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ORIGINAL CONTRIBUTION

Fructose and saturated fats predispose hyperinsulinemia in lean male rat offspring

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Abstract
Background Early exposure to suboptimal nutrition during perinatal period imposes risk to metabolic disorders later in life. Fructose intake has been associated with increases in de novo lipogenesis, dyslipidemia, insulin resistance, and obesity. Excess consumption of saturated fat is associated with metabolic disorders.
Aim of the study Objective of this animal study was to investigate morphological, metabolic, and endocrine phenotypes of male offspring born to dams consuming diets containing either 30% fructose, 9.9% coconut fat and 0.5% cholesterol (F + SFA) or 30% glucose, and 11% corn oil (C), 1 month before conception and during gestation and nursing.
Methods Proven male and female Sprague Dawley breeders were fed ad libitum with either F + SFA or C diet throughout the study. At weaning, five male pups from each group were sacrificed for determining morphological phenotypes. The other five male offspring from each group were rehabilitated to the C diet for an additional 12 weeks. At the age of 15 weeks, morphological phenotypes and blood biochemistries [glucose, insulin, growth hormone (GH), insulin-like growth factor-1 (IGF-1), corticosterone, and testosterone] of male adult offspring were then assessed.
Results Body weight (BW) and body length of the F + SFA male adult offspring was slightly smaller than the C. The BW-adjusted epididymal and retroperitoneal fat depots of the F + SFA adult offspring were significantly 18 and 44% smaller than the C, respectively. GH and IGF-1 were not different in adult offspring between groups. Fasted plasma insulin of the F + SFA adult offspring was 64% larger than the C ($P \leq 0.0001$) and homeostasis model assessment value was 55% larger ($P = 0.004$). There were negative correlations between fat depot sizes and plasma insulin in adult offspring.
Conclusions Our results suggest that, through fetal programming, an early exposure to both fructose and saturated fats may cause hyperinsulinemia and insulin insensitivity in the nonobese male rats later in life.

Keywords Adiposity · Metabolic programming · Fructose · Insulin · Saturated fat

Abbreviations

BW	Body weight
C	Control
F	Fructose
GH	Growth hormone
IGF-1	Insulin-like growth factor-1
SFA	Saturated fat

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Introduction

Obesity and impaired insulin actions on glucose and fatty acid homeostasis play an etiological role in development and progression of metabolic disorders, including metabolic syndrome and type II diabetes. Emerging evidence from animal and observational studies has suggested that, through the mechanism of fetal/metabolic programming of adult onset diseases, suboptimal nutrition experienced in early life enhances susceptibility to metabolic disorders later in life [1]. To date, a variety of behavioral and environmental factors works through this mechanism. Stress, hypertension, smoking, obesity, gestational diabetes, food deprivation, and a diet low in protein or high in fat have been found to affect unfavorably metabolic efficiency, growth trajectory, insulin sensitivity, obesity, lipid profile, and blood pressure [2–7]. However, the impact of quality and quantity of nutrition, as well as their interactions with environmental factors, through metabolic programming on risk of metabolic disorders and other diseases has not been extensively examined.

As abovementioned, fat and protein of maternal diet could predispose the risk of metabolic disorders in adulthood. Srinivasan and Patel [8] have showed in a few studies that, instead of sucking high fat milk from dams, rats artificially reared with a high polycose (a glucose polymer) formula during nursing period developed insulin resistance and obesity in adulthood. Further, glucose supply from the mother to the fetus during gestation contributed to the long-term metabolic effects later in life [9]. Therefore, quality and quantity of carbohydrates and fats received during the early life confer to significant health consequences in adulthood.

A typical American diet that is high in saturated fats and simple sugars and low in fruits and vegetables is associated with risk of metabolic disorders in adults [10]. Fructose, generally used as a sweetener as forms of sucrose or high fructose corn syrup, has become a staple carbohydrate in American diets and contributes to 10% of daily calorie intake. When fructose intake in humans is as high as that providing 400–800 kcal/day, fructose is associated with increased risk of dyslipidemia, insulin insensitivity, hypertension, obesity, and other metabolic defects, possibly due to the inability of fructose to prompt an optimal insulin response and increased de novo lipogenesis in liver [11]. However, the information about the impact of an early exposure to excess fructose and saturated fat via fetal/metabolic programming on morphology, physiology, and endocrinology later in life is lacking. Thus, we aim to examine the morphological, biochemical, and endocrine phenotypes of male rat offspring born to dams consuming a diet high in fructose and saturated fats prior to conception and during gestation and nursing.

Materials and methods

Diets

Table 1 illustrates the ingredients used in the two isocaloric and isoproteinic diets: control (C) and 30% fructose + 9.9% coconut fat + 0.5% cholesterol (F + SFA). Diets were made of semi-synthetic ingredients. Coconut oil was employed because of its stability and 92.1% of saturated fat content. Cholesterol was added to reflect high cholesterol intake in Westerners and increase hypercholesterolemia. Amino acid contents of the diets were identified and prepared based on the report of Clifford et al. [12]. Mineral and vitamin content of the C diet were consistent with the AIN-93 formulation. Diets were prepared using amino acid defined ingredients and manufactured by Dyets Inc. (Bethlehem, PA, USA).

Animals

The protocol was approved by the Institutional Animal Care and Use Committee of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. Proven male and female Sprague Dawley breeders (8 M, 8 F) were obtained from Charles River Laboratories (Wilmington, MA, USA). After arrival, female and male

Table 1 Nutrient compositions of two experimental diets, based on 1 kg diet

Ingredients	Control diet	Fructose + saturated fat diet
Amino acids[a] (g)	175.86	175.86
Cornstarch (g)	291.565	284.565
Dextrose (g)	300.0	0.00
Fructose (g)	0.0	300.0
Corn oil (g)	110.0	10.0
Coconut oil (g)	0.0	99.0
Cholesterol (g)	0.0	5
Pectin (g)	50.0	50.0
Mineral mix (AIN-93G) (g)	57.96	57.96
Choline chloride (g)	2.0	2.0
Sodium biocarbonate (g)	6.6	6.6
BHT (g)	0.015	0.015
Vitamin mix (AIN-93-VX) (g)	10.0	10.0
Total calories (kcal)	4124	4157

[a] Amino acid mix (g): L-alanine (3.495), L-arginine, free base (11.197), L-asparagine (5.999), L-aspartic acid (3.495), L-cystine (3.495), L-glutamic acid (34.997), glycine (23.305), L-histidine free base (3.297), L-isoleucine (8.217), L-leucine (11.088), L-lysine HCl (14.405), L-methionine (8.217), L-phenylalanine (11.603), L-proline (3.495), L-serine (3.495), L-threonine (8.217), L-tryptophan (1.742), L-tyrosine (3.495), L-valine (8.217)

rats were assigned randomly to one of the two diets (Fig. 1). The rational for feeding rats with experimental diets for a month was that the information about the critical window of fetal programming has not been fully elucidated even though the literature has suggested dietary influence during pregnancy and/or lactation in this regard. All rats were single housed with a 12:12 h light:dark cycle and fed ad libitum for 4 weeks. Food intake and body weight (BW) were recorded in the final week. Subsequently, each female was mated with a male in the same dietary group.

During the pregnancy and lactation periods, dams remained on their designated diet. Three days postpartum, litter size was adjusted to 8–10 in order to ensure that each pup would receive comparable nutrition. At weaning (day 21), five male pups from each dietary group were randomly selected and then euthanized. On the same day, the other five male offspring from each group were fed with the C diet for an additional 12 weeks. Body weights of male offspring were measured weekly.

Tissue collection of parental rats and pups

At weaning, five male pups and corresponding parental rats were killed with terminal exsanguinations under Aerrane^{TM} anesthesia. Subsequently, body length of pups from nose to the tip of tail was measured after euthanasia. Several internal organs were harvested and weighted. Fat depots were collected in pups and parental rats.

Blood and tissue collection of adult male offspring

Under Aerrane anesthesia, the maximum volume of overnight-fasted blood of adult offspring was collected from the posterior retro-orbital sinus into ETDA containing tubes. Following terminal exsanguinations by cardiac puncture under anesthesia, organ harvest was performed, including four adipose depots (epididymal, mesenteric, perirenal, and retroperitoneal fat pad) and several internal organs. Weights of fat depots provide a measure of adiposity [13]. Length from nose to the tip of tail was measured after euthanasia. Plasma was collected after centrifugation at 1,000 × *g* for 15 min at 4°C and then aliquots were stored at −80°C.

Plasma biochemistry in adult male offspring

Plasma insulin, testosterone, corticosterone, insulin-like growth factor-1 (IGF-1), and growth hormone (GH) were selectively measured because of their functions on growth rate and energy metabolism. They were determined using commercially available ELISA kits. Insulin (EZRMI-13 K) and GH (EZRMGH-45 K) were obtained from Millipore (Billerica, MA, USA) and IGF-1 (DSL-10-29200), testosterone (DSL-10-4000), and corticosterone (DSL-10-81100) from Diagnostic Systems Laboratories (Webster, TX, USA). Plasma glucose was measured using an enzymatic assay with an Olympus AU400 Clinical Chemistry Analyzer (Center Valley, PA, USA). Insulin sensitivity was estimated using the homeostasis model assessment (HOMA) equation, with a low value indicating high insulin sensitivity and vice versa [14].

Statistical analysis

Results were presented as mean ± SE. Differences between the control and F + SFA group were assessed using a Student's *t* test. Pearson's correlation test was performed to assess associations between measured parameters of adult offspring. $P \leq 0.05$ was considered significant. All statistical analyses were performed using JMP IN® (SAS Institute Inc., Cary, NC, USA).

Results

The influence of diets on parents

Food intakes of male and female rats were assessed 9 days before mating. Diet consumption did not differ between

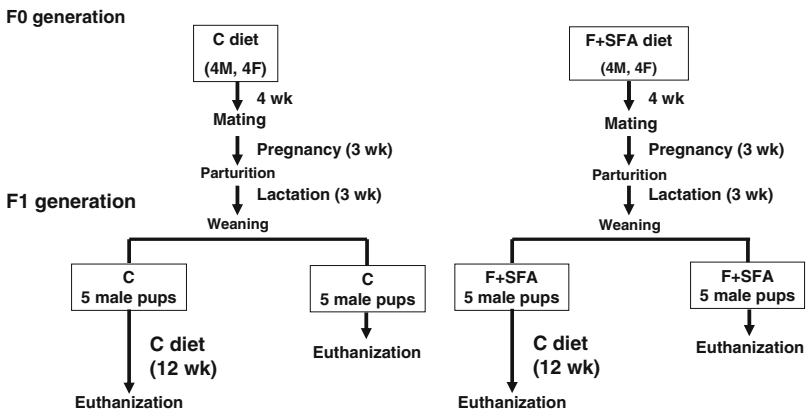

Fig. 1 Scheme of the study design. Abbreviations of experimental diets: *C* control, *F + SFA* fructose and saturated fats

Table 2 Body and organ weights of male offspring at the age of 3 weeks

	Control diet	Fructose + saturated fat diet
Body weight (g)	44.47 ± 3.87	39.56 ± 1.58
Body length (cm)	20.76 ± 1.27	18.23 ± 0.35
Brain (g)	1.23 ± 0.03 (2.85 ± 0.02)	1.05 ± 0.02‡ (2.71 ± 0.14)
Heart (g)	0.23 ± 0.02 (0.52 ± 0.02)	0.22 ± 0.01 (0.55 ± 0.02)
Kidney (g)	0.43 ± 0.04 (0.97 ± 0.02)	0.35 ± 0.01 (0.90 ± 0.03)
Liver (g)	1.30 ± 0.17 (2.87 ± 0.12)	1.38 ± 0.05 (3.51 ± 0.15***)
Lung (g)	0.42 ± 0.03 (0.95 ± 0.04)	0.39 ± 0.02 (0.99 ± 0.04)
Pancreas (g)	0.11 ± 0.03 (0.24 ± 0.03)	0.08 ± 0.00 (0.21 ± 0.02)
Small intestine (m)	0.50 ± 0.04	0.51 ± 0.02

All results were expressed as mean ± SE, $n = 5$. Results in the parentheses were %BW

Mean values significantly differ from the control, ***$P \leq 0.005$ and ‡$P \leq 0.0001$ tested by a Student's t test

groups, with an overall mean intake of 16.1 ± 0.9 and 20.0 ± 1.0 g/day for females and males, respectively. Mean 4-week weight gain of 23 ± 4 and 108 ± 6 g for females and males, respectively, was also not different between groups. However, F + SFA dams had a 99% larger liver size than C [C vs. F + SFA: 7.8 ± 0.5 g (3.1 ± 0.2% of BW) vs. 15.5 ± 1.2 g (5.8 ± 0.4%)], but F + SFA males did not display enlarged livers. The diets did not affect the sizes of heart, lung, kidney, pancreas, and small intestine. The diets did not affect the litter size at birth (C vs. F + SFA: 10.3 ± 0.3 vs. 13 ± 1 pub/litter).

Morphometrics of male offspring

At weaning, the diets did not affect BW and body length and sizes of heart, lung, pancreas, and small intestine of male pups (Table 2). However, the brain of F + SFA pups was 15% heavier than the C, but the difference was not significant after adjusted for BW. The BW-adjusted liver size of F + SFA pups was 22% larger than C while the absolute liver weights did not differ.

Mean BW of offspring from the age of week 3–13 did not differ between groups (Fig. 2). At week 14, unfasted BW of the F + SFA offspring was 11% smaller than the C. The growth rate from week 3 to 7 did not differ between groups (C vs. F + SFA: 38.5 ± 1.2 vs. 35.3 ± 2.5 g/week, $P = 0.27$). However, the C offspring grew 18.4% faster from week 7 to 14 than the F + SFA (C vs. F + SFA: 26.3 ± 1.2 vs. 22.2 ± 1.2 g/week, $P = 0.04$). At sacrifice, overnight-fasted BW, body length, and the sizes of brain, heart, kidney, liver, lung, pancreas, and small intestine of adult offspring did not differ between groups (Table 3). The BW-adjusted brain and kidney size of the F + SFA offspring was 18 and 13% larger than the C, respectively.

The sizes of four fat depots were determined as an indicative of adiposity. The F + SFA male offspring had 27 and 49% less fat accumulations in the epididymal and retroperitoneal depot than the C, respectively ($P = 0.003$ and 0.007). Particularly, the ratio of epididymal and retroperitoneal fat and sum of four depots to BW in the F + SFA male offspring were 18, 44, and 23% lower than the C, respectively ($P = 0.006$, 0.01, and 0.02).

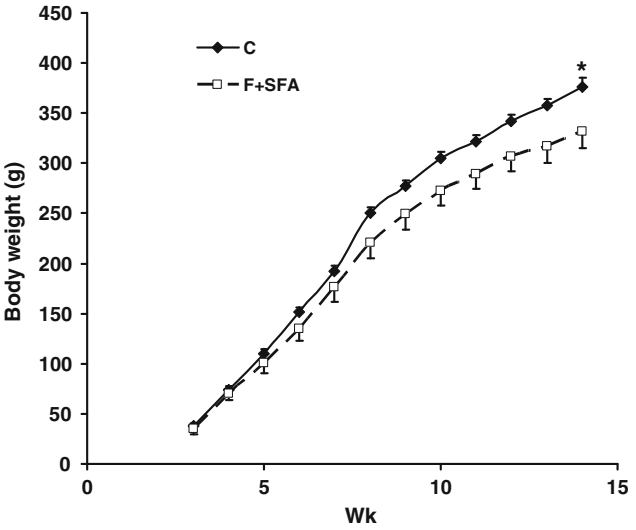

Fig. 2 Changes in body weight of male offspring from age of 3 to 14 weeks. Results were expressed as mean ± SE, $n = 5$. *Asterisk* denotes mean values at the same week differ, $P \leq 0.05$, tested by a Student's t test

Plasma biochemistry of male adult offspring

Corticosterone, testosterone, IGF-1, and GH concentrations of adult offspring did not differ between groups (Table 4). However, the F + SFA offspring had a 64% higher plasma insulin level than that of the C ($P \leq 0.0001$), but they had a similar plasma glucose level (Table 4). The F + SFA offspring has a 55% larger HOMA value than the C ($P = 0.004$).

Table 3 Body and organ weights of male adult offspring at the age of 15 weeks after an overnight fast

	Control diet	Fructose + saturated fat diet
Body weight (g)	350.20 ± 7.73	315.40 ± 15.4
Body length (cm)	43.22 ± 0.08	42.32 ± 0.09
Brain (g)	1.39 ± 0.19 (0.40 ± 0.03)	1.50 ± 0.33 (0.47 ± 0.02*)
Heart (g)	1.35 ± 0.06 (0.39 ± 0.02)	1.19 ± 0.09 (0.37 ± 0.01)
Kidney (g)	2.21 ± 0.08 (0.63 ± 0.02)	2.24 ± 0.10 (0.71 ± 0.01*)
Liver (g)	9.45 ± 0.70 (2.69 ± 0.17)	8.14 ± 0.34 (2.58 ± 0.04)
Lung (g)	1.79 ± 0.19 (0.51 ± 0.05)	1.44 ± 0.04 (0.46 ± 0.02)
Pancreas (g)	0.98 ± 0.06 (0.28 ± 0.01)	1.05 ± 0.13 (0.34 ± 0.05)
Small intestine (m)	0.88 ± 0.14	0.90 ± 0.34
Epididymal fat (g)	3.69 ± 0.17 (1.05 ± 0.04)	2.71 ± 0.16*** (0.86 ± 0.03**)
Mesenteric fat (g)	2.62 ± 0.19 (0.75 ± 0.04)	2.01 ± 0.23 (0.63 ± 0.06)
Perirenal fat (g)	1.27 ± 0.13 (0.36 ± 0.03)	1.01 ± 0.11 (0.32 ± 0.03)
Retroperitoneal fat (g)	2.49 ± 0.22 (0.71 ± 0.06)	1.26 ± 0.26** (0.40 ± 0.08**)
Total fat (g)	10.07 ± 0.60 (2.87 ± 0.13)	7.00 ± 0.72* (2.21 ± 0.18*)

Results were expressed as mean ± SE, $n = 5$. Results in the parentheses were %BW

Mean values significantly differ from the control, *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.005$ tested by a Student's t test

Table 4 Concentrations of plasma endocrines and glucose in male adult offspring at the age of 15 weeks

	Control diet	Fructose + saturated fat diet
Testosterone (μmol/L)	6.35 ± 1.99	5.82 ± 1.50
Corticosterone (mmol/L)	1.33 ± 0.34	1.46 ± 0.29
Insulin-like growth factor-1 (μmol/L)	166.16 ± 6.01	170.44 ± 7.29
Growth hormone (nmol/L)	593.02 ± 273.90	1023.16 ± 532.56
Glucose (mmol/L)	6.24 ± 0.38	5.93 ± 0.35
Insulin (μU/mL)	12.72 ± 1.41	20.88 ± 0.88‡
HOMA (insulin sensitivity)	3.59 ± 0.49	5.55 ± 0.52***

Results were expressed as mean ± SE, $n = 5$

Mean values significantly differ from the control, ***$P \leq 0.005$, $^{\ddagger}P \leq 0.0001$, tested by a Student's t test

Correlations in male adult offspring

Body weight was correlated with epididymal, mesenteric, perirenal, and retroperitoneal fat depot and total fat with the r-value at 0.80, 0.86, 0.63, 0.68, and 0.80, respectively ($P \leq 0.05$). Further, plasma insulin was negatively correlated with epididymal, mesenteric, perirenal, and retroperitoneal fat depot, total fat, and BW with r-value at −0.84, −0.69, −0.53, −0.67, −0.76, and −0.65, respectively ($P \leq 0.05$). There was also a positive correlation between glucose and testosterone ($r = 0.90$, $P = 0.0003$).

Discussion

Optimal pre- and postnatal nutrition is not only essential for the newborn wellbeing but also has an impact on health persistent to adulthood. Suboptimal maternal nutrition, such as diets low or high in proteins, impairs metabolism, endocrine function, and BW of the fetus and infant, resulting in an increased propensity for adult-onset health problems [15]. Our study provides another line of evidence that an early exposure to excess fructose and saturated fat modulated adiposity, BW, and endocrine functions at adulthood.

Gestational diabetes and hyperglycemia are associated with macrosomics of newborn and obesity later in life in model animals and people [16]. In rodent models, a diet containing 60% fructose has been prevalently employed to induce insulin resistance [17]. In this study, because such a high fructose intake did not reflect a general human diet, 30% fructose was administered instead of 60%. However, such amount of fructose contributed to 29.9% of caloric intake, which is in the range of 20–40% caloric intake from

fructose that is associated with an increased risk of dyslipidemia, insulin insensitivity, hypertension, obesity, and other metabolic defects in humans [11]. We found that the F + SFA male offspring did not display macrosomics at weaning and obesity at adulthood. This was contrary to increased BW and adiposity of 12-day-old mouse pups born to dams fed a diet containing 68.5% sucrose (34.25% fructose) and 6% corn oil [18] even though the main difference between this study and ours resided on fat content (9.9% coconut oil vs. 6% corn oil). However, because biochemistries of dams were not monitored, a more thorough and broad discussion on this discrepancy was limited. While BW of the male offspring at weaning did not differ between groups, the larger BW-adjusted liver size of the F + SFA pups at weaning than the C implicated an influence of maternal F + SFA-induced metabolic alternations on hepatic anatomy and/or physiology. The mechanism(s) responsible for this observation remains to be examined, particularly the F + SFA-induced biochemical and endocrine changes in dams during gestation and lactation.

Maternal nutrition is critical to postnatal growth trajectory and physiological and metabolic phenotypes of adult progeny [19–23]. Particularly, offspring born to mothers with placenta insufficiency that was induced by either uterine ligation or nutrition deficiency displayed development retardation and experience a period of catch-up growth in early life [24]. Based on the mismatched environmental theory that the expected environment after birth is not attained, such individuals face an increased likelihood of metabolic defects later in life. Our study showed that the maternal S + SFA diet suppressed growth of male offspring from the age of week 7–14 and subsequently led to a borderline lower BW and body length at the age of 15 weeks than the C even though all offspring were fed with the C diet after weaning. This suggests the intrauterine and neonatal exposure to both fructose and saturated fat, as well as consequent products generated in dams consuming this diet, might have a lifelong effect on anatomical developments.

Because of the global epidemic of obesity and its association with health problems, understanding of the development of obesity have become one of focal topics for nutritional investigations. While fat accretion primarily results from chronic positive energy balance, consumption of excess amounts of fructose links with visceral adiposity, metabolic syndrome, type II diabetes [25, 26]. A recent animal study also showed that the offspring of dams consuming a westernized "junk food" rich in fat, sucrose, and salt exhibited a larger perirenal fat mass even though they were rehabilitated to a chow diet [27]. In this study, we observed the F + SFA adult male offspring were 23% leaner than the C even though they all consumed the C diet after weaning. These findings were contrary to the findings of Ghusain-Choueiri and Rath [18] and Sedová et al. [28], which showed that the high maternal sucrose diets fed during pregnancy and nursing periods enhanced adiposity in neonate mice at the age of 12 days and male rats at weaning, respectively. These discrepancies might be inherent to diet formulations and the age of examination of adiposity of model animals. Further studies designed to provide information on feed intake and energy expenditure are required to elucidate the mechanisms by which F + SFA offspring had a lower grade of adiposity.

Increased fructose intake has been associated directly with the development of type II diabetes and metabolic syndrome possibly due to increased productions of uric acid and triglycerides [25, 26]. Our data showed that F + SFA male adult offspring who were exposed to fructose in early life but rehabilitated to the C diet for an additional 12 weeks had significant increases in circulating insulin and HOMA value. We speculate that gestational hyperglycemia and hyperinsulinemia might not be the contributing factors to the hyperinsulinemia in the adult offspring mainly because the F + SFA offspring were not born with macrosomia and became obese, as is normally observed in progenies born to diabetic mothers [24]. Further investigations in this area are required to substantiate our hypothesis.

There are three main limitations for this exploratory study. First, food intake of the male offspring from weaning to the age of 15 weeks was not monitored, which is very critical to revealing whether a lower calorie intake could be a contributing factor to the less body fat accumulation in the F + SFA offspring. Second, the effect of F + SFA-induced changes in biochemistries and hormones in dams were not determined. A recent study has showed the percentage of calories from sucrose was correlated with circulating leptin of overweight pregnant women [29]. This information is necessary to understand the mechanisms by which nutrient programming commands morphology and physiology of offspring later in life. Third, data generated from a rat model might not readily to be extrapolated to humans.

In conclusion, our study shows that an early exposure to both high fructose and saturated fats could predispose offspring to hyperinsulinemia and reduced adiposity, growth rate, and insulin sensitivity later in life. Further studies are warranted to examine the health of the progenies of mothers-to-be consuming a diet containing high amounts of fructose and saturated fat rich foods before conception and during gestation and nursing. Future studies are also required to elucidate the critical window and biochemical and molecular mechanisms of nutrient programming of fructose and saturated fats, particularly on hyperinsulinemia in adult male offspring.

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