35). Similarly, Mukai *et al* (36) demonstrated that fructose consumption during pregnancy may exert sex-specific effects on offspring. Their research indicated that excessive fructose intake during pregnancy modulated hepatic and hypothalamic AMPK, signalling pathways affecting carbohydrate metabolism in female offspring postnatally but not in male offspring.

Koo *et al* (1) found that high maternal fructose intake during pregnancy and lactation is associated with reduced fructokinase mRNA levels, hepatic lipid accumulation and increased expression of lipogenesis. However, these effects could involve interactions between RNA expression and sex hormones. Immunoblotting analysis demonstrated reduced expression and subsequent phosphorylation of proteins that act as energy sensors in female offspring exposed to fructose. The same study found differences in basal gene expression between female and male offspring after a maternal fructose diet, with a higher expression of pro-oxidant genes in female offspring than male offspring exposed to fructose. On the other hand, males exposed to fructose showed a higher expression level of genes responsible for synthesizing sodium transporter proteins

than female offspring whose dams had a fructose-rich diet, suggesting an interaction with sex hormones (1).

Maternal diets rich in fructose can impact multiple biological processes and functions through fetal programming, influencing brain development and altering the transcriptional expression of several genes involved in fructose metabolism, glycolysis/gluconeogenesis (10). These changes are associated with insulin resistance, impaired glucose tolerance, disruptions in fatty acid metabolism and altered insulin signalling. Notably, some of the physiological changes favor pathways related to 'glutamatergic synapses' and 'long-term depression' (31,32,35-37). Additionally, DNA methylation in the promoter region of the brain-derived neurotrophic factor (BDNF) gene, along with fructose intake, has been linked to persistent cognitive deficits in areas such as memory and learning. Furthermore, fructose consumption affects the expression of specific BDNF exons in the hippocampus of offspring, which may contribute to cognitive impairments (2).

Other studies did not compare the effects on male and female counterparts but provided different insights. Zou *et al* (32,30) examined RNA sequences and, using the Kyoto Encyclopedia of Genes and Genomes and Gene Ontology databases, concluded that maternal high fructose intake might alter gene expression related to fetal brain development, affecting neuronal signalling and synaptic plasticity. Meanwhile, other studies focused on different exposure periods. Mizuno *et al* (38) evaluated the impact of fructose consumption during gestation or lactation on the transcriptional regulation of neuro-steroidogenic enzymes, which are crucial for neuronal protection and synapse formation. They found that the expression of the peripheral benzodiazepine receptor was downregulated even when rats consumed fructose only during lactation. By contrast, fructose intake during gestation increased the expression of cytochrome P450 (11β)-2. They concluded that maternal fructose intake during gestation or lactation differentially affects the offspring's expression of hippocampal neuro-steroidogenic enzymes (38).

Previous findings indicate that epigenetic modifications can occur indirectly; maternal fructose consumption during gestation and lactation reduces butyrate synthesis, a fatty acid that promotes epigenetic remodeling by inhibiting proteins crucial for mitochondrial biogenesis in the hippocampus. Wu *et al* (39) investigated this phenomenon using chromatin immunoprecipitation assays, reverse transcription-quantitative PCR, western blotting, immunofluorescence and ELISA, first to evaluate the presence and expression of HDAC4 and BDNF, then to evaluate the binding of HDAC4 to BDNF promoters in the hippocampus. Their results showed that a maternal high-fructose diet alters hippocampal epigenetics in offspring by increasing nuclear accumulation of HDAC4, which represses BDNF transcription, a key molecule for learning and memory. These findings suggest transgenerational modulation due to chronic fructose consumption (2,33,39).

Interestingly, environmental stimulation has been reported to improve cognitive function in rats that developed cognitive impairment due to chronic fructose consumption during gestation. Wu *et al* (39) describe how providing toys and nesting material to these rats - and replacing them weekly-helped restore their cognitive function.

Several studies have shown that a high-fructose diet during gestation can lead to molecular changes, including altered gene expression and epigenetic modifications, which may impair synaptic plasticity, hippocampal neurogenesis and spatial memory (35,16). These findings underscore the importance of understanding how maternal fructose consumption can influence brain and metabolic development in offspring, with effects potentially varying by sex and impacting processes including carbohydrate metabolism, neuro-steroid regulation and enzymatic signalling pathways. Moreover, research suggests that environmental stimulation might help mitigate some cognitive deficits caused by maternal fructose exposure. Overall, the evidence highlights the need for further investigation into the complex relationships between maternal diet, fetal programming and offspring's long-term health and brain function, providing insights that could guide strategies to improve prenatal nutrition and support healthy brain development (Fig. 2C and Table I).

Brain characterization and cognitive function. Maternal nutrition during fetal and early postnatal development is critical in determining the risk of diseases that manifest later in the offspring's life. Increasing evidence suggests that reduced cognitive performance in offspring may be linked to maternal dietary intake and, *in utero*, environmental factors (12). These diseases are considered to develop through epigenetic mechanisms, a process referred to as developmental programming (33,38,40).

According to some studies, MDRF during gestation and lactation affects offspring learning and memory (35,38). Offspring of mothers exposed to fructose showed delays in finding the platform in the aquatic Morris maze, possibly due to oxidative stress in the hippocampus that triggers cognitive dysfunction. In addition, housing with toys and nesting material was observed to improve learning and memory in fructose-exposed hatchlings, highlighting the positive influence of environmental stimulation on neurogenesis. Other studies also revealed that latency time increased in the offspring of mothers with higher fructose consumption, resulting in longer training times and navigational disorientation, suggesting that MDRF may impact offspring cognitive development (35,38). Although studies in humans are limited, some evidence suggests an association between fructose and memory impairment. To assess cognitive status in a population with habitual sugar intake, Ye *et al* (41) conducted a study among middle-aged and older Puerto Ricans without diabetes, utilizing the Mini-Mental State Examination (MMSE). This tool assesses orientation, attention, memory, language and visuospatial skills. Their analysis revealed that sucrose and fructose were the sugars most consumed by this population. Notably, higher fructose intake was significantly associated with cognitive impairment, as indicated by lower MMSE scores (41).

It has been observed that gestational diabetes in rodents can lead to excessive activation of microglia in brain regions associated with memory and learning, resulting in anxious behaviors and increased sensitivity to stress in adulthood. Bukhari *et al* (22) proposed an experimental model that combines immune alterations and gestational diabetes using a 60% maternal diet-induced rat model of diabetes (MDRF)

along with neonatal inflammation induced by LPS. This combination led to an abnormal glucocorticoid response, which has been linked to neuropsychiatric disorders such as anxiety, depression and schizophrenia. Furthermore, neonatal LPS exposure treatment combined with an MDRF diet resulted in elevated IL-1β levels, indicating prolonged inflammation in postnatal rats. Anxious behaviors persisted into the juvenile stage, regardless of sex, highlighting the detrimental impact of gestational diabetes on behavior and suggesting long-term effects on quality of life. Additionally, studies (12,40,41) have reported that populations with high soft drink consumption exhibit poorer cognitive performance across multiple domains, including global cognition composite score, working memory, scanning and tracking abilities, executive function and MMSE scores. Given that fructose constitutes 55-60% of the total sugar content in popular soft drinks, evidence strongly suggests that fructose is a critical factor in triggering cognitive impairment (40).

Fetal programming, which influences behaviour, may exacerbate genetic predispositions to autism (42). High fructose intake during pregnancy has been shown to alter brain regions associated with autism spectrum disorder (ASD). Research indicates that dysregulated nutrition, including high fructose consumption during gestation and lactation, is linked to neurobehavioral disorders such as ASD, anxiety, learning deficits and even changes in eating behaviors (31,32,28,43). These findings underscore the importance of considering nutritional dysregulation and other factors in understanding the potential impact of fructose consumption on the development of neuropsychiatric diseases (31,32,28,43).

Over the past 4 decades, the prevalence of ASD has risen significantly. This has been associated with excessive dietary energy intake, particularly from fructose, accompanied by a rise in metabolic syndrome, which includes obesity, insulin resistance and hyperlipidemia. Research indicates that children born to mothers who are obese and/or diabetic face a heightened risk of developing ASD. Sedentary lifestyles and the consumption of large amounts of high-fructose corn syrup are considered to contribute to numerous cases of obesity and diabetes. Emerging evidence supporting a cause-and-effect relationship between metabolic syndrome and ASD underscores the need to improve education of parents on the effects of obesity on the mental health of their children. Medical communities, relevant government agencies, and private foundations have a responsibility to disseminate the implications of research on metabolic syndrome and ASD to the public (44).

Kisioglu and Nergiz-Unal (28) found that added sugars, such as fructose, contribute to obesity by altering appetite-related peptides that regulate the hypothalamic feeding system, specifically ghrelin and leptin. When these peptides become dysregulated, it can lead to dysfunctional hypothalamic signalling, resulting in increased hunger, excessive food intake and enhanced lipogenesis. Their research showed that fructose stimulates appetite by lowering circulating levels of leptin and reducing the suppression of ghrelin, which influences eating behavior and contributes to obesity (28).

The reviewed studies consistently demonstrate that exposure to MDRF during gestation and lactation significantly changes offspring's brain development and cognitive function. Therefore, it is essential to investigate the underlying mechanisms further to develop preventive and therapeutic strategies that can mitigate the adverse effects of fructose exposure during early life (Fig. 2D and Table I).

4. Conclusions

The findings from these studies suggest that chronic maternal fructose consumption during gestation and lactation may negatively impact offspring health by affecting mechanisms related to the regulation of food intake, motivation, learning, memory, and reproductive health. In experimental models, these adverse effects are associated with neuroinflammation, metabolic dysfunction, oxidative stress and transcriptional and epigenetic changes impairing cognitive and physical health (Table I). Additionally, these studies highlight the significant influence of maternal nutrition on offspring, emphasizing the potential transgenerational effects of fructose, which is consistent with Barker's hypothesis. They also underscore the complexity of factors involved in organogenesis and postnatal growth. Several studies demonstrate that identical external conditions can result in vastly different outcomes depending on factors such as sex or genetic predisposition, indicating that each case must be considered individually, even though malnutrition remains a primary factor.

While the present literature review provides valuable insights into the effects of maternal fructose consumption, some limitations must be acknowledged. Over 80% of the studies analyzed have been conducted in murine models rather than other animal models. This is primarily due to ethical considerations, greater experimental control, shorter reproductive cycles, and easier access to fetal and postnatal tissues, rendering murine models more suitable for research. However, despite their usefulness, murine models do not fully replicate human pregnancy. Differences in placental function, metabolism and lifespan may limit the direct applicability of findings to humans. Existing evidence suggests that excessive fructose intake during pregnancy may negatively impact fetal development and offspring health. Therefore, further human studies are necessary to confirm or challenge the mechanisms proposed in experimental animal models.

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Authors' contributions

ALUA, CDMU, JDGC and JAGV wrote the manuscript. JDGC edited the manuscript. JAGV conceived the idea of the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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