Severe Intrauterine Growth Restriction Is Associated With Higher Spontaneous Carbohydrate Intake in Young Women

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ABSTRACT: Intrauterine growth restriction (IUGR) is associated with metabolic disorders in adulthood. In rats, an early adverse environment alters food preferences in adult life. We investigated whether IUGR is associated with spontaneous macronutrient preferences in humans. Two thousand sixty-three participants from a Brazilian birth cohort were evaluated at 24 y of age using a food frequency questionnaire, physical examination, anthropometric measurements, and biochemical assays (glucose, insulin, cholesterol, and triglycerides). IUGR was defined by the birth weight ratio (BWR = birth weight/mean weight for gestational age). Individuals were classified as non growth restricted (BWR ≥0.85), moderately growth restricted (0.85 > BWR ≥ 0.75), and severely growth restricted (BWR <0.75). Severe IUGR women consumed a greater carbohydrate to protein ratio, even after controlling for social variables. There was a continuous association between growth restriction and later carbohydrate to protein ratio consumption in women. Women from both IUGR groups had a larger waist to hip ratio (WHR). The prevalence of metabolic syndrome was comparable between the groups. IUGR women preferred carbohydrates to protein in their regular diet, suggesting that spontaneous food choices may precede the appearance and contribute to the risk for metabolic diseases in this group. (*Pediatr Res* **65:** 215–220, 2009)

Studies have shown that low birth weight, a marker for adverse fetal conditions, is associated with metabolic disorders in adulthood, predicting insulin resistance and type 2 diabetes (1), hypertension (2), obesity (3) and cardiovascular disease (4), especially in cases where there is evidence of postnatal body weight catch-up during childhood. Thus, feeding patterns and accelerated weight gain during the postnatal period are crucial mediators of the risk for subsequent obesity, cardiovascular disease (5), and insulin resistance (6).

The developing organism may use the maternal intrauterine environment's hormonal milieu as a signal to indicate conditions that will exist in the postnatal environment (7) to favor the adaptation to the environment in which it will develop. Therefore, for a fetus reared in a stressful environment with possible shortage of nutrients, metabolic and neurochemical patterns would be adjusted very early during development favoring energy storage for the individual's survival.

Studies in animals propose that altered eating and exercise behaviors precede the development of obesity and insulin resistance (8–10). Exposure to a high fat diet further exacerbates the metabolic and cardiovascular abnormalities in these animals (8). In our previous studies in rats (11,12), we demonstrated that early life experience affects sweet food intake later in life. These findings would indicate that adverse perinatal events in humans could affect an individual's voluntary food choices for palatable foods, influencing the risk for metabolic diseases in adult life. We tested this hypothesis in a birth cohort followed to adulthood in Brazil (13).

To our knowledge, this is the first study to assess spontaneous nutritional preferences in adults born with intrauterine growth restriction (IUGR). Thus, the aim of this study is to investigate the possible impact of IUGR on eating preferences and risk factors for metabolic diseases in adult life.

SUBJECTS AND METHODS

This is a cross-sectional evaluation of a longitudinal, prospective cohort study involving subjects born in Ribeirão Preto (São Paulo, Brazil) from June 1, 1978 to May 31, 1979. There were 9067 births, of which 6973 babies' mothers resided in this city at the time of delivery and were included in the study (6827 singletons and 146 twin deliveries). Data from mothers and children, including anamnesis and anthropometry were collected by trained personnel at the moment of birth. The study was approved by the Ethics Committee of the University Hospital, Medical School of Ribeirão Preto.

The concept of IUGR was based on the birth weight ratio (BWR), the ratio between the newborn's weight and the local population's sex-specific mean birth weight for each gestational age. Individuals were classified as nonrestricted (BWR ≥0.85), moderately restricted (BWR <0.85 and ≥0.75), and severely growth restricted (BWR <0.75) (14).

In 2004, 2063 participants were reevaluated by anamnesis, physical examination, anthropometric measures, and biochemical assays. The detailed description of the cohort and the comparison of this sample with the original population have been published elsewhere (13). Briefly, the 2004 sample was comparable to the original population with regard to birth weight, birth length, and maternal age, although the sample was slightly wealthier. In this study, only singletons were included. Individuals born before 34-wk gestation were also excluded (because of the small number of such births, the BWR calculation was not accurate). Therefore, in the present study, we analyzed data from 2050 individuals.

Physical activity was evaluated using the CELAFISCS (15) and centre for disease control (CDC) (16), consensus considering criteria about frequency of activity and dividing individuals into the categories "active" and "sedentary." Maternal data were obtained by a standardized questionnaire soon after delivery, and demographic information was collected from official records (17). The subjects' data were obtained using a standardized questionnaire after their return for evaluation at 24 y of age.

Abbreviation: BWR, birth weight ratio

The subjects filled in a food frequency questionnaire, developed and adapted for the Brazilian population (18). The usual total caloric intake and the percentages of total calories derived from fat, carbohydrates, and protein were estimated using the DietPRO 4.0 professional program (Agromídia Software). The carbohydrate to protein ratio was calculated by dividing the amount of carbohydrates by the amount of protein consumed.

Weight, height, waist/hip ratio, and blood pressure were measured by trained personnel. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square meters (19). Biochemical measurements included fasting glucose, total cholesterol with fractions and triacylglycerol. Glucose was determined by the GOD/PAP human diagnostic colorimetric enzymatic method (Chronolab AG, Zug, Switzerland). Cholesterol and triacylglycerol were determined by an enzymatic colorimetric method using the Dade Behring XP test and apparatus (Dade Behring, Liederbach, Germany) and reagents from Dade Behring Dimension clinical chemistry.

Metabolic syndrome definition was based on the NCEP ATP III criteria (20), including three or more of the following factors: fasting glucose $\geq$100 mg/dL, blood pressure $\geq$130/85 mm Hg, triacylglycerol $\geq$150 mg/dL, HDL cholesterol >40 mg/dL for men and 50 mg/dL for women, and waist circumference >102 cm for men and 88 cm for women.

Statistical analysis. Biochemical measurements and macronutrient intake were evaluated using two-way analysis of variance (ANOVA) with gender and IUGR as factors followed by the Bonferroni *post hoc* test with interaction evaluation. The model was controlled for maternal (income, smoking, and schooling), and participant factors (smoking, schooling, current BMI, and physical activity). Socioeconomic status (SES) is known to influence food availability and consumption (21), and could impact both the individual's food consumption and the mother's nutrition during pregnancy and lactation. Household education impacts an individual's feeding behavior (22), and there is obvious effects of physical activity and body weight on feeding behavior. Smoking affects feeding related neuropeptides in animals, both when the exposure happens *in utero* (23) or in adulthood (24). Nicotine affects nutrient intake in humans (25). These variables were therefore identified as possible confounds and the analysis was adjusted accordingly. Anthropometric measurements' analysis had the current BMI excluded from the model. A χ^2 test was performed to compare the maternal and subjects data with the prevalence of metabolic syndrome. Linear regression was performed to search for associations between IUGR and later carbohydrate to protein ratio using BWR as a continuous variable. Statistical significance was assumed if the p value was $\leq$5%. Parametric continuous data were expressed as mean $\pm$ SEM.

Table 1. *Socioeconomic characteristics distribution of the subjects by birth weight ratio category*

	Severely restricted ($n = 66$)	Moderately restricted ($n = 154$)	No growth restriction ($n = 1830$)	p value
Maternal factors, n (%)				
Smoking (ever)				<0.001
No	33 (50.80)	99 (64.70)	1369 (76.40)	
Yes	32 (49.20)	54 (35.30)	423 (23.60)	
Family income (minimum wages), n (%)				0.003
<3 MW	12 (18.18)	24 (15.58)	182 (9.95)	
3 a 4, 9 MW	17 (25.76)	36 (23.38)	404 (22.08)	
5 a 9, 9 MW	18 (27.27)	49 (31.82)	560 (30.60)	
10 a 19, 9 MW	7 (10.61)	16 (10.39)	379 (20.71)	
≥20 MW	2 (3.03)	17 (11.04)	177 (9.67)	
Schooling, n (%)				0.125
<5 years	40 (62.50)	75 (49.02)	798 (44.51)	
5 to 8 years	14 (21.88)	41 (26.80)	497 (27.72)	
9 to 11 years	7 (10.94)	21 (13.73)	303 (16.90)	
≥12 years	3 (4.69)	16 (10.46)	195 (10.88)	
Subject's factors				
Sex, n (%)				0.533
Male	29 (43.90)	69 (44.80)	888 (48.50)	
Female	37 (56.10)	85 (55.20)	942 (51.50)	
Smoking, n (%)				0.292
Never smoked	47 (71.21)	116 (75.32)	1381 (75.46)	
Ex-smoker	4 (6.06)	12 (7.79)	137 (7.49)	
<5 cigarettes/day	2 (3.03)	7 (4.55)	118 (6.45)	
≥5 cigarettes/day	13 (19.70)	19 (12.34)	194 (10.60)	
Schooling, n (%)				<0.001
<8 years	21 (31.82)	27 (17.53)	268 (14.64)	
9 to 11 years	33 (50.00)	86 (55.84)	914 (49.95)	
≥12 years	12 (18.18)	41 (26.62)	648 (35.41)	

Chi-square analysis performed comparing birth weight groups. Totals may differ for some variables because of missing data.

RESULTS

Table 1 displays the maternal and subjects' characteristics. One thousand eight hundred thirty nonrestricted, 154 moderately, and 66 severely restricted individuals were included. The overall incidence of IUGR was 10.73% (7.51% moderately and 3.22% severely growth restricted). Evaluation happened at an average age of 23.91 y (SD = 0.71) ranging from 22 to 26 y. The prevalence of maternal smoking and low maternal income was greater in the restricted groups ($p <$ 0.001 and = 0.003 respectively). Subjects' income retained the same pattern of low income in the restricted groups ($p =$ 0.01), but the prevalence of smoking was not different between the groups ($p =$ 0.293).

χ^2 analysis indicated that women are more sedentary than men ($p <$ 0.01). However, the prevalence of sedentarism was not different between the IUGR groups in women (Severe IUGR = 32.4%; Moderate IUGR = 29.4%; No IUGR = 26.8%, $p =$ 0.30) or in men (Severe IUGR = 27.6%; Moderate IUGR = 13%; No IUGR = 14.5%, $p =$ 0.18).

The consumption of macronutrients is shown in Figure 1. The total caloric consumption was not different between the groups ($p =$ 0.429), although men consumed more calories than women ($p <$ 0.001), without interactions ($p =$ 0.220). Fat consumption was similar between the groups ($p =$ 0.561) and genders ($p =$ 0.280); however, an effect of sex and an interaction between gender and group was found for carbohydrate consumption, in which women ate more carbohydrates than men ($p =$ 0.049), and severely growth restricted women ate more carbohydrates than the non growth restricted women ($p =$ 0.041 for sex-group interaction; Severe IUGR women = 50.995%, IC95% = 48.458–53.533%; Moderate IUGR women = 47.624%, IC95% = 46.083–49.166%; Non-IUGR women = 47.095, IC95% = 46.632–47.559%). This was accompanied by a decreased ingestion of protein in the same group ($p =$ 0.014 for the interaction; Severe IUGR women = 13.965%, IC95% = 12.843–15.088%; Moderate IUGR women = 15.901%, IC95% = 15.219–16.583%; Non-IUGR women = 15.897, IC95% = 15.692–16.102%). These findings led to a higher carbohydrate to protein ratio in the severely growth restricted group ($p =$ 0.033 for sex and $p =$ 0.010 for the interaction; Severe IUGR women = 3.844, IC95% = 3.450–4.238; Moderate IUGR women = 3.189, IC95% = 2.950–3.428; Non-IUGR women = 3.137, IC95% = 3.066 to 3.209). The same results are found if the analysis is adjusted for current body weight instead of current BMI (data not shown). Regression analysis showed a continuous association between growth restriction and later carbohydrate to protein ratio consumption in women ($\beta =$ −0.825, IC-95%: −1.320 to −0.323).
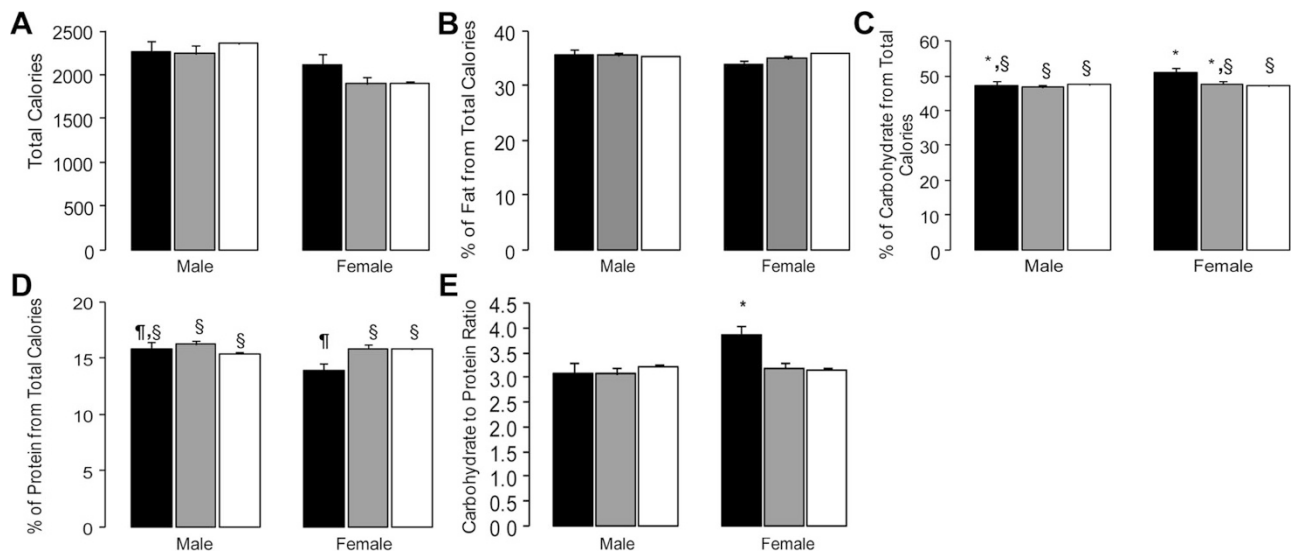
Figure 1. Nonadjusted mean and SEM of macronutrient consumption in severely restricted (Severe IUGR, *black bar*), moderately restricted (Moderate IUGR, *gray bar*), and nonrestricted (No IUGR, *white bar*) individuals. *A*: Total caloric intake. *B*: Percentage of the total calories derived from fat. *C*: Percentage of the total calories derived from carbohydrates. *D*: Percentage of the total calories derived from protein. *E*: carbohydrate to protein ratio. *Two-way ANOVA adjusted for maternal (income, smoking, and schooling) and participant factors (smoking, schooling, current BMI and physical activity) followed by interaction evaluation (sex *versus* group), $p < 0.05$. Different symbols on top of the bars demonstrate differences between the groups after the interaction evaluation.

Table 2. *Consumption of specific types of foods*

Food	Men			Women		
	Severe IUGR ($n = 29$)	Mild IUGR ($n = 69$)	No IUGR ($n = 888$)	Severe IUGR ($n = 37$)	Mild IUGR ($n = 85$)	No IUGR ($n = 942$)
Meat*	1.91 ± 0.17	2.12 ± 0.11	2.06 ± 0.03	1.65 ± 0.17	1.67 ± 0.10	1.78 ± 0.03
Milk	1.67 ± 0.24	1.60 ± 0.15	1.68 ± 0.04	1.48 ± 0.23	1.71 ± 0.14	1.75 ± 0.04
Bread	3.51 ± 0.28	3.57 ± 0.18	3.80 ± 0.05	3.91 ± 0.27	3.59 ± 0.16	3.58 ± 0.05
Fruits	1.24 ± 0.20	1.19 ± 0.13	1.21 ± 0.04	1.52 ± 0.19	1.29 ± 0.11	1.26 ± 0.03
Vegetables*	1.97 ± 0.44	2.95 ± 0.28	2.78 ± 0.08	3.75 ± 0.42	3.21 ± 0.26	3.21 ± 0.08
Calories derived from sweet foods	275.30 ± 42.16	268.26 ± 27.04	293.00 ± 7.61	297.52 ± 40.61	219.24 ± 24.67	237.79 ± 7.45
Fiber (g)*	16.85 ± 1.34	16.47 ± 0.86	16.79 ± 0.24	16.03 ± 1.29	14.40 ± 0.78	14.13 ± 0.24

For continuum data two way analysis of variance (ANOVA) (Sex *vs.* BWR-Group) was used. The test was followed by Bonferroni *post hoc* or interaction evaluation. Data expressed by mean ± standard error of mean. For categorical data, we used χ^2 test. Data expressed in *n* (%). Totals may differ for some variables because of missing data.

* Effect of sex. Meat, milk, bread, fruits and vegetables—number of portions per day.

IUGR, intrauterine growth restriction.

Table 2 depicts the consumption of specific types of foods. There were no differences between the groups regarding the consumption of milk, meat, bread, vegetables, fruits, and fiber ($p > 0.05$), nor in the mean total calories derived from sweet food.

Table 3 displays the anthropometric and biochemical data. IUGR individuals were smaller ($p < 0.001$) and lighter ($p = 0.005$) than nongrowth restricted individuals, but the BMI was only lower in the moderately growth restricted group in comparison with the nongrowth restricted group ($p = 0.035$). The waist to hip ratio (WHR) was larger in IUGR women ($p = 0.017$ for sex-group interaction; Severe IUGR women = 0.782, IC95% = 0.762–0.801; Moderate IUGR women = 0.773, IC95% = 0.762–0.785; Non-IUGR women = 0.757, IC95% = 7.53–7.60).

The prevalence of risk factors for metabolic syndrome, such as plasma fasting glucose, HDL and triacylglycerol did not

differ between the groups (Table 3), although there were gender effects as expected (data not shown).

DISCUSSION

Our results demonstrate a higher ingestion of carbohydrates in women born with severe IUGR. This was accompanied by a diminished consumption of protein, leading to a higher carbohydrate to protein ratio. To our knowledge, this is the first evidence indicating an association between IUGR and altered feeding preferences in humans. The effect persisted when confounders such as SES, current BMI, and smoking were considered. Furthermore, a continuous association was found between IUGR and the preference for carbohydrates in adulthood.

IUGR may be considered a metabolic stress that acts during a susceptible period, programming the hypothalamic circuitry

Table 3. *Anthropometry and prevalence of metabolic syndrome by birth weight ratio category and sex*

	Men			Women		
	Severe IUGR (n = 29)	Moderate IUGR (n = 69)	No IUGR (n = 888)	Severe IUGR (n = 37)	Moderate IUGR (n = 85)	No IUGR (n = 942)
Anthropometric data, mean (SEM)						
Length (cm)*,†	172.76 (0.90)	172.54 (0.80)	176.32 (0.22)	159.1 (1.20)	159.88 (0.66)	162.96 (0.21)
Weight (Kg)*,†	73.81 (2.95)	73.07 (1.75)	78.02 (0.50)	59.50 (2.55)	58.12 (1.50)	63.10 (0.46)
BMI (Kg/m^2)*	24.67 (0.85)	24.4 (0.49)	25.04 (0.15)	23.35 (0.87)	22.84 (0.57)	23.71 (0.16)
WHR‡	0.86 (0.011)	0.85 (0.007)	0.86 (0.002)	0.78 (0.010)§	0.77 (0.007)§	0.76 (0.002)
Prevalence of metabolic syndrome, number of cases (% of total)						
NCEP ATP III	4 (13.79%)	6 (8.69%)	110 (12.38%)	1 (2.70%)	3 (3.53%)	52 (5.52%)
Unknown	1 (3.44%)	1 (1.45%)	6 (0.67%)	1 (2.70%)	0	21 (2.23%)
χ^2 value			0.712			0.554

For continuum data two way ANOVA (Sex *vs.* BWR-Group) was used. The test was followed by Bonferroni *post hoc* or interaction evaluation. For categorical data we used χ^2 test. Data expressed in *n* (%). Totals may differ for some variables because of missing data. Statistical significance was assumed if *p* value was less than 0.05.

* Effect of sex.

† Effect of BWR-Group.

‡ Sex *vs.* BWR-group interaction.

§ Analysis of interaction, groups which CI95% differ from No IUGR group.

SEM, standard error of mean; IUGR, intrauterine growth restriction; BMI, body mass index; WHR, waist to hip ratio; NCEP-ATP III, national cholesterol education program, adult treatment panel III criteria for diagnosing metabolic syndrome.

responsible for appetite regulation, and/or the mesolimbic pathways responsible for the pleasure associated with the ingestion of highly palatable, preferred foods. The programming of the hypothalamic–pituitary–adrenal (HPA) axis has been proposed as a possible mechanism by which IUGR leads to increased risk for metabolic diseases in adulthood (26), and could also be involved in the establishment of feeding preferences. IUGR children have an exacerbated adrenocortical response to stress (27), and glucocorticoids stimulate behaviors mediated by the "reward" pathways, increasing palatable feeding in rats (28,29) and humans (30). The ingestion of preferred foods in the context of elevated glucocorticoids and insulin leads to an increased accumulation of abdominal fat (29). Interestingly, the waist/hip ratio was larger in IUGR women in our sample. This agrees with findings from the Dutch Famine in which BMI is increased in women exposed to undernutrition in early gestation (31). There is also a greater transfer of glucocorticoids across the placenta of female when compared with male fetuses (32), supporting the fact that differences in feeding were only associated with IUGR in women.

Although developmental programming is adaptive, in a situation where a mismatch between the early prenatal and the postnatal environments occurs, maladaptive consequences such as obesity may become prevalent (7). Intriguingly, neonatal leptin treatment reverses such programming in rats (33). The programming of leptin secretion, a hormone involved in the signaling of energy stores to central regulators, is a possible mechanism by which early life insults lead to increased risk for metabolic diseases in adulthood. Because this hormone is also related to appetite regulation and taste perception (34), altered leptin secretion could be involved in the establishment of feeding preferences in subjects who have suffered IUGR, leading to obesity and metabolic syndrome in later life.

The analysis of specific foods reveals that the effect of severe IUGR in increasing carbohydrate and decreasing pro-

tein consumption is distributed across different types of foods and is not because of the over or under consumption of any one food. This is important, because one could expect less meat and more bread intake in poorer families where IUGR would be more prevalent. Therefore, our findings are probably not related to SES but to a genuine preference in this group. The mean caloric intake from sweet foods was similar, but it is important to note that these foods are a mixture of different types of carbohydrates, protein, and fat. As with any dietary assessment tool, there are limitations to the use of our food frequency questionnaire. No questionnaire will retrieve unique aspects of dietary data unless it is designed to specifically assess them, and in this study, the focus was to classify individuals according to their preferred macronutrient class.

Shultis *et al.* (35) described associations between birth weight and the consumption of macronutrients in childhood that did not persist after gestational age and social variables were accounted for, except a negative association between birth weight and saturated fat intake at 43 mo of age. At this age, food intake is still very much influenced by parental behavior (36), and parents of low-birth weight children feed their babies differently to encourage them to grow larger (37). The same study did not find effects of low birth weight on feeding preferences at 7 y of age. In our study, we show that IUGR is associated with spontaneous macronutrient choices in adulthood, leading to increased carbohydrate and decreased protein consumption. It is possible that these preferences establish only after puberty, needing a specific hormonal milieu and/or fat distribution to be expressed. This hypothesis deserves further investigation, but is in accordance to our findings in rats (38).

The prevalence of metabolic syndrome was not different between the groups in this study. However, our sample is young and does not exclude the possibility that food choices in the growth restricted group would finally lead to an altered biochemical profile after a longer period of time. It may be that the differences in food preferences precede the establish-

ment of metabolic syndrome, predisposing the IUGR individuals to be more likely to develop metabolic syndrome. Although the prevalence of metabolic syndrome may appear high for the age group, studies conducted on different populations reveal a high prevalence of metabolic syndrome depending on the criterion used, with rates ranging from 12.4% to 28.5% among men and from 10.7% to 40.5% among women (39). A recent Brazilian study using national survey statistics (40) demonstrates a prevalence and gender distribution of overweight and obesity similar to our sample.

Recent data indicate that higher dietary glycemic load, because of replacing fats with carbohydrates or increasing the intake of rapidly absorbed sugars, predicts greater coronary heart disease risk (41). Physiologic hyperglycemia induces overproduction of superoxide by the mitochondrial electron-transport chain, resulting in inflammatory responses and endothelial dysfunction (42). Studies in overweight women have shown that diets with a decreased carbohydrate to protein ratio have positive effects on body composition, blood lipids, and glucose homeostasis (43,44). Therefore, the spontaneous preference for carbohydrates instead of protein, especially in the population of IUGR individuals, may play a role in the increased risk for metabolic disease largely reported in this group.

Our main finding was evident only in women. Importantly, women are more prone to eating disturbances; therefore, it is possible that the preference is clearer and/or appears earlier in women than in men. Although the effect size may appear small, when considering lifestyle variation and food consumption, even small but chronic increases in the intake of specific macronutrients could impact health. For instance, a higher spontaneous carbohydrate intake is associated with an increased risk for hemorrhagic stroke in women (45). Other studies have found that women are less physically active than men, as reported in our sample (46–48). Because our assessment is based in an overall estimation (including activity during work hours), this was expected because men are more likely to be enrolled in jobs requiring physical strength.

Some other limitations should be taken into consideration. The small number of IUGR individuals could underestimate the effect of IUGR on food consumption, particularly in men. Lack of precision in food questionnaires could lead to an underestimation of the proportion of protein in the diet and an overestimation of carbohydrate intake (49). However, in this case, the entire sample would be subjected to this same limitation. The food frequency questionnaire is based on usual dietary patterns and could reflect availability and convenience rather than actual preferences. In addition, the low SES associated with IUGR could play a role in feeding habits, because foods rich in carbohydrates are usually less expensive than protein. Our results though persisted even after controlling for such variables. Moreover, recent research shows that evaluations of habitual consumption using food frequency questionnaires correlate well with the actual preference for certain foods (50).

We did not collect data on breastfeeding during the neonatal period. Reliability of breastfeeding retrospectively collected data, especially in long-term follow-up studies is debatable

(51,52). Although some studies report a protective effect of breastfeeding against obesity in childhood (53), it is not known if these findings persist to later ages (54,55). The same is true for the influence of breastfeeding in food neophobia (56), reported in children but remaining to be investigated in adulthood. Therefore, we think that, if any, the impact of this variable in our findings is subtle.

In conclusion, we propose that an alteration in feeding preferences such as the increased preference for carbohydrate consumption associated with severe IUGR in women may further increase the risk for cardiovascular and metabolic diseases among these individuals. The quality of the fetal environment is thus associated with specific eating preferences in adulthood, and a chronic consumption of hyper palatable foods could contribute to the development of obesity and related disorders in IUGR individuals.

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