Appetite 120 (2018) 596–601

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Fetal growth interacts with multilocus genetic score reflecting dopamine signaling capacity to predict spontaneous sugar intake in children

Patrícia P. Silveira [a, b, c, *], Irina Pokhvisneva [a], Hélène Gaudreau [a], Leslie Atkinson [d], Alison S. Fleming [e], Marla B. Sokolowski [f], Meir Steiner [g], James L. Kennedy [h], Laurette Dubé [i], Robert D. Levitan [h], Michael J. Meaney [a, b, c], on behalf of the MAVAN research team

[a] Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University, Douglas Mental Health University Institute, Montreal, Quebec, Canada
[b] Sackler Program for Epigenetics & Psychobiology at McGill University, Montreal, Quebec, Canada
[c] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[d] Ryerson University, Toronto, Ontario, Canada
[e] Department of Psychology, University of Toronto, Toronto, ON, Canada
[f] Department of Ecology and Evolutionary Biology, University of Toronto, Toronto, ON, Canada
[g] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
[h] Department of Psychiatry, University of Toronto and Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[i] Desautels Faculty of Management, McGill Center for the Convergence of Health and Economics, McGill University, Montreal, Quebec, Canada

ARTICLE INFO

Article history:
Received 14 July 2017
Received in revised form
5 October 2017
Accepted 12 October 2017
Available online 14 October 2017

Keywords:
IUGR
Dopamine
Multilocus score
Palatable food intake

ABSTRACT

Background: We have shown that intrauterine growth restriction (IUGR) leads to increased preference for palatable foods at different ages in both humans and rodents. In IUGR rodents, altered striatal dopamine signaling associates with a preference for palatable foods.
Objectives: Our aim was to investigate if a multilocus genetic score reflecting dopamine-signaling capacity is differently associated with spontaneous palatable food intake in children according to the fetal growth status.
Methods: 192 four-year old children from a community sample from Montreal and Hamilton, Canada, were classified according to birth weight and administered a snack test meal containing regular as well as palatable foods. Intrauterine growth restriction was based on the birth weight ratio below 0.85; children were genotyped for polymorphisms associated with dopamine (DA) signaling, with the hypofunctional variants (TaqIA-A1 allele, DRD2-141C Ins/Ins, DRD4 7-repeat, DAT1-10-repeat, Met/Met-COMT) receiving the lowest scores, and a composite score was calculated reflecting the total number of the five genotypes. Macronutrient intake during the Snack Test was the outcome.
Results: Adjusting for z-score BMI at 48 months and sex, there was a significant interaction of the genetic profile and fetal growth on sugar intake [$\hat{\beta} = -4.56$, $p = 0.04$], showing a positive association between the genetic score and sugar intake in IUGR children, and no association in non-IUGR children. No significant interactions were seen in other macronutrients.
Conclusions: Variations in a genetic score reflecting DA signaling are associated with differences in sugar intake only in IUGR children, suggesting that DA function is involved in this behavioral feature in these children. This may have important implications for obesity prevention in this population.

1. Introduction

Intrauterine growth restriction (IUGR) refers to a situation in which the fetus does not reach its full growth potential during

* Corresponding author. Department of Psychiatry, McGill University, Montreal, Quebec H4H 1R3, Canada.
E-mail address: patricia.silveira@mcgill.ca (P.P. Silveira).

https://doi.org/10.1016/j.appet.2017.10.021
0195-6663/

pregnancy (Chatelain, 2000). IUGR results from placental dysfunction, which occurs in many prevalent conditions during gestation such as infections, hypertension, drug and tobacco exposure, as well as under or over nutrition (Nohr et al., 2005). The prevalence of IUGR is constant worldwide, affecting 7–15% of all births independent of regional economic development (Organization, 2004).

Epidemiological studies show that impaired fetal growth reflected in low birth weight is associated with increased risk for cardiovascular disease (Barker, Winter, Osmond, Margetts, & Simmonds, 1989; C. E.; Stein et al., 1996), type II diabetes (Hales & Barker, 1992; Phipps et al., 1993), and increased adiposity (Bettiol et al., 2007; Ravelli, Stein, & Susser, 1976) in adulthood. We and others provided evidence suggesting that IUGR individuals have altered food preferences from early infancy until adult age, favoring the intake of palatable foods that are rich in sugar and/or fat (Ayres et al., 2012; Barbieri et al., 2009; Lussana et al., 2008). This "thrifty-eating" phenotype could contribute to the development of chronic metabolic dysfunction.

A potential mechanism linking prenatal growth with altered eating and postnatal metabolic risk is changes in the central nervous system circuitry that underlie palatable food intake. The overconsumption of palatable or 'rewarding' foods likely reflects an imbalance in the relative importance of hedonic versus homeostatic signals (Egecioglu et al., 2011). Central to the neurobiology of the hedonic mechanisms is the mesolimbic dopamine (DA) system, which receives and integrates information related to both hedonic and homeostatic food stimuli (Murray, Tulloch, Gold, & Avena, 2014).

We have shown that dopamine-related behaviors such as impulsivity (Silveira et al., 2012) and poor inhibitory control (Reis et al., 2015; Reis et al., 2016) are important moderators of the association between IUGR and altered eating in children and adolescents. We also demonstrated that differential dopamine signaling in cortical and striatal regions is implicated in the specific adult food preferences associated with IUGR in rodents (Alves, Dalle Molle, Desai, Ross, & Silveira, 2015; Dalle Molle et al., 2015). Based on these various findings, we hypothesized that the exposure to an adverse environment culminating in IUGR moderates the association between a multilocus genetic score reflecting dopamine functioning and the consumption of palatable foods (sugar and/or fat) in preschool children.

2. Material and methods

2.1. General method

We used data from an established prospective birth cohort (Maternal Adversity, Vulnerability and Neurodevelopment - MAVAN) (O'Donnell et al., 2014). The study sample included 4-year old children from Montreal (Quebec) and Hamilton (Ontario), Canada. Eligibility criteria for mothers included age ≥18 years old, singleton pregnancy, and fluency in French or English. Mothers were excluded from the study if they had severe chronic illness, placenta previa, a history of incompetent cervix, impending delivery, or had a fetus/infant born at gestational age <37 weeks or born with a major anomaly. Birth records were obtained directly from the birthing units. Dyads were assessed longitudinally, with multiple assessments of both mother and child in home and laboratory across the child's development. Approval for the MAVAN project was obtained from obstetricians performing deliveries at the study hospitals and by the institutional review boards at hospitals and university affiliates: McGill University, l'Université de Montréal, the Royal Victoria Hospital, Jewish General Hospital, Centre Hopitalier de l'Université de Montréal, Hôpital Maisonneuve-Rosemont, St Joseph's Hospital, and McMaster University. Informed consent was obtained from the parents/guardians of the participants.

At 4 years of age children came to the laboratory for various food-related tasks, and their standing height, without shoes, was measured (to the nearest 0.1 cm) with the use of a stadiometer (Perspective Enterprises, PE-AIM-101, Portage, Michigan). Body weight, in light clothing, was measured (to the nearest 0.1 kg) with the use of a digital floor scale (TANITA BF625, Arlington Heights, Illinois). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). We calculated the z-scores for BMI at 48 months according to World Health Organization (WHO) standards (WHO, 2006).

2.2. Fetal growth restriction definition

The definition of IUGR was based on the birth weight ratio (BWR), namely, the ratio between the birth weight and the sex-specific mean birth weight for each gestational age for the local population (Kramer et al., 2001). A BWR of <0.85 was classified as IUGR (Kramer, Platt, Yang, McNamara, & Usher, 1999).

2.3. Snack test

Children and mothers were offered a test meal at approximately 10:30 a.m. including different types of foods in pre-weighed portions for 30 min: Frosted Flakes® (Kellogg's), sliced apple, muffin with chocolate drops, 3.25% milk, maple syrup flavored baked beans, croissant, cooked egg, cheddar cheese, All Bran® (Kellogg's), white bread, orange juice (Levitan et al., 2015; Silveira et al., 2014). Pre-weighed plates of the different foods were displayed in a buffet to which the child had total access. At the end of the session, the remaining foods were weighed again to measure the intake. Foods were chosen with the assistance of a nutritionist to represent local habitual snack items and to have similar colours (Addessi, Galloway, Visalberghi, & Birch, 2005). Mothers were instructed to offer a light breakfast to participants at home beforehand and not to share plates or influence the children's choices. Based on the nutritional content of each food and the amount eaten, we calculated the amount of fat, carbohydrates and protein ingested (Vozzo et al., 2003). The test meal was eaten in the laboratory, in a 30 m^2 room. A table with two sets of plates was placed in the center of the room, with chairs for mother and child on both sides (facing each other). A cushion was placed on the child's chair to facilitate accessibility of the different foods. Various efforts were made to standardize this procedure between subjects.

2.4. Genetic data and multilocus score definition

Saliva samples were collected and genotyping of the DNA was performed blind to the children's behavior and phenotype. The five polymorphisms, later used to create the multilocus genetic score, ANKK1/DRD2 markers (rs1800497 [Taq1A]), COMT Val158Met (rs4680) SNP, DRD2 (rs1799732 [−141delC]), DAT1 and DRD4 VNTRs were amplified with polymerase chain reaction (PCR) techniques with primers and conditions previously described (Davis et al., 2013). The construction of the multilocus genetic score was based on the biological functions described in the literature and on the approach proposed by Stice et al. (Stice, Yokum, Burger, Epstein, & Smolen, 2012), who showed that this multilocus genetic composite is positively correlated with the degree of activation of different brain regions in response to milkshake intake in contrast to a tasteless solution receipt. In this score, genotypes associated with putatively low DA signaling received a score of 0; those associated with putatively high DA signaling received a score of 1;

intermediate heterozygotes received a score of 0.5. Specifically, TaqIA A1/A1 (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991), DRD2-141C Ins/Ins carriers (Jonsson et al., 1999), DRD4-7 repeat carriers (Asghari et al., 1995), DAT1 10R/10R (Mill, Asherson, Browes, D'Souza, & Craig, 2002), and COMT Met/Met (Lachman et al., 1996) genotypes were assigned a score of 0 ("low"); TaqIA A2/A2, DRD2-141C Del/Del carriers, DRD4 non 7-repeat carriers, DAT1 9/9 carriers, and COMT Val/Val genotypes were assigned a score of 1 ("high"), and DRD2-141C Ins/Del, TaqIA A1/A2, DAT 1 9/10 and COMT Met/Val genotypes received a score of 0.5. The scores were then summed to create a multilocus composite.

2.5. Statistical analysis

Statistical analysis of the baseline characteristics was performed using Student's t-test for continuous data and chi-square test for categorical variables. A series of linear regression models were performed to investigate the association between fetal growth and the multilocus score as independent variables on the intake of the different macronutrients during the Snack Test, adjusting for BMI at the time of the test and sex. IUGR was analyzed as a categorical variable (normal birth weight or IUGR). Additional analyses were performed adjusting for ethnicity (children classified as Caucasians and non-Caucasians). Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 22.0 software (SPSS Inc., Chicago, IL, USA). Significance levels for all measures were set at $p < 0.05$.

3. Results

One hundred and ninety-two 48-month-old children were classified as IUGR or normal birth weight. Children born IUGR or non-IUGR did not differ in many confounders as can be seen in Table 1. Genotype distribution for each gene is depicted in Table 2. Hardy-Weinberg equilibrium criteria were met in all cases, except for DRD4 7-repeat ($p = 0.04$).

As seen in Table 3, a linear regression analysis showed a significant interaction between IUGR status and the multilocus score for sugars intake [$\widehat{\beta} = -4.56$, $p = 0.04$] during the Snack Test. The effect was specific for sugars as there were no significant interactions observed between IUGR status and the multilocus score for complex carbohydrates [$\widehat{\beta} = -2.62$, $p = 0.20$], fiber [$\widehat{\beta} = -0.39$, $p = 0.19$], protein [$\widehat{\beta} = -0.72$, $p = 0.55$] or fat [$\widehat{\beta} = -0.37$, $p = 0.82$]. Simple slopes analysis showed that in the IUGR group there was a positive relationship between the multilocus score (DA signaling genotype score) and the intake of sugars [$\widehat{\beta} = 4.01$, $p = 0.04$]. In other words, variations in dopamine signaling capacity were associated with differences in the consumption of sugars in IUGR children only. There was no significant effect of the dopamine multilocus genetic score on sugars intake in non-IUGR children [$\widehat{\beta} = -0.54$, $p = 0.60$], Fig. 1 A.

Fig. 1B depicts the data for total calories consumed during the Snack Test in IUGR and non-IUGR children. Although there were no significant interactions between IUGR and the multilocus genetic score on total caloric intake as seen in Table 3 [$\widehat{\beta} = -35.82$, $p = 0.21$], the graph suggests the existence of one outlier in the IUGR group with low multilocus score/high sugar intake. We performed a diagnostic check to see if this observation would have an impact on the regression coefficients, using a measure of influence, DFBETAS, which characterized it as an influential point. When excluding this subject from the analysis, the interaction between IUGR status and the genetic score became significant for total caloric consumption ($\widehat{\beta}=-58.38$, $p = 0.04$), and remained significant for sugars ($\widehat{\beta} = -6.17$, $p < 0.01$), but not for complex carbohydrates ($\widehat{\beta}=-3.70$, $p = 0.08$), fiber ($\widehat{\beta}=-0.49$, $p = 0.11$), protein ($\widehat{\beta}=-1.51$, $p = 0.22$), or fat ($\widehat{\beta}=-1.24$, $p = 0.46$).

We also repeated the analysis adjusting for ethnicity. The results were similar to the previously described: the interaction between IUGR and the genetic score remained significant for sugars ($\widehat{\beta}=-5.42$, $p = 0.03$), but not for total caloric consumption ($\widehat{\beta}=-32.58$, $p = 0.32$), for complex carbohydrates ($\widehat{\beta}=-2.29$, $p = 0.32$), fiber ($\widehat{\beta}=-0.27$, $p = 0.45$), protein ($\widehat{\beta}=-0.22$, $p = 0.88$), or fat ($\widehat{\beta}=0.04$, $p = 0.98$).

IUGR and non-IUGR children did not differ in the consumption of the different macronutrients as shown in Table 4.

4. Discussion

We showed here an interaction between fetal growth and a dopamine multilocus genetic score, suggesting that variation in the dopamine signaling capacity is positively correlated to spontaneous sugar intake in IUGR children at 48 months of age. This is in agreement to our study in rodents (Dalle Molle et al., 2015), in which altered levels of accumbal D2 receptors accompanied the increased preference for palatable foods in IUGR rats. Additionally, positron emission tomography studies show that the availability of striatal dopamine D2 receptor is decreased in obese individuals (Wang et al., 2001). Brain fMRI studies demonstrate that individuals with elevated multilocus composite scores show less activation in the striatum in response to monetary reward (Nikolova, Ferrell, Manuck, & Hariri, 2011; Stice et al., 2012). Moreover, a higher multilocus score is associated with food addiction, binge eating, food cravings and emotional overeating (Davis et al., 2013).

IUGR persistently affects the functioning of neuroendocrine axis such as the hypothalamic-pituitary-adrenal (HPA) axis (Osterholm, Hostinar, & Gunnar, 2012), as well as the sensitivity to insulin (Hales & Barker, 1992) and leptin (Desai, Gayle, Han, & Ross, 2007), and these hormones are known modulators of the mesolimbic dopaminergic system (Murray et al., 2014; Rouge-Pont, Deroche, Le Moal, & Piazza, 1998). For instance, variations in the HPA responsivity to acute stress influence palatable food intake in women (Epel, Lapidus, McEwen, & Brownell, 2001). Insulin sensitivity is

Table 1
Description of the baseline characteristics of the sample.

Sample characteristics	non-IUGR (n = 155)	IUGR (n = 37)	p-values
Females (%)[b]	50% (77)	51% (19)	0.85
Maternal age at birth (y) [a]	30.8 (4.6)	29.5 (4.9)	0.15
Maternal smoking during gestation (%)[b]	10% (14)	24% (7)	0.06
Maternal education below 10 years of schooling (%)[b]	3% (5)	6% (2)	0.62
Family income below LICO (%)[b]	16% (23)	17% (6)	0.95
Total duration of breastfeeding (weeks)[a]	29 (19)	28 (20)	0.74

Study participants' baseline characteristics according to IUGR status.
[a]Student's t-test and [b]chi-square test. Data are expressed as mean (standard deviation), or proportions (percentages).
LICO = Low Income Cut Off. Differences between IUGR and non-IUGR groups were not significant for all variables shown (all p-values >0.05).

Table 2
Genotype distribution in the study sample.

Gene		H-W equilibrium
DAT1 VNTR	10/10 (104, 54.2%); 9/10 (73, 38%); 9/9 (15, 7.8%)	p = 0.66
DRD2 141C (rs1799732) BstNI	Ins/Ins (142, 74%); Ins/Del (46, 24%); Del/Del (4, 2.1%).	p = 0.90
DRD4 VNTR	7R homozygous (4, 2.08%); 7R heterozygous (74, 38.5%); non-7R/non-7R (114, 59.4%)	p = 0.04
Taq IA (rs1800497)	A1/A1 (10, 5.2%); A1/A2 (55, 28.6%); A2/A2 (127, 66.1%)	p = 0.22
COMT (rs4680)	A/A (49, 25.5%); A/G (92, 47.9%); G/G (51, 26.6%)	p = 0.56

Criteria for Hardy Weinberg Equilibrium were met for all genes except for DRD4 VNTR.

Table 3
Estimated beta coefficients for analyses of different macronutrients consumption.

Macronutrients		$\widehat{\beta}$	p-values
Total calories consumption	z-BMI 48m	25.60	<0.01
	IUGR status	101.69	0.16
	Sex	45.91	0.01
	Multilocus score	23.35	0.35
	IUGR status x Multilocus score	−35.82	0.21
Sugar consumption (g)	z-BMI 48m	1.72	<0.01
	IUGR status	11.83	0.04
	Sex	4.60	<0.01
	Multilocus score	4.01	0.04
	IUGR status x Multilocus score	−4.56	0.04
Complex carbohydrates consumption (g)	z-BMI 48m	1.31	0.02
	IUGR status	6.34	0.22
	Sex	2.24	0.08
	Multilocus score	0.81	0.65
	IUGR status x Multilocus score	−2.62	0.20
Fiber consumption (g)	z-BMI 48m	0.06	0.48
	IUGR status	0.93	0.22
	Sex	0.26	0.16
	Multilocus score	0.29	0.26
	IUGR status x Multilocus score	−0.39	0.19
Fat consumption (g)	z-BMI 48m	1.07	0.02
	IUGR status	1.71	0.68
	Sex	1.49	0.14
	Multilocus score	0.03	0.98
	IUGR status x Multilocus score	−0.37	0.82
Protein consumption (g)	z-BMI 48m	0.80	0.02
	IUGR status	2.45	0.43
	Sex	0.98	0.20
	Multilocus score	0.73	0.50
	IUGR status x Multilocus score	−0.72	0.55

The baseline on the analysis was the IUGR group and female sex.

inversely associated with activation in the anterior cingulate, insula, orbitofrontal cortex and the frontal and rolandic operculum in response to palatable food cues in children (Adam et al., 2015). It has been shown that while mild hypoglycemia activates limbic-striatal brain regions in response to food cues to produce a greater desire for high-calorie foods, euglycemia activates the medial prefrontal cortex and decreases interest in food stimuli (Page et al., 2011). Therefore, it makes sense that variations in the sensitivity to glucocorticoids and insulin associated with fetal programming interact with the mesocorticolimbic response to palatable foods, consequently affecting intake as seen in the current study. In agreement with previous findings (Barbieri et al., 2009), we show here once more that the link between low birth weight and increased palatable food intake occurs before obesity emerges, and therefore is not secondary to its consequent metabolic disarrangements; these subtle nutritional differences may in fact mediate the development of adiposity in IUGR individuals, as proposed before (Portella et al., 2012; Portella & Silveira, 2014; Silveira et al., 2012).

With regard to the specificity to sugar, as mentioned above, it is in agreement to our previous data (Barbieri et al., 2009). However, other studies have found associations between low birth weight and other types of preference. For instance, studies of the Dutch famine have shown preference towards fats in older adults whose mothers were exposed to the famine (Lussana et al., 2008; A. D.; Stein, Rundle, Wada, Goldbohm, & Lumey, 2009). *Perälä et al* had similar findings, with a positive correlation of small size at birth and increased consumption of fats, as well as a lower intake of carbohydrates, sucrose, fructose, fiber and fruits in adults of 56–70 years old (Perälä et al., 2012). In a different sample, *Kaseva et al* demonstrate a higher intake of polyunsaturated fatty acids and essential fatty acids, and reduced use of vegetables, fruits, and milk products in very low birth weight at 19–27 years of age (Kaseva et al., 2013). It seems to us that despite the apparent discrepant food preferences described in the several studies, we should consider that these were performed at different ages and using diverse tools (questionnaires, food diaries and actual consumption, as in the current work). All of these variables may explain the differences (for instance, food preferences change as the individuals age) (Cooke & Wardle, 2005); in addition, all studies seem to

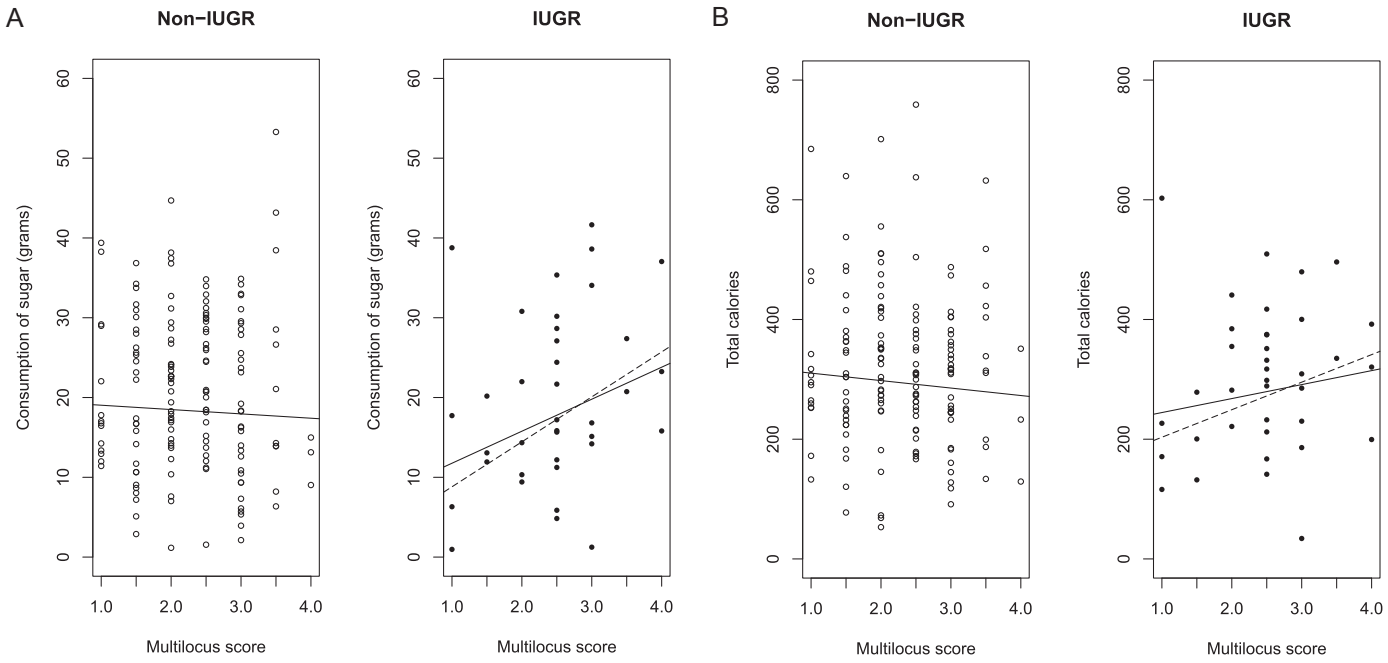

Fig. 1. Association between the multilocus score and sugars (A) and calories (B) intake in IUGR and non-IUGR children. Variation in the genetic score is associated with different sugar intake only in IUGR children. Dotted line represents the regression line when excluding an influential observation (see text for details). The predicted values for sugar consumption and total calories consumption were shown for females and z-BMI at 48 months = 0.54.

Table 4
Consumption of the different macronutrients by IUGR and non-IUGR children.

		Non-IUGR	IUGR	p-values
Total calories		318 (127)	300 (122)	0.44
Carbohydrates	Total (g)	37 (17)	36 (18)	0.70
	Total (%)	48 (15)	48 (14)	0.93
	Sugars (g)	21 (10)	20 (11)	0.63
	Sugars (%)	27 (11)	26 (10)	0.69
	Complex (g)	15 (9)	14 (9)	0.84
	Complex (%)	19 (8)	19 (9)	0.56
	Fiber (g)	2 (1)	2 (1)	0.99
	Fiber (%)	2 (2)	2 (2)	0.69
Fat	Total (g)	13 (7)	12 (6)	0.46
	Total (%)	37 (11)	37 (11)	0.95
Protein	Total (g)	12 (5)	11 (4)	0.45
	Total (%)	15 (4)	15 (3)	0.81

Data displayed as means (standard deviations). No significant differences in consumption were seen between the groups.

converge to an increased intake of palatable foods (sugar and/or fats) in IUGR children (Portella & Silveira, 2014).

This study reinforces the idea that IUGR associates with persistent alterations in the brain circuitry related to palatable food intake and energy expenditure (Alves et al., 2015; Cunha Fda et al., 2015; Dalle Molle et al., 2015). The importance of the current findings resides on the early identification of vulnerability to increased adiposity and its metabolic consequences, prompting the proposal of preventive measures and careful consideration of food preferences in these children in early pediatric care.

Conflicts of interest

The authors have nothing to disclose.

Acknowledgements

Authors contributions: conception or design of the work PPS, RDL, MJM; data collection: HG, MS, JLK, MJM; data analysis and interpretation: PPS, IP, LA, RDL, LD, MJM; drafting the article PPS, IP, RDL, MJM; critical revision of the article LA, ASF, MBS; final approval of the version to be published: PPS, IP, HG, LA, ASF, MBS, MS, JLK, LD, RDL, MJM.

This work was funded by the Toxic Stress Research network of the JPB Foundation. The MAVAN Cohort was funded by the Canadian Institutes for Health Research, the Ludmer Family Foundation, the Norlien Foundation (Calgary, Canada), the WOCO Foundation (London, Canada), the Blema & Arnold Steinberg Family Foundation, and the Faculty of Medicine of McGill University. Additional funding was provided by the Jacobs Foundation (Switzerland). We thank the MAVAN study group and all staff. The voluntary participation of all participants is greatly appreciated.

References

Adam, T. C., Tsao, S., Page, K. A., Hu, H., Hasson, R. E., & Goran, M. I. (2015). Insulin sensitivity and brain reward activation in overweight hispanic girls: A pilot study. *Pediatric Obesity, 10*, 30–36.

Addessi, E., Galloway, A. T., Visalberghi, E., & Birch, L. L. (2005). Specific social

influences on the acceptance of novel foods in 2-5-year-old children. *Appetite, 45*, 264–271.
Alves, M. B., Dalle Molle, R., Desai, M., Ross, M. G., & Silveira, P. P. (2015). Increased palatable food intake and response to food cues in intrauterine growth-restricted rats are related to tyrosine hydroxylase content in the orbitofrontal cortex and nucleus accumbens. *Behavavioural Brain Research, 287*, 73–81.
Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., & Van Tol, H. H. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry, 65*, 1157–1165.
Ayres, C., Agranonik, M., Portella, A. K., Filion, F., Johnston, C. C., & Silveira, P. P. (2012). Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. *International Journal of Pediatrics, 2012*, 657379.
Barbieri, M. A., Portella, A. K., Silveira, P. P., Bettiol, H., Agranonik, M., Silva, A. A., et al. (2009). Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. *Pediatric Research, 65*, 215–220.
Barker, D. J. P., Winter, P. D., Osmond, C., Margetts, B., & Simmonds, S. J. (1989). Weight in infancy and death from ischemic heart-disease. *Lancet, 2*, 577–580.
Bettiol, H., Sabbag, D., Haeffner, L. S. B., Barbieri, M. A., Silva, A. A. M., Portella, A., et al. (2007). Do intrauterine growth restriction and overweight at primary school age increase the risk of elevated body mass index in young adults? *Brazilian Journal of Medical and Biological Research, 40*, 1237–1243.
Chatelain, P. (2000). Children born with intra-uterine growth retardation (IUGR) or small for gestational age (SGA): Long term growth and metabolic consequences. *Endocrine Regulations, 34*, 33–36.
Cooke, L. J., & Wardle, J. (2005). Age and gender differences in children's food preferences. *British Journal of Nutrition, 93*, 741–746.
Cunha Fda, S., Dalle Molle, R., Portella, A. K., Benetti Cda, S., Noschang, C., Goldani, M. Z., et al. (2015). Both food restriction and high-fat diet during gestation induce low birth weight and altered physical activity in adult rat Offspring: The “similarities in the inequalities” model. *PLoS One, 10*, e0118586.
Dalle Molle, R., Laureano, D. P., Alves, M. B., Reis, T. M., Desai, M., Ross, M. G., et al. (2015). Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. *Brain Research, 1618*, 41–49.
Davis, C., Loxton, N. J., Levitan, R. D., Kaplan, A. S., Carter, J. C., & Kennedy, J. L. (2013). 'Food addiction' and its association with a dopaminergic multilocus genetic profile. *Physiology and Behavior, 118*, 63–69.
Desai, M., Gayle, D., Han, G., & Ross, M. G. (2007). Programmed hyperphagia due to reduced anorexigenic mechanisms in intrauterine growth-restricted offspring. *Reproductive Sciences, 14*, 329–337.
Egecioglu, E., Skibicka, K. P., Hansson, C., Alvarez-Crespo, M., Friberg, P. A., Jerlhag, E., et al. (2011). Hedonic and incentive signals for body weight control. *Reviews in Endocrine & Metabolic Disorders, 12*, 141–151.
Epel, E., Lapidus, R., McEwen, B., & Brownell, K. (2001). Stress may add bite to appetite in women: A laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology, 26*, 37–49.
Hales, C. N., & Barker, D. J. (1992). Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. *Diabetologia, 35*, 595–601.
Jonsson, E. G., Nothen, M. M., Grunhage, F., Farde, L., Nakashima, Y., Propping, P., et al. (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry, 4*, 290–296.
Kaseva, N., Wehkalampi, K., Hemiö, K., Hovi, P., Järvenpää, A. L., Andersson, S., et al. (2013). Diet and nutrient intake in young adults born preterm at very low birth weight. *Journal of Pediatrics, 163*, 43–48.
Kramer, M. S., Platt, R. W., Wen, S. W., Joseph, K. S., Allen, A., Abrahamowicz, M., et al., Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance, S. (2001). A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics, 108*, E35.
Kramer, M. S., Platt, R., Yang, H., McNamara, H., & Usher, R. H. (1999). Are all growth-restricted newborns created equal(ly)? *Pediatrics, 103*, 599–602.
Lachman, H. M., Papolos, D. F., Saito, T., Yu, Y. M., Szumlanski, C. L., & Weinshilboum, R. M. (1996). Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics, 6*, 243–250.
Levitan, R. D., Rivera, J., Silveira, P. P., Steiner, M., Gaudreau, H., Hamilton, J., et al. (2015). Gender differences in the association between stop-signal reaction times, body mass indices and/or spontaneous food intake in pre-school children: An early model of compromised inhibitory control and obesity. *International Journal of Obesity, 39*, 614–619.
Lussana, F., Painter, R. C., Ocke, M. C., Buller, H. R., Bossuyt, P. M., & Roseboom, T. J. (2008). Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. *American Journal of Clinical Nutrition, 88*, 1648–1652.
Mill, J., Asherson, P., Browes, C., D'Souza, U., & Craig, I. (2002). Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *American Journal of Medical Genetics, 114*, 975–979.
Murray, S., Tulloch, A., Gold, M. S., & Avena, N. M. (2014). Hormonal and neural mechanisms of food reward, eating behaviour and obesity. *Nature Reviews Endocrinology, 10*, 540–552.
Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology, 36*, 1940–1947.
Noble, E. P., Blum, K., Ritchie, T., Montgomery, A., & Sheridan, P. J. (1991). Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Archives of General Psychiatry, 48*, 648–654.
Nohr, E. A., Bech, B. H., Davies, M. J., Frydenberg, M., Henriksen, T. B., & Olsen, J. (2005). Prepregnancy obesity and fetal death - a study within the Danish National Birth Cohort. *Obstetrics and Gynecology, 106*, 250–259.
O'Donnell, K. G.,H., Colalillo, S., Steiner, M., Atkinson, L., Moss, E., Karama, S., et al. (2014). The maternal adversity vulnerability and neurodevelopment (MAVAN) Project: Theory and methodology. *Canadian Journal of Psychiatry, 59*, 497–508.
Organization, U. N. C. s. F. a. W. H. (2004). *Low Birthweight: Country, regional and global estimates*. New York: UNICEF.
Osterholm, E. A., Hostinar, C. E., & Gunnar, M. R. (2012). Alterations in stress responses of the hypothalamic-pituitary-adrenal axis in small for gestational age infants. *Psychoneuroendocrinology, 37*, 1719–1725.
Page, K. A., Seo, D., Belfort-DeAguiar, R., Lacadie, C., Dzuira, J., Naik, S., et al. (2011). Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. *Journal of Clinical Investigation, 121*, 4161–4169.
Perälä, M. M., Männistö, S., Kaartinen, N. E., Kajantie, E., Osmond, C., Barker, D. J., et al. (2012). Body size at birth is associated with food and nutrient intake in adulthood. *PLoS One, 7*, e46139.
Phipps, K., Barker, D. J., Hales, C. N., Fall, C. H., Osmond, C., & Clark, P. M. (1993). Fetal growth and impaired glucose tolerance in men and women. *Diabetologia, 36*, 225–228.
Portella, A. K., Kajantie, E., Hovi, P., Desai, M., Ross, M. G., Goldani, M. Z., et al. (2012). Effects of in utero conditions on adult feeding preferences. *Journal of Developmental Origins of Health and Disease, 3*, 140–152.
Portella, A. K., & Silveira, P. P. (2014). Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. *Annals of the New York Academy of Sciences, 1331*, 15–33.
Ravelli, G. P., Stein, Z. A., & Susser, M. W. (1976). Obesity in young men after famine exposure in utero and early infancy. *New England Journal of Medicine, 295*, 349–353.
Reis, R. S., Bernardi, J. R., Steiner, M., Meaney, M. J., Levitan, R. D., & Silveira, P. P. (2015). Poor infant inhibitory control predicts food fussiness in childhood – a possible protective role of n-3 PUFAs for vulnerable children. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA), 97*, 21–25.
Reis, R. S., Dalle Molle, R., Machado, T. D., Mucellini, A. B., Rodrigues, D. M., Bortoluzzi, A., Bigonha, S. M., et al. (2016). Impulsivity-based thrifty eating phenotype and the protective role of n-3 PUFAs intake in adolescents. *Translational Psyhchiatry, 6*, e755.
Rouge-Pont, F., Deroche, V., Le Moal, M., & Piazza, P. V. (1998). Individual differences in stress-induced dopamine release in the nucleus accumbens are influenced by corticosterone. *European Journal of Neurosciences, 10*, 3903–3907.
Silveira, P. P., Agranonik, M., Faras, H., Portella, A. K., Meaney, M. J., Levitan, R. D., et al. (2012). Preliminary evidence for an impulsivity-based thrifty eating phenotype. *Pediatric Research, 71*, 293–298.
Silveira, P. P., Portella, A. K., Kennedy, J. L., Gaudreau, H., Davis, C., Steiner, M., et al. (2014). Association between the seven-repeat allele of the dopamine-4 receptor gene (DRD4) and spontaneous food intake in pre-school children. *Appetite, 73*, 15–22.
Stein, C. E., Fall, C. H. D., Kumaran, K., Osmond, C., Cox, V., & Barker, D. J. P. (1996). Fetal growth and coronary heart disease in South India. *Lancet, 348*, 1269–1273.
Stein, A. D., Rundle, A., Wada, N., Goldbohm, R. A., & Lumey, L. H. (2009). Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 Years differ according to the reference population used. *Journal of Nutrition, 139*, 1555–1561.
Stice, E., Yokum, S., Burger, K., Epstein, L., & Smolen, A. (2012). Multilocus genetic composite reflecting dopamine signaling capacity predicts reward circuitry responsivity. *Journal of Neuroscience, 32*, 10093–10100.
Vozzo, R., Wittert, G., Cocchiaro, C., Tan, W. C., Mudge, J., Fraser, R., et al. (2003). Similar effects of foods high in protein, carbohydrate and fat on subsequent spontaneous food intake in healthy individuals. *Appetite, 40*, 101–107.
Wang, G. J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., et al. (2001). Brain dopamine and obesity. *Lancet, 357*, 354–357.
WHO. (2006). In W. H. Organization (Ed.), *Multicentre Growth Reference Study Group: WHO child growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development* (p. 312). Geneva.