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Repercussions of maternal exposure to high-fat diet on offspring feeding behavior and body composition: a systematic review

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Review

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Abstract

Maternal nutrition is an environmental determinant for offspring growth and development, especially in critical periods. Nutritional imbalances during these phases can promote dysregulations in food intake and feeding preference in offspring, affecting body composition. The aim of this review is to summarize and discuss the effects of maternal high-fat diet (HFD) on offspring feeding behavior and body composition. A search was performed in the PUBMED, SCOPUS, Web of Science, and LILACS databases. Inclusion criteria were studies in rodents whose mothers were submitted to HFD that assessed outcomes of food or caloric intake on offspring and food preference associated or not with body weight or body composition analysis. At the end of the search, 17 articles with the proposed characteristics were included. In these studies, 15 articles manipulated diet during pregnancy and lactation, 1 during pregnancy only, and 1 during lactation only. Maternal exposure to a HFD leads to increased food intake, increased preference for HFDs, and earlier food independence in offspring. The offspring from HFD mothers present low birthweight but become heavier into adulthood. In addition, these animals also exhibited greater fat deposition on white adipose tissue pads. In conclusion, maternal exposure to HFD may compromise parameters in feeding behavior and body composition of offspring, impairing the health from conception until adulthood.

Introduction

Feeding behavior can be defined as the psychobiological aspects related to food choices, frequency and duration of meals, as well as in other aspects the complex interaction between homeostatic and hedonic mechanisms in relation to the environment[1,2]. Food intake represents a component of homeostatic feeding behavior and represents the amount of food ingested by an individual[3]. The regulation of food intake occurs centrally in the hypothalamus, a structure composed of nuclei formed by subpopulations of orexigenic and anorectic neurons that control the energy balance[3]. These neurons express molecules, such as pro-opiomelanocortin and agouti-related peptide (AgRP), which modulate caloric intake and energy expenditure[1]. Thus, hypothalamic cells act as nutritional sensors in response to energy status in body, playing an important role in obesity pathophysiology[4].

Obesity in humans is characterized by body mass index ≥ 30 kg/m^2, associated with an excessive accumulation of fat in abdominal region[5,6]. Studies reveal that obesity has tripled since 1975, reaching more than 650 million adults and 45 million children worldwide in 2016, becoming a pandemic[7]. The increase in prevalence of obesity is also due to increased availability and consumption of processed foods rich in saturated fat, refined sugars, and sodium, considered palatable foods[8-10]. This dietary profile has favored the early onset of type 2 diabetes mellitus, hypertension, and obesity, which represent potential programmers of deleterious effects on offspring health[11,12]. Thus, experimental studies with maternal hyperlipidic experimental diets try to understand the mechanisms involved in these outcomes[13,14].

In this current health context, during some critical developmental stages, such as pregnancy and lactation, offspring may have a greater predisposition to obesity and its comorbidities[15]. The perinatal period is a critical phase marked by the formation of organs and systems through gene expression, cellular hyperplasia, and hypertrophy[16]. In this stage of development, the mother–child binomial is most vulnerable to external modulations, such as maternal feeding[13]. Exposure to a high-fat diet (HFD) represents a model of maternal obesity induction and causes morphological, behavioral, and cellular changes in offspring[17,18]. This excessive maternal nutrient intake disrupts eating behavior, especially dietary intake and preference, affecting the offspring's

weight and body composition[13,19,20]. Thus, this systematic review evaluated the repercussions of maternal perinatal exposure to HFDs on offspring feeding behavior and body composition.

Material and methods

For the elaboration of this systematic review, the authors followed the recommendations present in the checklist of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA Statement). Our systematic review was carried out by publication of protocol in the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) platform, with free access to interested parties.

Search strategy

The search and selection of articles was conducted by two independent reviewers (Chaves, W. F. and Silva, J. M.) and performed in the LILACS, Web of Science, SCOPUS, and PUMBED databases in February 2019. In searching the databases, the following MESH (Medical Subject Headings) terms were applied: "high-fat diet," "maternal exposure," "pregnancy," "lactation," and "feeding behavior". Duplicates were removed from the articles retrieved through the searches. Initially, titles and summaries were screened, following by assessment of full texts for eligibility against our pre-specified inclusion/exclusion criteria. Any disagreements between the researchers were resolved by consulting a third independent reviewer (Pinheiro, I. L.).

Eligibility criteria

The population of interest was limited to pups from mothers exposed to a HFD during gestation and/or lactation, rodents of any species, sex, and age. Our first outcome included all types of feeding behavior evaluation. Subsequently, articles were searched for information on body weight or body composition assessment. There were no year nor language limitations for the inclusion of studies. Articles that did not present the criteria of population eligibility, intervention, comparison, and outcomes were excluded (Table 1).

Table 1. Eligibility criteria applied in this study

	Inclusion criteria	Exclusion criteria
Population	Offspring of rodents with any age	Genetically modified animals
intervention	Maternal exposure (gestation and/or lactation) to diets with high-lipid content in the composition (high-fat diet)	Studies where maternal diet energy content was modified by reducing offer; studies where macronutrient or energy manipulation was performed using beverage drinks (e.g., water with glucose); studies where the only diet manipulation occurred in micronutrients content
Comparison	Maternal exposure to diet with normal-lipid and other macronutrients content in the composition	No one
Outcomes	Primary outcomes: food intake, nutrients/energy intake, food search, behavioral satiety sequence (BSS), and food preference Secondary outcomes: body weight, body mass index (BMI), Lee's index (LI), body composition, body fat weight	No one
Publication parameters	There was no restriction of articles date and languages	No one

Data extraction

The data extraction was performed after the complete reading of articles previously selected according to the eligibility criteria by two independent researchers. The third researcher was consulted when there were differences or doubts. The key data were collected, such as names of authors, year of publication, species of animal, composition of diets, intervention period, post-weaning diet, parameters analyzed, and main offspring results. The data were transcribed into a table according to outcomes, these being feeding behavior or somatic/body composition.

Assessment of methodology quality

The evaluation of methodological quality of studies included in this systematic review was performed using the tool known as SYRCLE risk of bias (RoB)[21]. The tool was applied individually to the articles included and independently by the reviewers. The SYRCLE RoB consists of 10 questions related to random sequence generation, baseline characteristics, allocation concealment, random housing, blinding of participants and personnel, random outcome data, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. These questions were judged as having high, uncertain, or low RoB. The Kappa test was applied after this phase to measure the level of agreement in the assessment of RoB between the first and second reviewers. The information from this step was synthesized through a figure obtained with Review Manager software version 5.3, also used in the elaboration of study flowchart (Fig. 1).

Results

During the first stage in searching the electronic databases (Web of Science, PUBMED, Lilacs, and SCOPUS) a total of 3356 articles were found. Subsequently, 1316 duplicates were removed. A total of 2040 articles had titles and abstracts screened from which 1934 articles were eliminated because they did not address the eligibility criteria (Table 1) in the title and abstract. Full text was read in 106 articles, with then being excluded 89 articles through the exclusion criteria (Table 1). All articles found were published in English. The steps of conducting the research are described in the flowchart below (Fig. 1).

Assessment of quality of studies

The evaluation of RoB applied between the reviewers resulted in Kappa = 0.65, classified as substantial level of agreement[22] (Fig. 2). In the studies, seven authors reported randomizing the animals[23-29]. In relation to the baseline characteristics, eight articles did not report the baseline characteristics of their subjects in the

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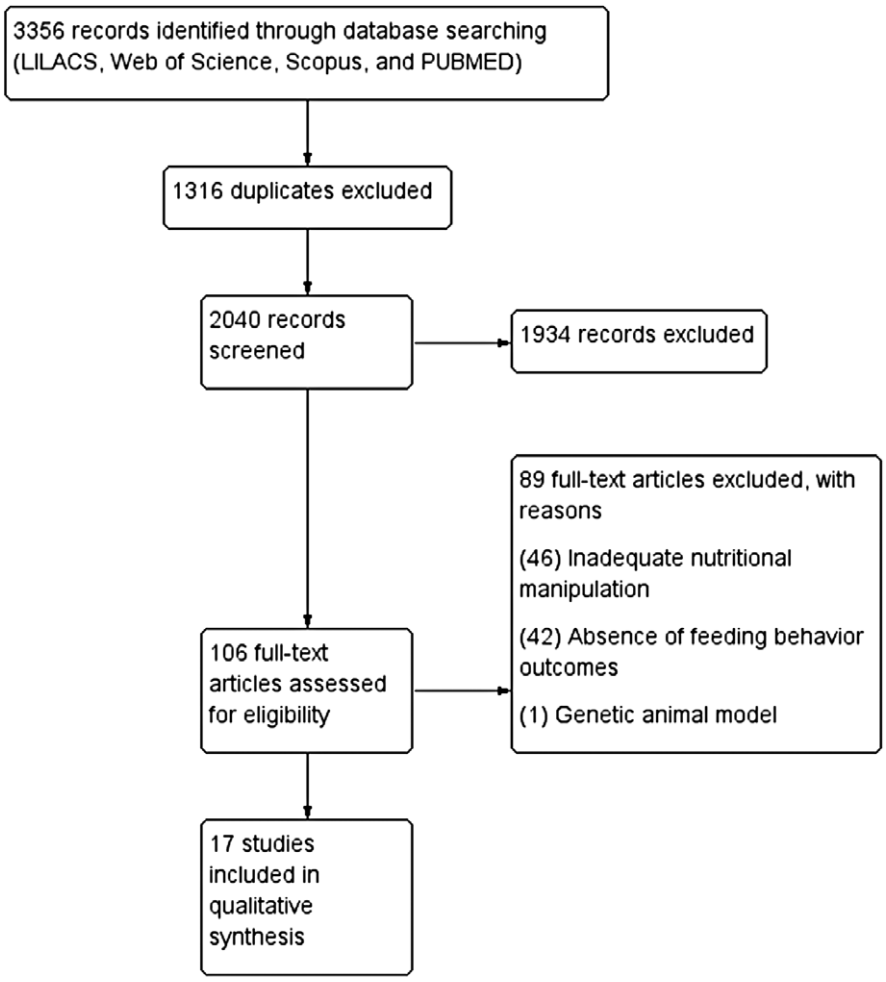

Fig. 1. Flowchart of study selection process applied in the present study.

text[28,30-36]. None of the articles recorded the procedure for blinding the allocation of animals to groups. The researchers responsible for data collection were not reported in any of included articles. No article was clear about randomization in accommodation or selection of animals for collection of results. The article by Kojima, Catavaro, and Rinaman presented the criteria for exclusion of animals from experimental groups in the evaluation of the results[37]. Five articles presented a selection of results[26,29,35,36,38]. Finally, other types of risks of bias were identified in four articles for lack of important information such as mating procedure, adaptation to diets, characteristics, and environment of vivarium[25,27,37,39].

Methodological profile of studies

The studies included used the following types of rodents: Sprague-Dawley (n = 7)[27-29,32,37-39], Wistar (n = 2)[23,24], Long Evans (n = 1)[30], C57BL/6 (n = 4)[31,33,35,36], Swiss (n = 2)[25,26], and FVB albino mice (n = 1)[34]. Ten articles evaluated the male offspring (n = 10). Several studies used only females pups (n = 3) or both sexes (n = 4). The nutritional manipulation was performed through diets with a caloric contribution of lipids ranging from 10% to 19% for control diet versus 30% to 76% for HFDs. This manipulation was more frequent during gestation and lactation (n = 15)[23-26,28-32,34-39], but there were also interventions only at gestation (n = 1)[27] or lactation (n = 1)[33]. Only comparisons of offspring of groups fed on a control diet after weaning, except the articles that evaluated food search, were selected. All articles included (n = 17) presented some proposed feeding behavior-related outcomes, but two articles did not show defined body composition outcomes (n = 15)[24-31,33-39]. Food intake (n = 10)[23-28,33-35,39], caloric intake (n = 6)[24,29,30,32,33,36], food preference (n = 4)[23,31,32,38], and independent feeding (n = 1)[37] were used to evaluate outcomes related to components of feeding behavior. Other outcomes were obtained by measuring body weight (n = 15)[24-31,33-39], body composition (n = 12)[24-29,31,33-35,38,39], and body length (n = 1)[27].

Main results on offspring feeding behavior

The results of outcomes related to feeding behavior were described according to the analyzed parameters (Table 2). Food intake was the most frequently mentioned outcome, but presented high variability in results among the articles selected. Melo *et al.* and Lemes *et al.* showed an increase in food intake in young males from HFD mothers[25,26]. Rahman *et al.* also found an increase in food intake in young males, but from mothers exposed to HFD only during pregnancy[27]. Cardenas-Perez *et al.*, on the other hand, did not observe difference of food intake in young females from HFD mothers[24]. Long-term evaluation showed hyperphagia in both male and female offspring whose mothers had been exposed to HFD in the perinatal period according to Sun *et al.* (the males) and Reynolds *et al.* (the females)[28,39]. On the other hand, Volpato *et al.*, Turdi *et al.*, Tsuduki *et al.*, and Camacho *et al.* did not find any difference in long-term food intake for either male or female offspring from HFD mothers[23,33-35]. Caloric intake made no difference between groups

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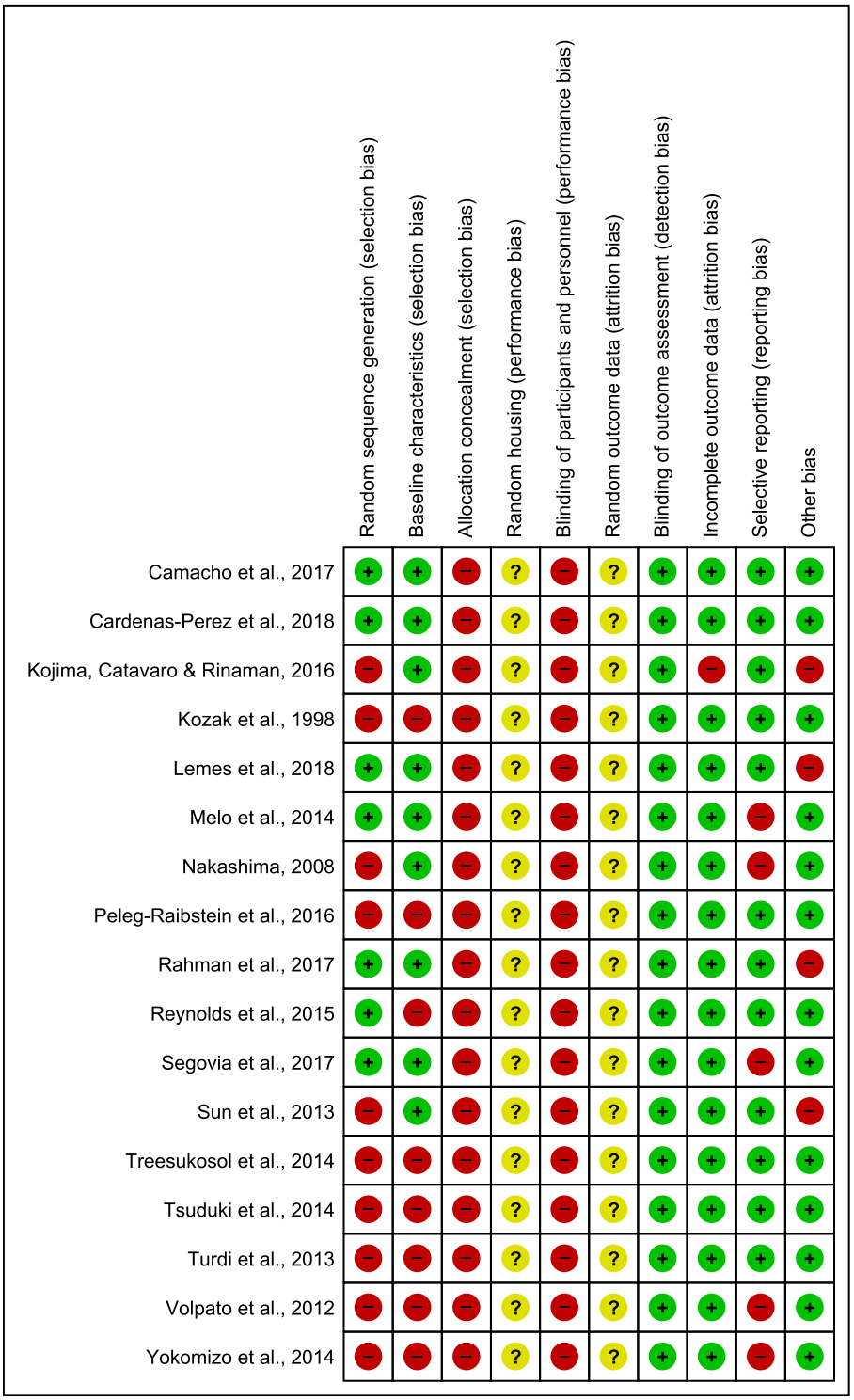

Fig. 2. Risk of bias (RoB) summary of studies: review authors' judgments about each RoB item for each included article. + (green) low RoB, – (red) high RoB, and ? (yellow) unclear RoB. (For interpretation of references to color in this figure, the reader is referred to the web version of this article.)

according to Yokomizo *et al.*, Tsuduki *et al.*, Segovia *et al.*, and Cardenas-Perez *et al.*[24,29,33,36]. In contrast, Kozak *et al.* showed a reduction in caloric intake in young females from HFD mothers[30].

Higher preference for palatable foods such as sweetened drinks, alcohol, and HFDs was observed when food preference for offspring from HFD mothers was evaluated. These results were evidenced over the long term in both male and female offspring, according to Nakashima, Treesukosol *et al.*, Peleg-Raibstein *et al.*, and Camacho *et al.*[23,31,32,38]. The independent feeding test has as its main objective to identify the beginning of a search for solid foods during lactation in the food transition phase. Kojima, Catavero, and Rinaman found that offspring from HFD mothers started earlier to search and eat their mothers solid food than offspring from the control mothers[37].

Main results in the offspring body composition

Offspring somatic growth is a complementary result that helps understanding the repercussions caused by changes in feeding behavior (Table 3). Body weight is the secondary outcome most

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Table 2. Summary of main results in feeding behavior

Author (year)	Strain	Diet composition	Intervention period	Diet post-weaning	Parameters analyzed in offspring	Main results in Offspring
Kozak *et al.*, 1998	Long-Evans	HFD (76% kcal fat) Control (16% kcal fat)	Gestation/ Lactation	Control	1. Caloric intake	1. ↓ caloric intake at 3 and 5 days after weaning in females from HFD mothers ($p < 0.05$)
Nakashima, 2008	Sprague-Dawley	HFD (42.7% kcal fat) Control (10.7% kcal fat)	Gestation/ Lactation	Control	1. Food preference	1. ↑ preference for the HFD diet (same of mother) in the 2nd week after weaning in females and until to 5th in males from HFD mothers ($p < 0.05$)
Volpato *et al.*, 2012	C57BL/6	HFD (49% kcal fat) Control (19% kcal fat)	Gestation/ Lactation	Control	1. Food intake	1. There was no difference in food intake of males with 18 weeks old from HFD or control mothers
Sun *et al.*, 2013	Sprague-Dawley	HFD (60% kcal fat) Control (13.5% kcal fat)	Gestation/ Lactation	Control	1. Food intake	1. ↑ in food intake at the 7th and 8th weeks after weaning in males from HFD mothers ($p < 0.05$)
Turdi *et al.*, 2013	FVB albino mice	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Food intake	1. There was no difference in food intake at 4 months after weaning in males from HFD mothers
Melo *et al.*, 2014	Swiss mice	HFD (46.2% kcal fat) Control (11.5% kcal fat)	Gestation/ Lactation	Control	1. Food intake	1. ↑ in food intake at 28 days in males from HFD mothers ($p < 0.05$)
Treesukosol *et al.*, 2014	Sprague-Dawley	HFD (60% kcal fat) Control (14% kcal fat)	Gestation/ Lactation	Control	1. Caloric intake 2. Food preference	1. ↑ in caloric intake on the 6th day of evaluation in males with 11th week old from HFD mothers ($p < 0.05$) 2. ↑ in food preference for HFD on the 6th day of evaluation in males with 11th week old from HFD mothers ($p < 0.05$)
Yokomizo *et al.*, 2014	C57BL/6 J	HFD (62% kcal fat) Control (18% kcal fat)	Gestation/ Lactation	Control	1. Caloric intake	1. There was no difference in caloric intake in both sexes at 6, 14, and 20 weeks old
Reynolds *et al.*, 2015	Sprague-Dawley	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Food intake	1. ↑ in food intake from 30th to 150th days old in females from HFD mothers ($p < 0.05$)
Tsuduki *et al.*, 2015	C57BL/6 J	HFD (30% kcal fat) Control (12.5% kcal fat)	Lactation	Control	1. Food intake 2. Caloric intake	1. There was no difference in food intake of weaning until the 11th week of life in males from HFD or control mothers 2. There was no difference in caloric intake of weaning until the 11th week of life in males from HFD or control mothers
Kojima, Catavero, & Rinaman, 2016	Sprague-Dawley	HFD (60% kcal fat) Control (13.5% kcal fat)	Gestation/ Lactation	-	1. Independent feeding	1. ↑ in independent feeding at 17th and 18th days old in offspring of both sexes from HFD mothers ($p < 0.05$)
Peleg-Raibstein *et al.*, 2016	C57BL/6 N	HFD (60% kcal fat) Control (10.7% kcal fat)	Gestation/ Lactation	Control	1. Food preference	1. ↑ in preference for HFD diet, alcohol and sweetened drink at 13th week old offspring in both sexes from HFD mothers ($p < 0.001$–0.0001)
Camacho *et al.*, 2017	Wistar	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Food intake 2. Food preference	1. There was no difference in food intake from 2nd to 32nd week old in females from HFD mothers 2. ↑ in food preference for HFD diet from 2nd to 32nd in females from HFD mothers ($p < 0.05$)
Rahman *et al.*, 2017	Sprague-Dawley	HFD (57.5% kcal fat) Control (10.6% kcal fat)	Gestation	Control	1. Food intake	1. ↑ in food intake from 27th to 29th day old in males from HFD mothers ($p < 0.05$)
Segovia *et al.*, 2017	Sprague-Dawley	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Caloric intake	1. There was no difference in caloric intake from weaning to 150th days old in males from HFD mothers
Cardenas-Perez *et al.*, 2018	Wistar	HFD (45% kcal fat) Control (11% kcal fat)	Gestation/ Lactation	Control	1. Food intake 2. Caloric intake	1. There was no difference in food intake from 24th to 48th days old in males from HFD mothers 2. There was no difference in caloric intake from 24th to 47th days old in males from HFD mothers
Lemes *et al.*, 2018	Swiss mice	HFD (46% kcal fat) Control (11% kcal fat)	Gestation/ Lactation	Control	1. Food intake	1. ↑ in food intake at 28th days old in males from HFD mothers ($p < 0.05$)

Table 3. Summary of main results in body composition

Author (year)	Strain	Diet composition	Intervention period	Diet post-weaning	Parameters analyzed in offspring	Main results in Offspring
Kozak *et al.*, 1998	Long-Evans	HFD (76% kcal fat) Control (16% kcal fat)	Gestation/ Lactation	Control	1. Body weight	1. ↓ in body weight at 3 and 21 days in females from HFD mothers ($p < 0.01$–0.001)
Nakashima, 2008	Sprague-Dawley	HFD (42.7% kcal fat) Control (10.7% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. There was no difference in body weight in both groups and sexes from 20th to 55th days old 2. There was no difference in body composition in both groups and sexes from 20th to 55th days old
Volpato *et al.*, 2012	C57BL/6	HFD (49% kcal fat) Control (19% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. There was no difference in birthweight and weaning, but there was a ↑ from 7th to 12th weeks old in males from HFD mothers ($p < 0.05$) 2. ↑ in epididymal and retroperitoneal adipose tissue weight, associated with ↓ no inguinal adipose tissue weight at 3 months old in males from HFD mothers ($p < 0.05$)
Sun *et al.*, 2013	Sprague-Dawley	HFD (60% kcal fat) Control (13.5% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↑ in body weight from 5th day to 18th week old in males from HFD mothers ($p < 0.05$) 2. ↑ in subcutaneous and retroperitoneal adipose tissue weight at 14th weeks old in males from HFD mothers ($p < 0.05$)
Turdi *et al.*, 2013	FVB albino mice	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↑ in body weight from 1st at 16th weeks old in males from HFD mothers ($p < 0.05$) 2. ↑ in epididymal adipose tissue weight at 4 months old in males from HFD mothers ($p < 0.05$)
Melo *et al.*, 2014	Swiss mice	HFD (46% kcal fat) Control (11% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↓ in birthweight, associated with ↑ from 14th to 28th days old in males from HFD mothers ($p < 0.05$) 2. ↑ in epididymal and retroperitoneal adipose tissue weight at 28th days old in males from HFD mothers ($p < 0.05$)
Yokomizo *et al.*, 2014	C57/BL6J	HFD (62% kcal fat) Control (18% kcal fat)	Gestation/ Lactation	Control	1. Body weight	1. ↑ in birthweight and 4th until 6th weeks old in both sexes from HFD mothers ($p < 0.01$–0.05)
Reynolds *et al.*, 2015	Sprague-Dawley	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↓ in birthweight, associated with ↑ in body weight from 10th to 22nd days old in females from HFD mothers ($p < 0.05$) 2. ↑ in retroperitoneal adipose tissue weight at 24 days old in females from HFD mothers ($p < 0.05$)
Tsuduki *et al.*, 2015	C57BL/6 J	HFD (30% kcal fat) Control (12.5% kcal fat)	Lactation	Control	1. Body weight 2. Body composition	1. ↑ in body weight at 3rd days old in males from HFD mothers ($p < 0.05$) 2. ↑ in mesenteric, epididymal and perirenal adipose tissue weight at 11th weeks old in males from HFD mothers ($p < 0.05$–0.01)
Kojima, Catavero, & Rinaman, 2016	Sprague-Dawley	HFD (60% kcal fat) Control (13.5% kcal fat)	Gestation/ Lactation	-	1. Body weight	1. ↑ in birthweight until 21st days old in both sexes from HFD mothers ($p < 0.05$)
Peleg-Raibstein *et al.*, 2016	C57BL/6 N	HFD (60% kcal fat) Control (10.7% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↑ in body weight from 21st to 120th days old in both sexes from HFD mothers ($p < 0.05$) 2. ↑ in visceral and subcutaneous adipose tissue volume at 120th days old in both sexes from HFD mothers ($p < 0.05$)
Rahman *et al.*, 2017	Sprague-Dawley	HFD (57.5% kcal fat) Control (10.6% kcal fat)	Gestation	Control	1. Body weight 2. Body composition 3. Body length	1. ↑ in body weight at 28th days old from HFD mothers ($p < 0.01$) 2. ↑ in epididymal adipose tissue at 30th days old in males from HFD mothers ($p < 0.01$) 3. ↑ in body length at 29th days old in males from HFD mothers ($p < 0.01$)
Segovia *et al.*, 2017	Sprague-Dawley	HFD (45% kcal fat) Control (10% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↑ in body weight from weaning to 150th days old in males from HFD mothers ($p < 0.05$) 2. ↑ in adipose tissue at 150th days old in males from HFD mothers ($p < 0.05$)
Cardena-Perez *et al.*, 2018	Wistar	HFD (45% kcal fat) Control (11% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↑ in body weight at 6th and 7th weeks old in males from HFD mothers ($p < 0.05$) 2. ↑ in adipose tissue at 60th days old in males from HFD mothers ($p < 0.01$)
Lemes *et al.*, 2018	Swiss mice	HFD (46% kcal fat) Control (11% kcal fat)	Gestation/ Lactation	Control	1. Body weight 2. Body composition	1. ↓ in birthweight, associated with ↑ from 18th to 28th days old in males from HFD mothers ($p < 0.001$) 2. ↑ in epididymal and retroperitoneal adipose tissue weight at 28th days old in males from HFD mothers ($p < 0.001$)

frequently evaluated in included studies. Regarding birthweight, Melo *et al.*, Reynolds *et al.*, and Lemes *et al.* observed that offspring from HFD mothers had low birthweight compared to offspring from the control group[25,26,28]. However, Yokomizo *et al.* and Kojima, Catavero, and Rinaman reported that pups from HFD mothers were heavier at birth[36,37]. Nakashima and Volpato *et al.* did not identify differences in body weight and birthweight in young male rodents from HFD mothers[35,38]. Kozak *et al.* were the only author that reported lean animals from HFD mothers during lactation[30]. All authors who evaluated body weight over a long term reported an increase in this parameter from weaning until adulthood in offspring from HFD mothers[24,27-29,31,34,39].

Body fat weight and fat distribution on the body are representative parameters in evaluation of body composition in laboratory animals. Young animals from HFD mothers presented most deposition of body fat, especially in the retroperitoneal, mesenteric, and epididymal areas, according to five articles[24-28]. In other studies, a similar pattern was found for fat deposition in adult rodents of both sexes[29,33-35,39]. In contrast, Nakashima was the only author that did not observe significant difference in body composition in young offspring from HFD mothers[38]. Rahman *et al.* were the only researcher to measure body length and identified that young offspring from HFD mothers were larger than the control animals[27].

Discussion

The main results of the articles included in this systematic review describe changes in feeding behavior and body composition in offspring, promoted by maternal HFDs during the perinatal period. Regarding the outcomes in feeding behavior, the offspring of HFD mothers were reported to have increased food intake in the young animals[25-28,39] but not maintained in adulthood[23,34,35]. On the other hand, in studies that evaluated caloric intake, there was no difference between groups of different ages[24,29,33,36]. Greater preference for palatable foods (rich in sugars, fat, and sodium) in offspring of mothers exposed to HFD during pregnancy and lactation was observed[23,31,32,38]. Feeding independence occurred earlier in the offspring of HFD mothers[37]. Increased body weight[24-29,31,33,34,36,37,39], length[27], and changes in body composition through increased long-term fat deposition[24-29,31,33-35,39] were also observed in these offspring.

The increase in food intake found in this review reveals possible early changes in the regulation of energy homeostasis on offspring[25-27,40]. Significant orexigenic signaling is observed by increasing the density of neuropeptide Y (NPY)/AgRP-expressing neurons in the arched and paraventricular nuclei of the hypothalamus in offspring of mothers fed a HFD[20,25]. This set of morpho-functional changes that occur in the hypothalamus promotes hyperphagic behavior, also impacting body composition and glycemic control in offspring[20]. In association, offspring present hypothalamic resistance to neural and humoral satiety signals, such as serotonin, leptin, and insulin[25,40].

Systemic inflammation and oxidative stress represent two of the main mechanisms that trigger the maternal programming effect on food intake[13]. The first traces of deleterious effects caused by maternal HFD occur during pregnancy, when there is an increased expression of tumor necrosis factor alpha (TNF-α) in fetal tissues as well as insulin resistance[19,41]. Maternal exposure to HFD affects the expression of inflammatory cytokines and free radicals in immune cells such as microglia[42]. In the placenta, immune cells express Toll-like 4 receptors that increase the concentration of inflammatory mediators such as TNF-α and interleukins 1β, 6, and 17 in response to exposure to the HFD diet[43,44].

Maternal exposure influences the offspring's food choice, such as the preference for palatable foods (rich in sugars, fat, and/or sodium) in adulthood[14,31,32,38,45]. This response, generated by maternal programming, could be related to increased hypothalamic expression of endocannabinoid receptors (CB1 and CB2) in offspring, regardless of gender, accompanied by an increase in palatable food intake during the dietary preference tests[45,46]. Disorders in the dopaminergic signaling pathways are also observed in offspring after maternal exposure to palatable diets[47]. Dopamine and its receptors (D1 and D2) regulate reward system responses. The maternal HFD diet promotes methylation of dopaminergic and cannabinoid system genes by increasing their expression[48].

In addition, some methodological variances among articles may explain some differences among the research results regarding food intake. Maternal HFD protocols containing 30–45% kcal/lipids did not promote changes in food intake[23,24,29,33,34]. In these studies, when the offspring were exposed to additional factors, such as re-exposure to HFD or isolation stress, changes in food intake were observed[24,33,34]. Furthermore, that dietary protocol seems not to have promoted inflammation or changes in mitochondrial genes in the offspring's hypothalamus, factors related to impaired regulation of food intake[24,29]. On the other hand, protocols containing 46–60% kcal/lipids were more effective in the development of hyperphagia in offspring[25-27,31,32,39]. The maternal diet was the main stimulus that induced leptin resistance, increased proliferation of NPY neurons, and their gene expression[25,26]. Diets with kcal/lipid content greater than 60% showed inconclusive effects on the offspring's food intake[30,36]. Additionally, these protocols did not promote changes in the expression and proliferation of NPY neurons in different hypothalamic nucleus, with hyperphagia only related to re-exposure to HFD[30,36].

Low birthweight in offspring of HFD mothers was evidenced in this systematic review[25,26,28]. Adequate intrauterine development is dependent on maternal nutrition, placental functioning, and trophic signs[49]. Given this, intake of HFD diets by the parent may cause a nutritional and inflammatory imbalance that compromises fetal-placental circulation and may restrict offspring growth[50]. This condition predisposes the mother to develop preeclampsia, a complication characterized by hypertension and endothelial dysfunctions in the placental vessels capable of compromising the supply of nutrients to the fetus[51,52]. This makes the offspring susceptible to low birthweight, prematurity, and lower perinatal survival rate[52,53].

Increased white adipose tissue (WAT) deposition in pads represents the most frequent change in body composition caused by fetal programming by maternal HFD. In offspring, fat oxidation attained in the process of cellular respiration in metabolic tissues such as skeletal muscle and brown adipose tissue (BAT) is impaired[18,54]. In consequence, there is a reduction in energy expenditure caused by the reduction in lean mass percentage in association with changes in mitochondrial protein expression[55]. In metabolic tissues, mitochondrial dysfunction occurs by reducing the expression of UCP-1, Pgc1, and Cox7a1, uncoupling proteins that play a key role in the progress of the thermogenesis process[54,56]. Another aggravating factor is the increase of populational density of the NPY and AgRP neurons in the hypothalamus favoring BAT inhibition, contributing to the positive energy balance and WAT surplus energy stock[25,57,58].

In relation to body weight, the HFD (76% kcal/lipids) protocol used by Kozak *et al.* promoted a reduction in the offspring's body

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weight during lactation. This result can be associated with the capacity of maternal HFDs, such as ketogenic diets, to stimulate weight loss by favoring the oxidation of body fat reserves[59]. On the other hand, the absence of difference in body weight observed by Nakashima may be related to measurement at specific ages; preference for HFD observed in animals could influence the increase in body weight over the long term, as observed in other articles[29,31,39]. Birthweight was an inconclusive result in the articles by Kojima, Catavero, and Rinaman and Volpato *et al.* Despite this, insulin resistance, fat deposition in the liver, and increased triglycerides were observed at birth, relevant changes that can lead to later development of obesity and metabolic syndrome[35,37].

Conclusion

Maternal exposure to HFD during pregnancy and/or lactation can modify the feeding behavior in offspring from HFD mothers. In young animals, an increase in food intake was identified, with no change in caloric intake over the short term. Greater preference for palatable foods, however, persisted over the long term in these animals. In addition, despite low birthweight, offspring had increased body weight and deposition of WAT over the long term.

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