

## BMI gain and insulin resistance among school-aged children: a population-based longitudinal study in the Brazilian Amazon

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### Abstract

Investigation of the determinants of metabolic outcomes associated with non-communicable diseases is increasingly important in developing countries, but such parameters have not been explored extensively during childhood. The present study assessed the impact of weight gain, measured as BMI-for-age Z-scores, on glucose and insulin concentrations, homeostasis model assessment index of insulin resistance (HOMA-IR) values, and systolic and diastolic blood pressure during school years among Amazonian children. A population-based prospective study of 696 children aged >4 to ≤10 years with complete anthropometric information at baseline (51% females and 86% of mixed race) was carried out; 411 children had data on metabolic parameters after a median follow-up period of 2.0 years (range 1.7–2.6 years). During follow-up, there was a significant increase in the proportion of overweight children (BMI-for-age Z-score >1) from 10.1 to 15.8% ( $P=0.003$ ). In linear regression models adjusted for the child's sex, age, race/ethnicity, baseline household wealth, birth weight and pubertal development stage, for each unit of BMI-for-age Z-score variation during follow-up, an increase of 8.58 (95% CI 7.68, 9.60) pmol/l in fasting plasma insulin concentrations and 1.47 (95% CI 1.30, 1.66) in HOMA-IR values was observed. There was no significant impact of weight gain on glucose concentrations and systolic and diastolic blood pressure. In conclusion, we found evidence that an increase in BMI during a 2-year period affected insulin resistance during school years. Considering the significant increase in overweight in this age group, special attention should be paid to monitoring increases in BMI in children from the Brazilian Amazon.

**Key words:** Children: BMI gain: Insulin resistance: Brazilian Amazon

Obesity, diabetes and high blood pressure are among the most significant features of the cardiometabolic disease and risk factor epidemic at the beginning of the twenty-first century<sup>(1)</sup>. Analyses carried out using population-based health surveys highlight the importance of investigating determinants in developing countries, given the critical shift of the mortality burden of non-communicable diseases from developed regions worldwide because of a broad epidemiological transition<sup>(1,2)</sup>.

There is evidence of an association between growth and weight in early life and metabolically compromised parameters. Weight status and visceral adipose tissue have been shown to be associated with insulin resistance since school years in recent cross-sectional studies<sup>(3,4)</sup>. In addition, data from five prospective birth cohort studies carried out in Brazil, Guatemala, India, the Philippines and South Africa indicate a higher likelihood of overweight and elevated blood

pressure among young adults because of a faster relative weight gain after the age of 2 years<sup>(5)</sup>. These studies also indicate that a faster weight gain after 4 years of age is positively associated with glucose intolerance. Insulin resistance in adulthood has been reported to be associated with weight gain from birth to adulthood in India, the Philippines and South Africa<sup>(6)</sup>.

Determinants of such metabolic parameters during childhood have not been explored very extensively, particularly in developing regions, where there is still a lower prevalence of overweight and obesity in the population. In view of the social and health inequalities related to non-communicable diseases, which are greatest among the poor<sup>(7)</sup>, monitoring these parameters could help provide possible interventions before adulthood and optimise healthier outcomes. Therefore, a population-based prospective study was carried out in the Brazilian Amazon to assess the impact of weight gain

**Abbreviations:** HDI, Human Development Index; HOMA-IR, homeostasis model assessment index of insulin resistance.

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on glucose and insulin concentrations, insulin resistance, and systolic and diastolic blood pressure ascertained during school years.

## Experimental methods

### Study population

This longitudinal study was conducted in Acrelândia, a frontier town located 112 km from Rio Branco, the capital of the State of Acre in the Western Brazilian Amazon region. By 2007, the town had 11 520 inhabitants at baseline, of which 44% resided in an urban area, comprising mainly migrants from Southeastern and Southern regions of Brazil engaged in commercial agriculture and cattle farming. According to the Human Development Index (HDI), a summary estimate of the dimensions of health, education and population income, Acrelândia exhibited very low human development in 2000 (HDI: 0.451). By 2010, the town had reached a medium human development level (HDI: 0.604), but, of note, the relative position occupied by Acrelândia by the HDI during that decade dropped from the 3904th to 4055th in a total of 5565 Brazilian municipalities<sup>(8)</sup>. An initial population-based cross-sectional survey of child health and nutrition enrolled a total of 1225 children aged  $\leq 10$  years (98.0% of those eligible for the study)<sup>(9)</sup>. A follow-up assessment was carried out in December 2009 and 909 children of those included at baseline (74.2%) were identified.

The present analyses focused on school-aged children who were  $>4$  to  $\leq 10$  years and had complete anthropometric information in 2007 ( $n$  696; 96.0% of those initially enrolled in this age group). In 2009, these children were invited for a clinical examination for pubertal development evaluation, blood pressure measurement and blood sample collection and also for updating their anthropometric data.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the ethical review board of the School of Public Health, University of São Paulo, Brazil. Written informed consent was obtained from parents or guardians before enrolment.

### Field procedures and laboratory methods

As has been described previously<sup>(9)</sup>, during baseline household interviews with each participant's mother or guardian, information on the child's sex, age, race/ethnicity, nutritional history and recent morbidity was collected. The presence of twelve household assets was determined to generate a wealth index, which was divided into quartiles<sup>(10)</sup>. Maternal characteristics and child's birth weight were recorded as continuous variables, and then they were classified into categories based on the frequency and/or conceptual/biological meaning. Thus, for maternal education, mothers who had completed up to elementary school ( $\leq 4$  years) were compared with those who had completed middle school (5–8 years) or high school or more ( $\geq 9$  years); for maternal age,  $\leq 21$ , 22–34, and  $\geq 35$  year age groups were used.

Birth weights were retrieved from child health cards, and children who were born with a low birth weight ( $\leq 2500$  g) were examined in relation to children of intermediate (2500–3500 g) and higher ( $> 3500$  g) birth weights.

Children's anthropometric measurements were obtained directly by trained research assistants using standardised procedures and calibrated equipment in all study assessments and recorded in duplicate<sup>(11)</sup>. Weight was measured to the nearest 100 g using an electronic scale (Tanita model HS-302), and height was measured to the nearest mm using stadiometers (in 2007 with the Seca model 208 and in 2009 with the WCS (Cardiomed)). BMI was computed as weight (in kg) divided by height (in  $m^2$ ) and was used to calculate BMI-for-age Z-scores using the WHO Child Growth Standards<sup>(12)</sup> for children aged  $\leq 5$  years and the WHO Growth Reference Data for children aged  $> 5$  years<sup>(13)</sup>, with the WHO AnthroPlus software. Children were classified as overweight when BMI-for-age Z-scores  $> 1$ <sup>(13)</sup>.

During clinical examinations in 2009, trained research assistants ascertained pubertal development according to the Tanner stages<sup>(14)</sup> and measured blood pressure after 5 min of rest using an automatic digital device with appropriate cuff sizes. The mean of three measurements of systolic and diastolic blood pressure was used. A sample (5 ml) of fasting venous blood was collected from the children and serum and plasma samples were shipped to São Paulo on dry ice and frozen at  $-70^\circ\text{C}$  until further analysis. Glucose concentrations were determined with the automatic enzymatic method using hexokinase. For children aged  $\geq 10$  years, increased plasma glucose concentrations were defined as glucose concentrations  $\geq 5.55$  mmol/l<sup>(15)</sup>. Insulin concentrations were determined by fluoroimmunoassay, and hyperinsulinaemia was defined as fasting insulin concentrations 90 pmol/l or 120 pmol/l for prepubescent and pubescent children, respectively<sup>(16,17)</sup>. The homeostasis model assessment index of insulin resistance (HOMA-IR) was calculated as insulin (pmol/l)  $\times$  glucose (mmol/l)/135<sup>(18)</sup>. Based on a population-based study among US adolescents, participants with HOMA-IR values  $> 4.39$  were classified as insulin resistant<sup>(19)</sup>.

### Statistical analyses

Outcomes of interest were the metabolic parameters ascertained among the school-aged children in 2009 (systolic and diastolic blood pressure, glucose concentrations, insulin concentrations, and HOMA-IR values). Main exposure was variation in weight gain, measured as differences in BMI-for-age Z-scores from 2007 to 2009 in this age group.

First, the general socio-economic, maternal and child characteristics were compared in each study assessment using the  $\chi^2$  test for categorical variables and the paired  $t$  test for continuous variables. Metabolic parameters were compared by Tanner stages in 2009 with  $t$  test for normally distributed variables and with the Wilcoxon rank-sum test for non-normally distributed variables. Linear regression models were used to estimate the impact of variation in weight gain during follow-up on each of the metabolic parameters. All estimates were initially adjusted in crude

models for baseline BMI-for-age Z-score and child's sex, age and race/ethnicity. Models for systolic and diastolic blood pressure were also adjusted for the child's height at the follow-up assessment. Finally, fully adjusted models for each metabolic parameter considered all covariates in the crude models with further control for baseline household wealth, child's birth weight and Tanner stage at the last assessment. Non-normally distributed variables were log-transformed before analyses in the regression models. *P* values (two-tailed) are presented for all statistical tests. STATA 11.2 (StataCorp) was used for all analyses.

## Results

Among the 696 children with complete anthropometric information and aged >4 years at baseline, 50.6% were females and 86.1% were of mixed race. By 2007, the BMI-for-age

Z-score was positively associated with male sex ( $P=0.01$ ), household wealth ( $P=0.04$ ) and child's birth weight ( $P<0.001$ ). The main characteristics across the study assessments are given in Table 1. During the follow-up from 2007 to 2009 in this age group, the mean variation in BMI-for-age Z-scores was equivalent to 0.14 (SD 0.53). Between the two assessments, there was a significant increase in the mean BMI-for-age Z-score from  $-0.24$  (SD 0.99) to  $-0.05$  (SD 1.13) ( $P=0.01$ ) and in the proportion of overweight children from 10.1 to 15.8% ( $P=0.003$ ).

A total of 507 children with exposure information at baseline were evaluated in 2009. Of these, 411 had data on metabolic parameters after clinical examination. The median follow-up period was 2.0 years (range 1.7–2.6 years). There was no difference in children lost to follow-up and children included in the analyses, except for mean age at baseline and sex distribution. Participants not included in the analyses

**Table 1.** Characteristics of the school-aged children with complete anthropometric information at each study assessment, Acrelândia, Brazil

(Number of participants and percentages; mean values and standard deviations)

	2007		2009		<i>P</i> *
	<i>n</i>	%	<i>n</i>	%	
Total†	696‡		507		
Sex					0.36
Female	352	50.6	270	53.2	
Male	344	49.4	237	46.8	
Age (years)					<0.001
Mean	7.1		9.1		
SD	1.8		1.8		
Race/ethnicity					0.90
White	57	8.9	39	8.4	
Mixed race	551	86.1	402	87.0	
Black	32	5.0	21	4.6	
Household wealth index					0.81
First quartile (lowest)	156	22.5	104	20.5	
Second quartile	191	27.4	140	27.6	
Third quartile	178	25.6	129	25.5	
Fourth quartile (highest)	170	24.5	134	26.4	
Maternal educational level (years)					0.93
≤ 4	286	42.4	210	41.5	
5–8	200	29.7	150	29.6	
≥ 9	188	27.9	146	28.9	
Maternal age (years)					0.73
≤ 34	502	72.1	361	71.2	
≥ 35	194	27.9	146	28.8	
Birth weight (g)					0.64
≤ 2500	42	6.7	37	8.0	
2501–3500	372	59.6	266	57.3	
> 3500	210	33.7	161	34.7	
BMI-for-age Z-score†					<0.001
Mean	−0.24		−0.05		
SD	0.99		1.13		
Overweight§	70	10.1	80	15.8	0.003
Height-for-age Z-score†					<0.001
Mean	−0.29		−0.35		
SD	0.95		0.93		
Stunting	22	3.2	18	3.6	0.71

\* *P* values were calculated using the  $\chi^2$  test for categorical variables and the paired *t* test for continuous variables.

† BMI-for-age and height-for-age Z-scores were calculated according to the WHO growth references.

‡ Total may be different from 696 because of missing data.

§ Overweight was defined as a BMI-for-age Z-score above 1.

|| Stunting was defined as a height-for-age Z-score below  $-2$ .

**Table 2.** Distribution of the metabolic parameters of the school-aged children according to Tanner stage, Acrelândia, Brazil, 2009

(Mean values and standard deviations for normally distributed variables; medians and interquartile ranges (IQR) for non-normally distributed variables)

	Tanner stages						P*
	Prepubertal			Pubertal			
	n	Mean	SD	n	Mean	SD	
Glucose (mmol/l)	235	5.03	0.47	145	5.16	0.40	0.006
Insulin (pmol/l)	223			131			<0.001
Median		29.4			47.4		
IQR		20.4, 39.6			30.0, 75.6		
HOMA-IR	218			131			<0.001
Median		1.09			1.71		
IQR		0.74, 1.47			1.15, 2.92		
Systolic blood pressure (mmHg)	242	100.1	8.6	148	98.8	10.0	0.16
Diastolic blood pressure (mmHg)	242	62.4	6.3	148	62.6	7.0	0.75

HOMA-IR, homeostasis model assessment index of insulin resistance.

\*P values were calculated using the *t* test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables.

were slightly younger at baseline (difference 1.01 years, 95% CI 0.75, 1.26 years), and the follow-up rate was 3.7% higher among the females (*P*=0.02).

The metabolic parameters of the school-aged children were compared according to Tanner stages in 2009 (Table 2). Pubescent participants had higher glucose concentrations, insulin concentrations and HOMA-IR values. Increased plasma glucose concentrations, defined as glucose concentrations  $\geq 5.55$  mmol/l for children aged  $\geq 10$  years (*n* 164), were detected in 20.1% of the children. Among prepubescent (*n* 223) and pubescent (*n* 131) participants altogether, hyperinsulinaemia was observed in 5.0% of the children. In addition, 5.1% (*n* 19) of all children with available data were considered insulin resistant, with HOMA-IR values  $> 4.39$ . Among the insulin-resistant participants, fifteen were girls and ten were classified as pubescent. Also, twelve of these children were overweight (BMI-for-age Z-score  $> 1$ ).

Weight gain from 2007 to 2009 measured as the difference in BMI-for-age Z-scores was associated with higher insulin concentrations and HOMA-IR values among the school-aged children, after adjustment for sex, age, race/ethnicity, baseline household wealth, birth weight and Tanner stage (Table 3). For each unit of BMI-for-age Z-score, insulin concentrations and HOMA-IR values increased by 8.58 (95% CI 7.68, 9.60) pmol/l and 1.47 (95% CI 1.30, 1.66), respectively. No association with either systolic or diastolic blood pressure values was found.

### Discussion

In the present study, weight gain during follow-up among the school-aged children living in the Brazilian Amazon was found to be related to higher insulin concentrations and insulin resistance values, as measured by HOMA-IR. Also,

**Table 3.** Linear regression coefficients for the association of weight gain (in units of BMI-for-age Z-score) with metabolic parameters among the school-aged children, Acrelândia, Brazil, 2007–9

( $\beta$ -Coefficients and 95% confidence intervals)

	n	Weight gain BMI-for-age Z-score difference*					
		Crude†			Adjusted‡		
		$\beta$	95% CI	<i>r</i> <sup>2</sup>	$\beta$	95% CI	<i>r</i> <sup>2</sup>
Glucose (mmol/l)	402	0.07	-0.01, 0.16	0.01	0.07	-0.01, 0.16	0.12
Insulin (pmol/l)	376	8.82	7.86, 9.94	0.11	8.58	7.68, 9.60	0.42
HOMA-IR	371	1.52	1.35, 1.71	0.11	1.47	1.30, 1.66	0.41
Systolic blood pressure (mmHg)	411	-0.41	-2.17, 1.35	0.01	-0.69	-2.48, 1.09	0.06
Diastolic blood pressure (mmHg)	411	0.06	-1.20, 1.32	0.01	-0.10	-1.38, 1.18	0.06

HOMA-IR, homeostasis model assessment index of insulin resistance.

\*BMI-for-age Z-scores were calculated according to the WHO growth references.

†Linear regression models for crude estimates included the difference in BMI-for-age Z-scores for the 2007–9 period, the baseline BMI-for-age Z-score value, and child's sex, age, and race/ethnicity. Models for systolic and diastolic blood pressure were additionally adjusted for the child's height at the follow-up assessment. Insulin concentration and HOMA-IR values were log-transformed before analysis and estimates reported in this table were then exponentiated back to the original scale.

‡Fully adjusted estimates were controlled for the baseline BMI-for-age Z-score value, child's sex, age, and race/ethnicity, baseline household wealth, and child's birth weight and Tanner stage at the last assessment. Models for systolic and diastolic blood pressure were additionally adjusted for the child's height at the follow-up assessment. Insulin concentration and HOMA-IR values were log-transformed before analysis and estimates reported in this table were then exponentiated back to the original scale.

there was a significant increase in overweight in this age group during the study period (2007–9).

As expected, the results of the present study confirm the physiological increase in insulin resistance during pubertal development<sup>(17)</sup>, as evidenced by the significantly higher insulin concentrations and HOMA-IR values among pubescent participants. Mean HOMA-IR values and occurrence of hyperinsulinaemia were lower during school years in Acrelândia children when compared with that found in other investigations in developing areas. A population-based study with 6132 healthy children and adolescents in Mexico<sup>(20)</sup> has found that the absolute mean HOMA-IR value is equal to 2.89 (SD 0.70). Nonetheless, we did observe a significant influence of weight gain on insulin resistance, after adjustment for the child's sex, age and Tanner stage, among other covariates. In line with these findings, weight gain during childhood, and more specifically fat mass as measured with dual-energy X-ray absorptiometry, has been found to be associated with higher insulin resistance among 238 children aged 7–13 years in the UK<sup>(21)</sup>. Similar associations have also been reported in developing areas with regard to insulin resistance as the outcome among adults in longitudinal investigations. Higher increases in BMI between childhood or adolescence and adulthood have been reported to be positively associated with higher HOMA-IR values in rural communities in India<sup>(22)</sup>. Conditional weight gains as early as from birth to 2 years of age have been shown to be associated with insulin resistance during young adulthood in three other birth cohort studies conducted in developing countries<sup>(6)</sup>.

As insulin resistance has a key role in metabolic changes and is a risk factor for the development of type 2 diabetes as well as is closely related to BMI from an early age<sup>(23)</sup>, it is important to note that the longitudinal impact of weight gain observed in the present study was accompanied by a significant increase in overweight during a relatively short follow-up period, from 10.1 to 15.8% in 2 years. Although these values may not be extremely high, the increasing prevalence of overweight and obesity worldwide<sup>(24)</sup> is a public health concern. In this sense, the results of the present study shed light on the dual burden of disease affecting children in rapidly changing environments, which commonly lack material and structural resources, but progressively promote the development of chronic disease risk and, therefore, call for action in preventing both under- and over-nutrition in a timely manner<sup>(25,26)</sup>.

There are some limitations to the present study. Although the overall follow-up rate was high, there were differences between the children included and those not included in the analyses with regard to baseline age and sex, and the potential implications are difficult to assess. In addition, there was only one measurement available for the metabolic outcomes studied, but assessment of such parameters was done during earlier stages of life when compared with other prospective investigations. Although several study cohorts have found evidence for a role of growth in blood pressure in adulthood<sup>(5,27–29)</sup>, associations of weight gain with systolic and diastolic blood pressure during school years could not be

verified in the present study, possibly because of the shorter follow-up period.

The present study also has several strengths, including its longitudinal, population-based design, the ability to control for pubertal development, and the use of direct and standardised anthropometric measurements expressed as WHO Z-scores.

In conclusion, we found evidence for an impact of weight gain on insulin resistance after only a 2-year period during school years. Considering the significant increase in overweight in this age group, special attention should be paid to monitoring increases in BMI in children from the Brazilian Amazon.

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The authors' contributions are as follows: B. H. L. contributed to the study design and data collection, conducted data analyses, participated in data interpretation, wrote the initial draft of the article, and was involved in the review of the article; S. G. A. G. participated in data collection and interpretation and was involved in the review of the article; M. A. C. implemented and supervised all study protocols, was responsible for project management, participated in data interpretation, and was involved in the review of the article.

None of the authors has any conflicts of interest to declare.

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## Appendix

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