









Research Article

Oxidative Stress Profile of Mothers and Their Offspring after Maternal Consumption of High-Fat Diet in Rodents: A Systematic Review and Meta-Analysis

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Maternal exposure to the high-fat diet (HFD) during gestation or lactation can be harmful to both a mother and offspring. The aim of this systematic review was to identify and evaluate the studies with animal models (rodents) that were exposed to the high-fat diet during pregnancy and/or lactation period to investigate oxidative stress and lipid and liver enzyme profile of mothers and their offspring. The electronic search was performed in the PUBMED (Public/Publisher MEDLINE), EMBASE (Ovid), and Web of Science databases. Data from 77 studies were included for qualitative analysis, and of these, 13 studies were included for meta-analysis by using a random effects model. The pooled analysis revealed higher malondialdehyde levels in offspring of high-fat diet groups. Furthermore, the pooled analysis showed increased reactive oxygen species and lower superoxide dismutase and catalase in offspring of mothers exposed to high-fat diet during pregnancy and/or lactation. Despite significant heterogeneity, the systematic review shows oxidative stress in offspring induced by maternal HFD.

1. Introduction

During gestation, the developing fetus is totally dependent on the maternal environment for nutrition [1]. The intra-uterine environment is a crucial determinant in the fetal programming of chronic diseases in adulthood. This concept is called Fetal Origin of Adult Diseases (FOAD) [2]. However, after several studies, this term has been extended to DOHaD (Developmental Origins of Health and Disease) [3] and encompasses from the pregestational state (oocytes), gestation, and postnatal periods involving the entire period

of postnatal development and maturation from childhood to adolescence [4] although it is controversial. There is also other evidence about these periods which the DOHaD includes that spread worldwide through the “First 1000 Days” campaign, which supports the importance of the nutritional status of infants and nursing mothers during the fetal and neonatal periods until two years after birth comprising between 280 days before birth and approximately 730 infantile days after birth [5]. Although there is no single consensus, research-involving DOHaD thematic purposes to raise awareness about nutrition and health have been investigated [4].

According to the World Health Organization (WHO), malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients [6], leading to undernutrition or overnutrition [7]. The population is leaving traditional diets that are rich in fibers and grain for diets that include increased levels of sugars, oil, and animal fats [8]. There are five times more obese than malnourished adult people worldwide [6].

The excess of high-fat diet (HFD) consumption is associated with the establishment of permanent state of inflammation [9] and an increased availability of some nutrients, such as free fatty acids, and the glucose overloads the whole cascade of the electron transport chain and consequently increases the production of reactive oxygen species [9, 10]. The increased oxidative environment can be a vicious cycle between inflammatory processes [11]. These disorders in the organism can contribute to the establishment of metabolic diseases [9, 11]. Furthermore, the excessive ROS causes cumulative oxidative damage to macromolecules, including DNA, proteins, and membrane lipid [12].

Maternal consumption of HFD is an important factor that causes harm to both mothers and their offspring [13, 14]. In the last decades, epidemiological evidence has shown that intrauterine life conditions influence growth, body composition, and the risk of developing chronic diseases [15]. Animal studies also indicate that overnutrition during pregnancy induces phenotypic changes that can enhance susceptibility to diseases in adult offspring [16, 17], such as hyperglycemia [18], obesity [19–21], and metabolic syndrome [22]. The maternal HFD consumption also causes oxidative stress on offspring [23, 24]. However, the mechanisms are largely unknown. Lin et al. [25] suggested that the maternal redox state affects the placenta and consequently the fetal development changing transcription factors and abnormal gene expression of antioxidant defenses of the fetuses. In addition, the adverse effects of oxidized molecules, such as lipids and proteins, at critical windows of the fetal development (prenatal or postnatal) “program” the susceptibility to the metabolic syndrome [23].

Epidemiological studies in humans are limited in their ability to assess the influence of diet during pregnancy to offspring phenotype because it is difficult to distinct the effects of intrauterine and post-natal maternal exposure and genetic factors [24]. Therefore, research involving adequate experimental models is relevant, not only for ethical reasons but also due to uncontrollable variables, such as lifestyle, socioeconomic, nutritional, and genetic factors. Hence, the objective of this systematic review was to identify and evaluate the studies with animal models (rodents) that were exposed to the HFD during pregnancy and/or lactation period to investigate oxidative stress of mothers and their offspring.

2. Methods

2.1. Literature Search. This systematic review was undertaken in accordance with the PRISMA [26] and registered on PROSPERO-International Prospective Register of Systematic Reviews (Protocol number CRD42019120418). The literature search was performed on April 30, 2020, on titles,

abstracts, and keywords in PUBMED (Public/Publisher MEDLINE), EMBASE (Ovid), and Web of Science databases. The following Medical Subject Headings (MeSH) and their synonyms were used in different combinations and variations with the Boolean operators “OR” and “AND” to yield a sensitive and comprehensive, yet relevant collection of possible articles “high-fat diet,” “oxidative stress,” “triglyceride,” “cholesterol,” “low-density lipoprotein,” “high density lipoprotein,” “Alanine transaminase,” “alanine aminotransferase,” and “rodent” (see Supplementary Table S1 for complete search strategy). Our primary outcome was to evaluate oxidative stress levels of mothers and their offspring. The secondary outcomes were to investigate the lipid and liver enzyme profile of mothers and their offspring. Besides the electronic search, other sources were used, such as hand searching and screening of reference lists.

Additional records were included from review articles and author-based searches. The searches were restricted to original studies that were published in the English language in scientific journals submitted to the peer-review process without year restriction. Two reviewers (RQMS and VPG) independently screened the titles, abstracts, and full-text manuscripts. Disagreements were resolved in consensus discussions with a third reviewer (DCD).

2.2. Eligibility Criteria. Original animal studies were included in the data set only if they fulfilled the following criteria:

- (1) Types of participants: these are rats and mice of any age; nonrodents, spontaneously obese; and genetically modified animals; ex vivo and *in vitro* studies involving human subjects were excluded.
 - (2) Types of intervention: studies on dams are subjected to an HFD around gestation (before and/or during the whole or any part of pregnancy) or lactation. HFD was considered chow-based HFD from any fat type (e.g., lard and vegetable oils). The % of fat and time of diet exposure were not limited. Custom-made diet (i.e., cafeteria), high-fiber diet, high-calorie diet, high-glucose diet, low-fat diet in short, and any other diets than non-high-fat diet were excluded.
 - (3) Comparisons: animals that were fed a standard diet were included. The evaluation of articles presenting other forms of manipulation (i.e., surgery, drugs, stress, and exercise) was not considered.
 - (4) Types of outcome measures: the included primary outcomes were oxidative stress of the dams and their offspring.
- (i) Oxidative stress status: malondialdehyde/thiobarbituric acid reactive substances (MDA/TBARS) (lipid oxidation), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities, 8-hydroxy-2'-deoxyguanosine (8-OHdG-DNA oxidation), quantification, and scavenging reactive oxygen species (ROS)

Secondary outcomes included the following:

- (i) Lipid profile: triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) concentrations
- (ii) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities

2.3. Data Extraction. Pairs of reviewers (RQMS and GV) independently extracted data into an excel spreadsheet. The following information was extracted from studies presenting eligibility criteria: publication characteristics (first author, title, publication year, and journal), animal strain, intervention, and control diets (nutrient content, period and time of administration, proportion of Kcal, and age of the start of intervention), specific methods used for assessment of oxidative stress, lipid and liver enzyme profile, and maternal and offspring outcomes [sample size (n), mean, standard deviation (SD), and standard error (SE)]. When data were provided in graphical images, we extracted data using WebPlotDigitizer 4.2 (<https://apps.automeris.io/wpd/>). If relevant data were unclear, we contact authors to provide further information.

2.4. Risk of Bias Assessment. Risk of bias for animal studies was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE's tool), which was evaluated in ten steps: three of selection (random group allocation, group similar at baseline, and blinded group allocation); two of them on performance (random housing and blinded intervention); two of detection (random and blinded outcome assessment); one of attrition bias (reporting of drop-outs); one reporting (selective outcomes); and one to other potential bias [27]. Included studies were assessed independently by two reviewers (RQMS and GV), and any discrepancies were solved by discussion. The items were classified as low, unclear, or high risk of bias (see Supplementary Figure S2). The score of all the articles was defined as the percentage of 0 to 100% and each category [27]. We assessed the risk of bias of studies included in meta-analysis and did not exclude studies based on high risk of bias.

2.5. Statistical Analysis. Statistical analysis and forest plots were conducted using Review Manager [28]. Studies were considered for meta-analysis if interventions were considered to be similar in terms of period and length of exposure, more than two studies were available, all outcome data could be obtained, and assessment of outcomes were considered comparable. We presented separate pooled effects for dams and their offspring. If a study using the same methods for intervention and control groups reported outcome data separately for sex, the respective groups were pooled using the recommendations in the Cochrane Handbook [29]. When the outcome was measured in different age cohorts, we then considered more than one outcome from the same study. In case of when the outcome was assessed in multiple tissues in the same animal (e.g., blood, liver, and mesentery), only one assessment was included in the meta-analysis to avoid dou-

ble counting the sample size. We conducted meta-analysis on the levels of oxidative and antioxidative stress markers for continuous variables, and the effect sizes were pooled and presented as standardized mean difference (SMD) since the outcomes were measured in different units across the included studies. Forest plot was generated by the software to illustrate the individual and pooled effect sizes along with 95% confidence interval (CI) using random effects models due to anticipated heterogeneity. The association of percentage of fat and death age and primary outcomes was assessed a using random effects metaregression model. All metaregression results were generated using R version 1.3.1093 (The R Foundation, Vienna, Austria). Between-study heterogeneity was calculated using I^2 statistics, and we considered any degree of heterogeneity. We defined according to I^2 cut-offs of low for <40%, moderate for 30-60%, substantial for 50-90%, and considerable for >75% [24]. p value less than 0.05 was considered to be statistically significant. Publication bias was not assessed in the included studies because there were an insufficient number of studies for this assessment (i.e., less than 10 studies included in the meta-analysis) [29].

3. Results

3.1. Search Results. Initial electronic searching using three databases yielded a number of 2372 of citations. In addition, 33 articles were added from other sources. The removal of 662 duplicates resulted in 1710 individual articles to be subjected to inclusion and exclusion criteria. Firstly, the inclusion and exclusion criteria were imposed on title and abstract (removal of 1515) and secondly on study design and methods (removal of 119). Finally, 77 citations were selected for review and are shown in Figure 1 [13, 14, 20, 21, 23, 25, 30–100]. Of these studies, 68 evaluated lipid and hepatic enzyme profile and 21 evaluated oxidative stress profile with 12 overlaps (i.e., studies that presented both outcomes).

3.2. Characteristics of Studies That Evaluated Stress Oxidative Profile. The first reports assessing the effects of maternal HFD on oxidative stress of dams and/or offspring were published in 2009 [40]. All studies were published in the last ten years. The characteristics of the selected maternal results are shown in Table 1. Data could be retrieved from 4 studies with six comparisons that provided sufficient data for meta-analysis [14, 25, 44, 47]. Only two rodent species have been used in the included studies: mice (C57Bl/6) [14, 48] and rats (Sprague-Dawley and Wistar) [25, 44]. Fat content in maternal HFD was 40% [30], 45% [14], and 49% [44] calories from fat (control group 10 and 11%), and the main source was the animal-derived fats (lard). The duration of the intervention was 19 (pregnancy only) [25], 42 (pregnancy and lactation) [44], 63 (prematuring period, pregnancy, and lactation) [14], and 113 (prematuring period, pregnancy, and lactation) [47] days. Feeding was reported as *ad libitum* in the included studies. All studies reported the MDA levels as outcome, one investigated the maternal scavenging capacity on reactive oxygen species [25], and other two studies [44, 47] showed antioxidant enzymes as outcome. Different

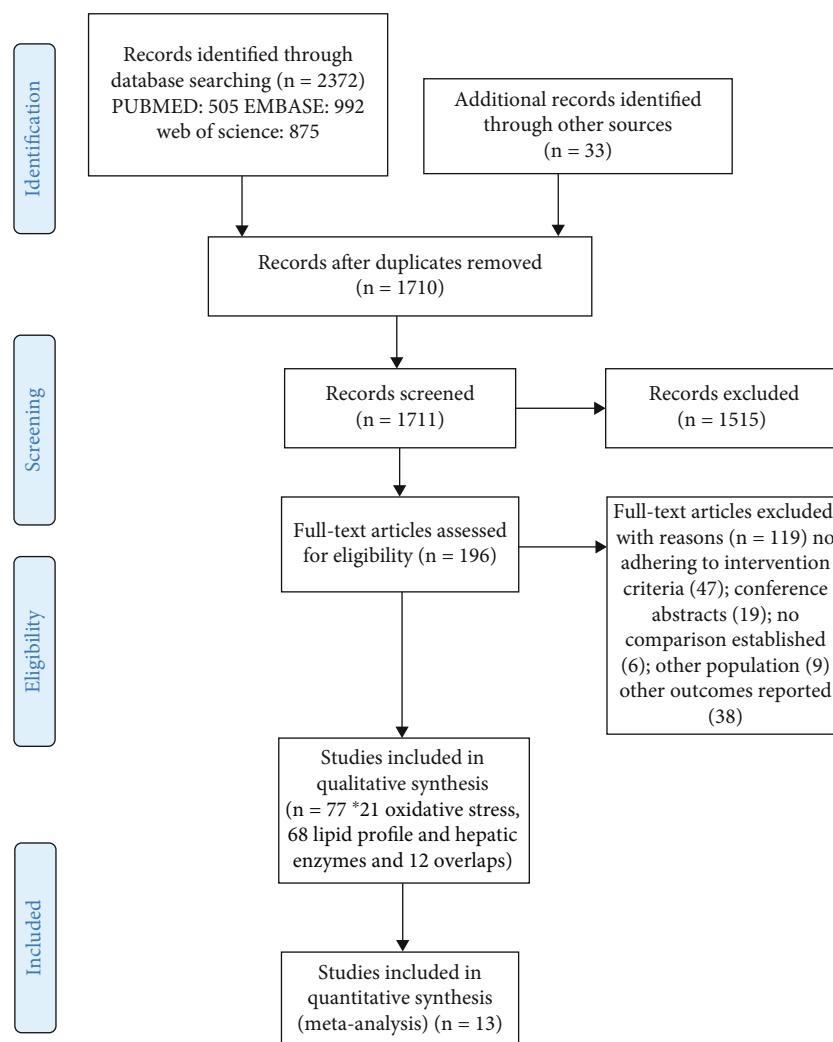


FIGURE 1: Flow diagram of selection of articles based on PRISMA guidelines (<http://www.prisma-statement.org>).

samples were tested in the included studies, all studies used blood samples [14, 25, 47], two used the liver [14, 25], one used the mammary tissue [47], and one used placenta [25].

Table 2 provides an overview of the study characteristics and outcome measures of the offspring effects. We extracted data from 18 studies that described 49 independent comparisons; however, not all necessary data for meta-analysis could be extracted from papers [23, 25, 30–42, 45, 46]. Out of 18 selected studies, ten [23, 25, 33–38, 45, 46] used rats (four Sprague–Dawley and six Wistar) and eight studies [30–32, 34, 39–41, 43] used mice (C57BL/6). Data from eleven studies were obtained from male offspring [30–33, 37–40, 42, 43, 46], and six studies used groups of mixed sex [25, 34–36, 41, 45], whereas only one study represented data obtained from females [23]. The death age of the offspring was between one day after birth [25] and 650 days old [38, 40]. Among the included studies, there were no consistent patterns with respect to characteristics of HFD. Fat content in maternal HFD ranged from 29% [36] to 62% [41] calories from fat and the control group from 10 to 20%. The lard was the main fat component used by animal-derived fats in the twelve studies [23, 25, 30, 33,

36–39, 41, 43, 45, 46]; other two studies [34, 35] used vegetal oils; and four studies did not report the fat component used [31, 32, 40, 43]. The duration of maternal HFD exposure ranges from 19 [25] to 141 days [38, 45], while the offspring HFD exposure ranges from 1 [25, 35, 40] to 650 postnatal day [38, 45].

The largest number of comparisons was reported on offspring's levels of MDA (36/49), SOD activity (25/49), and GPx (24/49) while a limited number of studies reported comparisons of ROS (14/49), CAT activity (12/49), 8-OHdG (4/49), and Thiols groups (2/49). The oxidative stress levels were evaluated in sixteen (33%) liver samples; blood samples were assessed in fifteen assays (31%). Other samples were also used, three (6%) used sperm, three (6%) used tests, four (8%) used mesentery, two (4%) tested islet, two (4%) used femoral artery, two (4%) tested kidney, one used mesentery vessels (2%), and another one (2%) used cardiomyocytes (Table 2).

3.3. Characteristics of Studies That Evaluated Lipid and Hepatic Enzyme Profile. Supplementary Table S2 shows the period of maternal exposure to diet and the assessments of

TABLE 1: Maternal oxidative stress repercussions.

References	Animal	Kcal of fat/ main fat source	Maternal HFD consumption (days)	Outcomes of dams						
				MDA	ROS	SOD	CAT	GPX	Scavenging capacity of reactive oxygen species	Sample evaluated
Lin et al., [25] ^a	Rats (Sprague-Dawley)	40%/lard	19	↑	NM	NM	NM	NM	↓	Blood
Lin et al., [25] ^b	Rats (Sprague-Dawley)	40%/lard	19	↑	NM	NM	NM	NM	↓	Placenta
Gonçalves et al., [44] ^a	Rats Wistar	71%/lard	42	↔	NM	↔	↔	NM	NM	Liver
Gonçalves et al., [44] ^b	Rats Wistar	71%/lard	42	↔	NM	NM	NM	NM	NM	Blood
Kim et al., [14] ^a	Mice (C57BL/6)	45%/lard	63	↑	NM	NM	NM	NM	NM	Blood
Kim et al., [14] ^b	Mice (C57BL/6)	45%/lard	63	↑	NM	NM	NM	NM	NM	Liver
Harphoush et al., [47] ^a	Mice (C57BL/6)		113	↑	NM	↓	↓	↓	NM	Blood
Harphoush et al., [47] ^b	Mice (C57BL/6)		113	↑	NM	↓	↓	↓	NM	Mammary tissue

MDA: malondialdehyde; ROS: reactive oxygen species; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; ROS: scavenging capacity of reactive oxygen species; NM: not measured.

maternal lipid and hepatic biomarkers. The HFD exposure ranges from 19 to 141 days [25, 61]. The biochemical parameters analyzed were TG, TC, HDL, LDL, and ALT. Of the 21 assessments on maternal TG level, 16 (76%) presented increased levels [14, 20, 25, 35, 43, 48, 51, 52–60], four (19%) showed no change [21, 49, 53, 55], and one (5%) showed a decreased level [50]. The maternal TC level was presented in ten evaluations, eight (80%) were increased [14, 20, 21, 40, 56, 60, 61], one (10%) showed no change [55], and another (10%) was decreased [20]. Of the four analyses of maternal HDL, two (50%) presented an increase [56], and the other two (50%) presented no change [14, 25]. Two studies (100%) evaluated maternal LDL assessments and showed higher levels of this biomarker [56]. The only paper with maternal analysis of ALT showed no change [14].

The period of maternal diet exposure, characteristics of offspring (sexes and death age), and biochemical measurements of the offspring are presented in Supplementary Table S3. The HFD exposure ranges from 21 to 154 days [23, 37, 61–64, 74, 88, 89]. In relation to gender, 31 articles verified both genders [21, 35, 36, 41, 50, 54, 57, 58, 60–62, 64–66, 68, 71, 72, 80–82, 84–92, 94, 96, 99]; 23 studies analyzed males [14, 18, 30–33, 37, 40, 42, 48, 51–53, 55, 56, 63, 74, 75, 77, 78, 83, 91, 93, 100], 11 evaluated females [23, 59, 67, 70, 73, 76, 79, 87, 88, 95, 97], and only one did no report on the offspring sex [69]. The ranged age for the offspring was between one day after birth [21, 30, 35, 40, 50, 52, 53, 55, 62, 89] and 360 days old [71]. The observed biochemical parameters were TG, TC, HDL, LDL, ALT, and AST. Of the 141 assessments about TG, 65 (46%) verified higher levels, 71 (50%) showed no change, and five (4%) presented lower levels. Of all 86 evaluations about TC, 21 (24%) showed increased levels, 58 (68%) verified no

change, and seven (8%) observed lower concentrations. There were 33 HDL assessments in the offspring. Of these, three (9%) were increased, 26 (79%) presented no abnormal HDL levels, and four (12%) had decreased concentrations. Furthermore, in 20 analyses of LDL of the offspring, seven (35%) presented higher levels, 12 (60%) of them showed no change, and one (5%) observed lower level. The AST enzymatic activity of the liver of the offspring was increased in one article (12.5%), and in seven (87.5%), no change was observed. Of the 11 studies about ALT measurements, four (36%) presented higher activity, and seven of them (64%) had no change. Given the substantial level of heterogeneity in the studies that assess lipid and hepatic enzyme profile, we did not present a quantitative analysis for this outcome.

3.4. Effects of HFD on Stress Oxidative Status in Dams and Offspring. Four studies were included in the meta-analysis on MDA levels in dams that received HFD compared with controls [14, 25, 44, 47]. The MDA levels of included studies were measured from day 19.5 of pregnancy to the end of lactation. The effect size of MDA was not different in mothers exposed to HFD compared to control, SMD 2.15 (95% CI: -0.21 to 4.52, $p < 0.07$; $I^2 = 89%$) (Figure 2). Two studies were included in the meta-analysis on SOD (SMD: -2.62; 95% CI: -9.15 to 3.90, $p = 0.43$; $I^2 = 94%$) and CAT (SMD: -0.73; 95% CI: -1.56 to 0.09, $p = 0.08$; $I^2 = 92%$) were not different in mothers exposed to HFD compared to control (Supplementary Figure S1).

Data on MDA levels of the offspring were available from five studies [23, 37, 42, 43, 45] between 21 and 650 days of life. Two studies were included two times in meta-analysis as the MDA levels were analyzed in two separate age cohorts (90 and 180 days) [23, 37]. Another study was included

TABLE 2: Continued.

References	Animal	Kcal of fat/main fat source	Maternal HFD consumption (days)	Sex offspring	Death age (days)	Outcomes of offspring					Sample evaluated		
						MDA	8-OHdG	ROS	SOD	CAT		GPX	Thiols
Rodriguez-Gonzalez et al., [38] ^b	Rats (Wistar)	46%/lard	141	M	450	↑	NM	NM	NM	NM	NM	Blood	
Rodriguez-Gonzalez et al., [38] ^c	Rats (Wistar)	46%/lard	141	M	650	↔	NM	NM	NM	NM	NM	Blood	
Rodriguez-Gonzalez et al., [38] ^d	Rats (Wistar)	46%/lard	141	F	110	↔	NM	NM	NM	NM	NM	Blood	
Rodriguez-Gonzalez et al., [38] ^e	Rats (Wistar)	46%/lard	141	F	450	↑	NM	NM	NM	NM	NM	Blood	
Rodriguez-Gonzalez et al., [38] ^f	Rats (Wistar)	46%/lard	141	F	650	↔	NM	NM	NM	NM	NM	Blood	
Rodriguez-Gonzalez et al., [38] ^g	Rats (Wistar)	46%/lard	141	M	110	↑	NM	↔	↔	NM	↑	NM	Liver
Rodriguez-Gonzalez et al., [38] ^h	Rats (Wistar)	46%/lard	141	M	450	↑	NM	↑	↔	NM	↓	NM	Liver
Rodriguez-Gonzalez et al., [38] ⁱ	Rats (Wistar)	46%/lard	141	M	650	↑	NM	↑	↔	NM	↓	NM	Liver
Rodriguez-Gonzalez et al., [38] ^j	Rats (Wistar)	46%/lard	141	F	110	↑	NM	↔	↑	NM	↔	NM	Liver
Rodriguez-Gonzalez et al., [38] ^k	Rats (Wistar)	46%/lard	141	F	450	↑	NM	↑	↔	NM	↔	NM	Liver
Rodriguez-Gonzalez et al., [38] ^l	Rats (Wistar)	46%/lard	141	F	650	↑	NM	↑	↓	NM	↓	NM	Liver
c ^a	Mice (C57BL/6)	45%/unidentified	42	M	21	↑	NM	↑	NM	NM	NM	Liver	
Cao et al., [43] ^b	Mice (C57BL/6)	45%/unidentified	42	M	84	NM	NM	↔	NM	NM	NM	Liver	
Ito et al., [34] ^a	Mice (C57BL/6)	31%/oil vegetable +animal fat	42	M/F	21	↔	NM	NM	NM	NM	NM	Liver	
Ito et al., [34] ^b	Mice (C57BL/6)	31%/oil vegetable +animal fat	42	M/F	77	↔	NM	NM	NM	NM	NM	Liver	
Yokomizo et al., [41] ^a	Mice (C57BL/6)	62.20%/lard	42	M	140	NM	↑	NM	NM	NM	NM	Islet	
Yokomizo et al., [41] ^b	Mice (C57BL/6)	62.20%/lard	42	F	140	NM	↔	NM	NM	NM	NM	Islet	
Torrens et al., [39] ^a	Mice (C57BL/6)	45%/lard	70	M	105	NM	NM	↑	NM	NM	NM	Femoral artery	
Torrens et al., [39] ^b	Mice (C57BL/6)	45%/lard	70	M	210	NM	NM	↑	NM	NM	NM	Femoral artery	
Tozuka et al., [40] ^a	Mice (C57BL/6)	57.50%/unidentified	79	M	1	↔	NM	NM	NM	NM	NM	Blood	
Tozuka et al., [40] ^b	Mice (C57BL/6)	57.50%/unidentified	79	M	10	↑	NM	NM	NM	NM	NM	Blood	
Tozuka et al., [40] ^c	Mice (C57BL/6)	57.50%/unidentified	79	M	21	↑	NM	NM	NM	NM	NM	Blood	
Tozuka et al., [40] ^d	Mice (C57BL/6)	57.50%/unidentified	79	M	70	↔	NM	NM	NM	NM	NM	Blood	

TABLE 2: Continued.

References	Animal	Kcal of fat/main fat source	Maternal HFD consumption (days)	Sex offspring	Death age (days)	MDA	8-OHdG	ROS	SOD	CAT	GPX	Thiols	Sample evaluated
Glastras et al., [32]	Mice (C57BL/6)	43%/unidentified	84	M	224	NM	↑	NM	NM	NM	NM	NM	Kidney
Glastras et al., [31]	Mice (C57BL/6)	43%/unidentified	84	M	224	NM	↑	NM	NM	NM	NM	NM	Kidney
Brighenti et al., [30]	Mice (C57BL/6)	49%/lard	98	M	10	NM	NM	NM	↓	↔	↔	NM	Liver

MDA: malondialdehyde; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; ROS: reactive oxygen species; SOD: superoxide dismutase; CAT: catalase; GPX: glutathione peroxidase; NM: not measured.

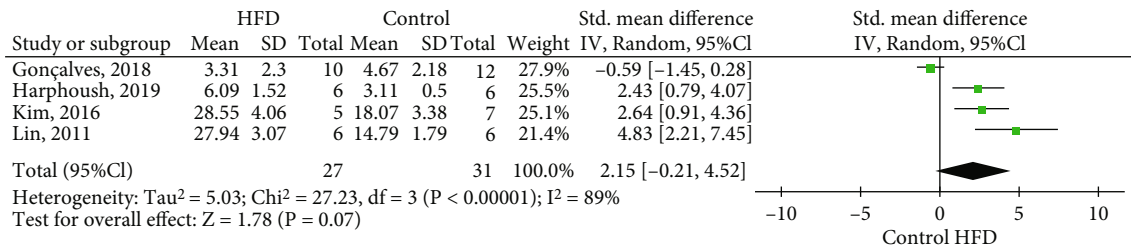
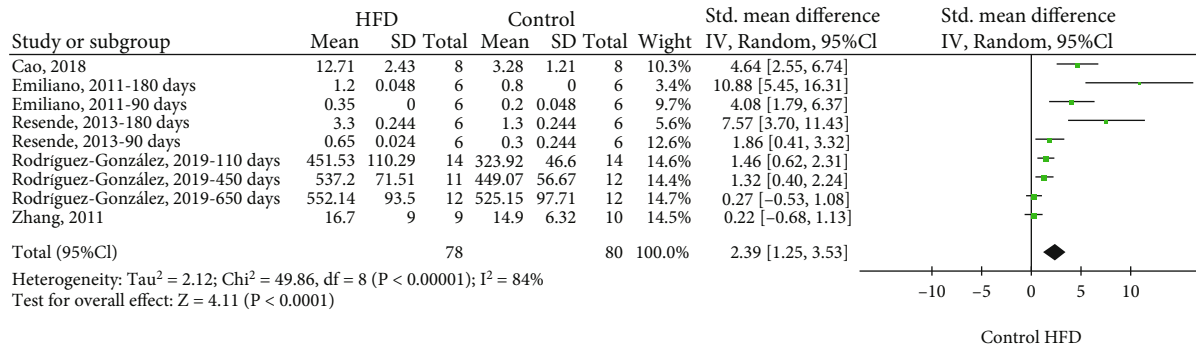
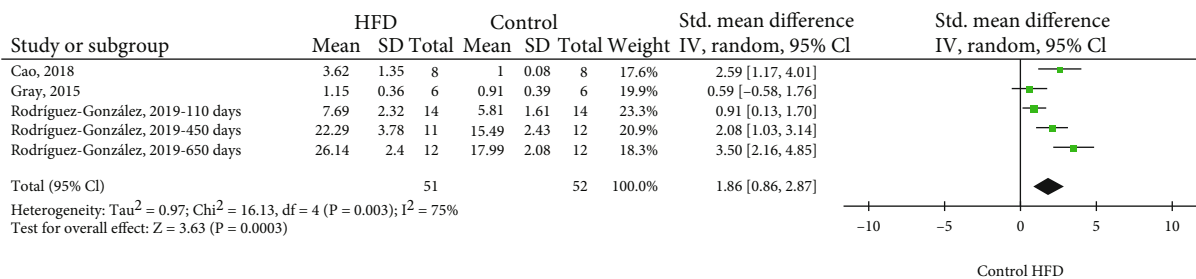


FIGURE 2: Meta-analysis of HFD maternal consumption on MDA levels compared with controls. HFD: high-fat diet; 95% CI: 95% confidence interval; IV: inverse variance.



(a)



(b)

FIGURE 3: Meta-analysis of MDA levels (a), ROS levels (b) of the offspring from mothers exposed to HFD. HFD: high-fat diet; 95% CI: 95% confidence interval; IV: inverse variance.

according to the separate age cohorts (110, 450, and 650) [40]. The MDA levels of the offspring were higher in dams exposed to HFD compared to a standard diet (SMD 2.39) (95% CI: 1.25 to 3.53, $p < 0.0001$; $I^2 = 84%$) (Figure 3(a)).

The evaluation of ROS occurred in three studies [33, 43, 45] between 21 and 650 days of life [33, 43, 45]. One study was included three times due to assessment in different age cohorts (110, 450, and 650 days) [40]. The ROS assessment of the offspring was higher in dams exposed to HFD compared to a standard diet (SMD 1.86) (95% CI: 0.86 to 2.87, $p = 0.0003$; $I^2 = 75%$) (Figure 3(b)).

SOD activity was obtained from seven studies between 1 and 650 days of life [25, 30, 46]. Two studies were included two times in meta-analysis as the MDA levels were analyzed in two separate age cohorts (90 and 180 days) [23, 37]. Furthermore, another study was included according to the separate age cohorts (110, 450, and 650) [45]. SOD activities were decreased in the offspring of dams exposed to HFD compared to standard diet. The effect size was -2.11 (95% CI: -3.23 to -0.99, $p < 0.0002$; $I^2 = 87%$) (Figure 4(a)).

10 comparisons were included the GPX activity analysis from six studies [23, 30, 36, 37, 45, 46] between 10 and 650 days of life. [30, 36, 46]. Two studies were included two times in meta-analysis because GPX activity was detected in different age cohorts (90 and 180 days) [23, 38]. Another study was stratified according to separate age cohorts (110, 450, and 650 days) [41]. GPX activity was not different in the offspring of dams exposed to HFD compared to those of dams given a standard diet. The effect size was -0.69 (95% CI: -1.56 to 0.18, $p = 0.12$; $I^2 = 84%$) (Figure 4(b)).

CAT activity was obtained from five studies between 10 and 180 days of life [23, 30, 36, 37, 46]. Two studies were included two times in meta-analysis since they detected the CAT activity in different age cohorts (90 and 180 days) [23, 37]. CAT activity was lower in the offspring of dams exposed to HFD compared to those of mothers given a standard diet. The effect size was -1.17 (95% CI: -2.32 to -0.02, $p = 0.05$; $I^2 = 82%$) (Figure 4(c)).

Eight studies could not be included in the pooled analysis because of the lack of information of sample size [30–34,

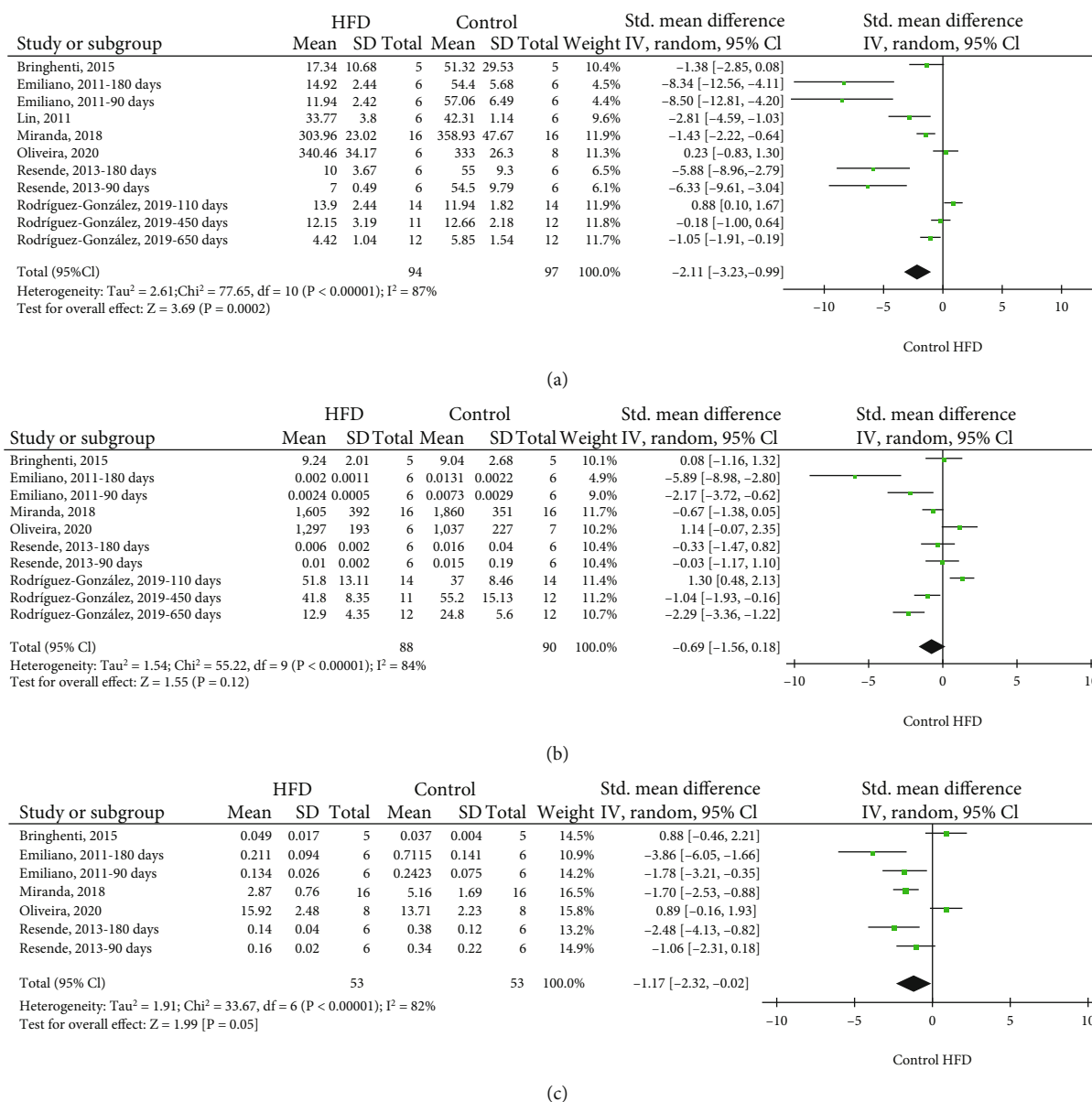


FIGURE 4: Meta-analysis of SOD activity (a), GPx activity (b), and CAT activity (c) of the offspring from mothers exposed to HFD. HFD: high-fat diet; 95% CI: 95% confidence interval; IV: inverse variance.

35, 38–41]. One study could not be pooled as it was the single study that evaluate the 8OHdG levels showed higher levels in male offspring of mothers exposed to HFD during pregnancy and lactation (SMD: 2.83; 95% CI: 1.04 to 4.62, $p = 0.002$); however, the female offspring comparison showed no difference between group (SMD: 0.51; 95% CI -0.65 to 1.66, $p = 0.39$) [41].

3.5. Metaregression. The results of metaregression show that with increasing of age, the GPx ($p = 0.0032$) and CAT ($p < 0.0001$) levels significantly decrease and the ROS levels significantly increase ($p = 0.047$) (Table 3).

3.6. Risk of Bias in Studies. All included studies were assessed on risk of bias. The results can be found in Figure 5 and in Supplementary Figure S2 in the supplemental material in

more detail. Following the results of the SYRCLE Risk of Bias tool, most of the included papers had an overall unclear risk of bias because of poor or even absence of reporting of essential information. Information about random sequence generation was absent in four studies (19% high risk, 81% unclear risk). Although 14 of the included studies reported the baseline characteristics (14 studies—67% were low risk), and seven studies omitted this information (33% were unclear risk). There is no description about concealment of the allocation sequence in the included studies (21 studies—100% were unclear risk). Information about performance bias, such as animals randomly housed, were unclear in 21 studies (21 studies—100% were unclear risk); care and blinded investigation of intervention/exposure of each animal was deficient (21 studies—100% of them were unclear risk). Furthermore, detection bias was considered

TABLE 3: Summary of findings of metaregression analysis across all offspring outcomes.

Outcome	Covariate	Number of comparison	Coefficient	95% CI	SE	<i>z</i>	<i>p</i> value	<i>R</i> ²	<i>I</i> ²
MDA	% fat	12	0.572	-0.0898 1.2337	0.3376	1.6941	0.0902	0	77.20%
	Death age	12	-0.0037	-0.008 0.0006	0.0022	-1.6906	0.0909	0	78.88%
SOD	% fat	15	-0.0637	-0.1945 0.0671	0.0667	-0.9542	0.34	0	84%
	Death age	15	0.002	-0.0024 0.0064	0.0023	0.8852	0.376	0	84.00%
GPx	% fat	14	-0.0392	-0.1502 0.0718	0.0567	-0.6922	0.4888	0	81.32%
	Death age	14	-0.0052	-0.0087 -0.0018	0.0018	-2.9465	0.0032	37.38%	71.40%
CAT	% fat	8	-0.0226	-0.1511 0.106	0.0656	-0.3442	0.7307	0	82.86%
	Death age	8	-0.0207	-0.0288 -0.0126	0.0041	-5.0183	<0.0001	96.93%	10.79%
ROS	% fat	8	0.543	-1.6153 2.7013	1.1012	0.4931	0.622	0	69.65%
	Death age	8	0.0035	0 0.0069	0.0017	1.9866	0.047	32.96%	55.47%

CI: confidence interval; SE: standard error; HFD: high-fat diet.

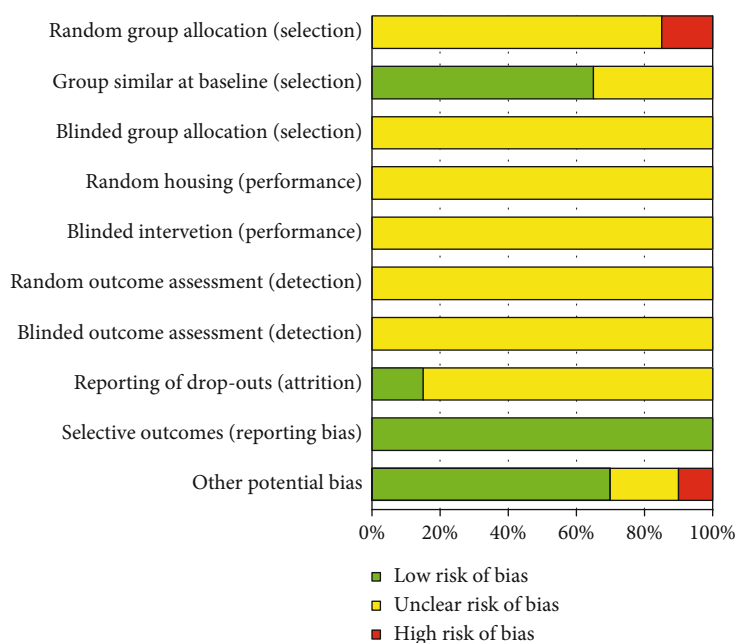


FIGURE 5: Risk of bias score for each risk item in animal studies, as assessed using the SYRCLE tools.

unclear risk due to no information of random selection for outcome assessment and blinding outcome assessor (21 studies—100%). While more than 86% (18 studies were unclear risk) of the not included studies reported unclear attrition bias, only 14% correctly described incomplete outcome data (3 studies were low risk). The reporting bias was classified as low risk (21 studies—100%). A low risk of other bias was scored for fifteen studies (71%), the other four studies were unclear (19%), and two studies showed conflict of interest (10% were high risk).

4. Discussion

4.1. Overview of Findings. This review is aimed at studying and summarizing the literature regarding oxidative stress and lipid and hepatic profile induced by maternal high-fat

diet (HFD) consumption on the dams and their offspring. We found 68 studies that evaluated lipid and hepatic enzymatic profile and 21 studies about the effects of HFD on oxidative stress markers in rats and mice. Our pooled analysis of oxidative stress levels suggests that HFD consumption during pregnancy and/or lactation significantly increases MDA levels in dams and their offspring. Furthermore, there were increased ROS and decrease of SOD, GPx, and CAT activities in the offspring. Another factor that can influence the results is age of descedants; older animals have decreased in antioxidant enzymes activities and increased ROS. These studies included pooled analysis; all offspring were fed a standard diet after weaning, so the changes observed in the levels of stress oxidative markers were independent on offspring's diet. Systematic reviews are commonly used for human studies [101, 102]. However, in reviews using animal

models, predominantly, rodents have been highlighted [103–109]. Rodents (mice and rats) are ideal models to induce metabolic alterations [107] and suitable for exploring the mechanisms related to DOHaD [108]. Considering these and other advantages, rodents were employed in this review.

The HFD exposure is associated with dyslipidemia, which involves higher triglycerides, total cholesterol, and LDL concentrations, as well as a reduction in HDL-cholesterol levels [109, 110]. Furthermore, the excessive energy and hypertriglyceridemia can cause the increased hepatic content of triglycerides in the liver [36, 113]. Then, an overload in the liver results in increased ALT and AST activities [112, 113], which are enzymatic biomarkers of the hepatic damages [36]. After the consumption of HFD, the mothers showed abnormal lipid profile, and most studies reported increased TG and TC concentrations. However, the results in offspring are divergent in relation to these biomarkers. The heterogeneity of the experimental design (such as time of maternal exposure to HFD, amount of fat in the feed, and age of offspring death) was a determining factor for the divergence of the outcomes found in these studies. Therefore, it was not possible for the meta-analysis to be performed. We found that LDL, HDL, ALT, and AST levels were lower in the studies using HFD. Although the consumption of HFD can lead to dyslipidemia and liver damage, it was not evident in most studies. However, it is possible that the association of these biomarkers and the model used are not sufficient to translate the damage caused by maternal consumption of HFD.

To establish a broad search, there was no year limitation of the included studies. In this context, the articles were related to the last ten years and this might be explained because the investigations on developmental plasticity and fetal programming have been started in the last years [3, 114].

4.2. Variability of Diets Used in the Researches. In this review, only articles that used diets with a higher fat content than the control group were evaluated. The major source was lard, which mainly consists of nonessential fatty acids [115]. Some studies have used plant-originated fat, which contains essential fatty acids (polyunsaturated) [116, 117]. According to Tellechea et al. [115], maternal exposure to the diet rich in lard is directly related to metabolic syndrome-related phenotypes in offspring rats. Besides that, essential fatty acids contain fundamental nutrients to fetal and postnatal development and normal cell function [118]. However, an excess may injure and have adverse consequences to offspring [118]. The different sources, concentrations, and periods of exposure to HFD might be responsible for the heterogeneity of results on reproductive and biochemical parameters [107]. Several authors present the energy from fat (% Kcal) and others in centesimal composition. For this review, to standard these comparisons, the fat values were presented in % Kcal. Considering that carbohydrate provides four calories/gram, protein provides four calories/gram and fat provides nine calories/gram; these values were considered in our review [119].

4.3. Oxidative Stress. The redox status, nutritional and environmental factors play an important role in the susceptibility

to oxidative stress and other metabolic alterations [120]. Oxidative stress occurs due to increased production of reactive oxygen species (ROS) and/or failure of the antioxidant system [30]. In our meta-analyses, this imbalance was observed in offspring, in which malondialdehyde (MDA) and ROS were shown to be elevated and the antioxidant enzymes decreased. In the qualitative analysis, MDA, 8-hydroxy-2'-deoxyguanosine (8-OHdG), and ROS were analyzed as the prooxidants or lipid peroxidation products included in this review. MDA is the final product of lipid peroxidation measured by the quantification of thiobarbituric acid reactive substances (TBARS) [121]. 8-OHdG is one of the major products of DNA oxidation [122]. These biomarkers represent a detrimental environment for both mothers and their offspring [123–125]. The association between HFD and higher prooxidant levels can be explained by endothelial dysfunction [35] and increased inflammatory process [31, 42].

The enzymatic antioxidant system composed of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), the three main endogenous antioxidants, is triggered according to the organism requirement to protect itself against the oxidative insult caused by maternal HFD exposure [23]. The lower antioxidant profile observed in this meta-analysis might be due to the enzymatic rapid consumption and depletion [126]. The reduction of antioxidants represents an attempt to stabilize ROS [127].

The balance between prooxidants and antioxidants is the key of organism homeostasis, but there are several factors to be considered with aging and senescence that stress is directly associated with phenomenon of oxidative stress [128]. The exact mechanism of oxidative stress-induced aging is still not clear, but probably increased ROS levels lead to cellular senescence, a physiological mechanism that stops cellular proliferation in response to damages that occur during replication [129]. Furthermore, according to the results of this review, we believe that intrauterine insults may highlight oxidative stress in aging.

It is important to note that several outcomes are evaluated in blood samples for biochemical analysis (plasma or serum) [14, 23, 25, 40, 42]. Blood is an effective material for the evaluation of biochemical profile because it informs the health state at the collection time [130]. The second type of sample most used is the liver [14, 25, 30, 34, 36, 42]. The hepatic tissue undergoes maturation stages during late gestation and early postnatal life. Hence, the liver is highly susceptible to a maternal inadequate nutrition [131]. There were also few determinations in other samples, such as the mesentery [23, 33, 37], kidney [31, 32], placenta [25], islet [41], sperm and testis [38], cardiomyocytes [35], and femoral artery [39]. The nonuniformity of the samples is related to the objectives of each research.

An inadequate feeding during the prenatal period likely increases the risk to chronic diseases, such as diabetes and metabolic changes, during adult offspring life [132, 133]. The overnutrition during pregnancy is a risk factor for the mother and their offspring because insults may generate later life physiological and metabolic changes in the offspring [134], corroborating the DOHaD theory [3].

4.4. Risk of Bias and Gaps in the Literature. The selected articles were evaluated with an appropriate assessment

instrument for bias risk, which was applied to experimental models [27]. A design with low-risk of bias describes the process of randomization, such as bias origin and their influence in the results [135]. It was verified most articles only cited randomization of animals; however, they correctly described no process. The blindness of researchers and data analysis were also an argument for bias, which was neglected in the studies. This fact probably occurs because of the difficulty for blinding during management with animals and diet. Then, the implementation of more appropriate methodologies could reduce the bias, contributing to improving the reliability and interpretation of results [106].

The contribution of our systematic review was the identification of gap in the existing review about maternal HFD consumption and oxidative stress. Other reviews only show how maternal HFD consumption has an effect on blood glucose [104, 106], body weight [47], metabolic syndrome [116], cardiometabolic parameters [136], and growth [137] of the offspring.

4.5. Limitations and Strengths. In this review, there are methodological limitations of the included studies. Firstly, the complete description of diet composition, in both the control and HFD groups, because they are at times ignored by the authors or not clearly reported. However, by neglecting this information, the investigators hinder the interpretations and make the impractical reproducibility of these studies [138]. Secondly, the selected articles present a variability of the standard diet (control group) characteristics, which causes difficulty for comparison among the experimental groups and control groups from different studies, showing that there is no consensus in the researches involving HFD. The American Institute of Nutrition (AIN) published the use of formula to standard chow for experimental rodents, AIN-93G, which shows all the necessary nutrients to be used during the early growth phase and during reproduction [139]. Despite these limitations, this review presents with strengths, such as an extensive view of the literature. We used different databases with a large number of terms and keywords to increase the number of searches. In addition, we also showed the consequences for both mothers and their offspring with exclusion of confounding postnatal diet effects.

5. Conclusion

The current systematic review suggests that maternal HFD causes oxidative stress in offspring influencing the prooxidants and antioxidants in a mother and offspring. Although the writing of a definitive conclusion is difficult given the substantial heterogeneity found in the included studies, we found that maternal exposure to HFD with 40% fat for 19 days during the pregnancy period can negatively impact the oxidative stress levels in maternal organism, which “programs” the offspring and leads to the inadequate repercussions. When the an evaluation is performed in older offspring (around 90 days old), the time of maternal HFD consumption would need to be a little longer and the amount of fat in the diet would have to approximately be 47% to show effects on oxidative stress levels in offspring

and to obtain results with translational importance. Therefore, if the interest is to evaluate the maternal outcomes using HFD on their offspring, it is necessary to introduce this diet with a higher exposure time along with a higher proportion of fat. HFD impairs not only the mother but also the offspring postnatal life during their adulthood. Studies that highlight these findings are important for the development of intervention measures for the treatment/prevention of this condition.

Data Availability

All data is available in Supplementary Materials.

Conflicts of Interest

The authors have declared that no competing interests exist.

Authors' Contributions

RQMS is responsible for the conceptualization, data curation, formal analysis, investigation, methodology, validation, writing—original draft preparation, and writing—review and editing. GV is involved in the conceptualization, data curation, formal analysis, investigation, methodology, and writing—review and editing. VGP and TSS participated in data curation, investigation, and writing—review and editing. YKS contributed in the data curation, investigation, validation, and writing—review and editing. RBG also contributed in validation and writing—review and editing. GTV and DCD are also responsible for the conceptualization, data curation, formal analysis, investigation, methodology, validation, supervision, writing—original draft preparation, and writing—review and editing. All authors read and approved the final manuscript.

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Supplementary Materials

Supplementary 1. Table S1: file search strategy.

Supplementary 2. Table S2: maternal biochemical repercussions.

Supplementary 3. Table S3: biochemical repercussions of offspring.

Supplementary 4. Figure S1 File: meta-analysis of HFD maternal consumption on SOD and CAT activities compared with controls. HFD: high-fat diet.

Supplementary 5. Figure S2 File: risk of bias summary.

Supplementary 6. Figure S3 File: PRISMA 2009 checklist.

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