Received: 9 November 2021 | Revised: 24 February 2022 | Accepted: 5 March 2022

DOI: 10.1002/ajhb.23745

SHORT REPORT

American Journal of Human Biology WILEY

Insulin sensitivity as a predictor of longitudinal changes on body mass index in Brazilian adolescents

Valéria Lima da Cruz[1] | **Mauro Felippe Felix Mediano**[2,3] | **Vitor Barreto Paravidino**[1,4] | **Fabiana Alves Neves**[5] | **Tayanne de Oliveira Malafaia**[5] | **Luiz Fernando Rodrigues Junior**[3] | **Anibal Sanchez Moura**[5] | **Rosely Sichieri**[1]

[1]Department of Epidemiology, Institute of Social Medicine, State University of Rio de Janeiro, Rio de Janeiro, Brazil

[2]Evandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

[3]Department of Research and Education, National Institute of Cardiology, Rio de Janeiro, Brazil

[4]Department of Physical Education and Sports, Naval Academy - Brazilian Navy, Rio de Janeiro, Brazil

[5]Laboratory of Nutrition Physiology and Development, Department of Physiological Sciences, Institute of Biology, State University of Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence
Mauro Felippe Felix Mediano, Evandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Avenida Brasil, 4365, Manguinhos, Rio de Janeiro, Brazil.
Email: mffmediano@gmail.com

Funding information
Brazilian National Research Council, Grant/Award Number: 500404/2003-8

Abstract

Objectives: We aimed to investigate the effect of insulin sensitivity and insulin resistance status at baseline on longitudinal body mass index, and the possible effect modification by sex.

Methods: This is a secondary analysis of a randomized intervention community trial, in which a subgroup of 84 adolescents, aged between 10 and 12 years, were analyzed. Body weight, height, and body mass index (BMI) were determined before and after 8 months of follow-up. Glucose and serum insulin were examined at baseline and IR was defined based on the homeostasis model assessment—insulin resistance (HOMA-IR), with a cutoff >2.5 for both genders. Linear mixed-effects models were performed to evaluate the influence of HOMA-IR at baseline on BMI changes over time. Models were adjusted for age, pubertal stage, and stratified by sex.

Results: The sample comprised 65.4% of girls and the prevalence of overweight/obesity was 54.7% among girls and 50.0% among boys. The overall prevalence of IR was 75.3%, of which 60.7% for boys and 83.0% for girls. We found an interaction effect by sex ($p = .004$) for HOMA-IR as a continuous variable, with a decreased BMI rate of change among boys ($\beta = -0.13$; $p = .03$) but not for girls ($\beta = +0.03$; $p = .36$). Longitudinal BMI changes considering IR status at baseline (IR vs. non-IR) did not demonstrate any statistically significant difference for both boys (−0.1 vs. +0.4; $p = .28$) and girls (+0.7 vs. +1.0; $p = .44$).

Conclusion: Increased HOMA-IR values at baseline were associated with greater BMI reduction over time among boys but not girls, with no influence of IR status.

1 | INTRODUCTION

Insulin resistance (IR), a reduction in cellular insulin sensitivity associated with an increased plasma levels of insulin that are necessary to maintain the usual glucose uptake for cellular metabolism, is generally associated with obesity and could be an early adaptive system to decrease excessive body weight gain by reducing fat tissue deposition (Eckel, 1992; Maffeis et al., 2002).

However, while some authors have demonstrated that IR facilitated weight loss (Mediano & Sichieri, 2011), others observed that IR was either associated with weight gain (Howard et al., 2004) or had no effect on weight change (Votruba & Jensen, 2011; Wedick et al., 2009). These conflicting results could be either attributed to the differences in intervention strategies to promote weight loss (such as diet composition and physical exercise parameters), or to the differences in the characteristics of the studied populations, such as age, race, or sex (Mediano & Sichieri, 2011; Votruba & Jensen, 2011; Wedick et al., 2009).

Moreover, few studies evaluated the association between insulin sensitivity (including IR status) and weight change in adolescents (Heinemann, 2002), which may explain some unsuccessful results demonstrated by intervention studies designed to reduce excessive weight gain in adolescents (Abdel Rahman et al., 2018). Therefore, the present study aimed to investigate whether insulin sensitivity and IR status were associated with longitudinal body mass index (BMI) changes in Brazilian adolescents, and how these possible associations were modified by sex, as women are different to men concerning the actions of insulin, the susceptibility to develop insulin resistance, and the metabolic and cellular response to treatments that affect insulin sensitivity (Mittendorfer, 2005).

2 | MATERIALS AND METHODS

The present study is a secondary analysis of a randomized intervention community trial designed for investigating whether discouraging students from drinking sugar-sweetened beverages could prevent excessive weight gain in adolescents from public schools in a metropolitan area of Brazil (Sichieri et al., 2009). The intervention focused on encouraging water consumption instead of sugar-sweetened carbonated beverages through a healthy lifestyle education program, delivered via classroom activities (quizzes, games, song, and drawing competitions), distributed in ten 1-h sessions, during 7 months of one school year. Also, banners were hung promoting water consumption, and water bottles with the logo of the campaign were given to children. Data collection was performed at baseline, in March 2005, and at the end of follow-up, in December 2005.

The eligibility criteria were students aged between 10 and 12 years old (in order to reduce the amplitude of the pubertal stage in the study) whose blood samples were collected at baseline. From the 426 adolescents that had at least one measurement of blood data, 84 were randomly selected for laboratory insulin measurement and included in the study. Overweight/obese and eutrophic adolescents were sampled in a 1:1 ratio to increase the study power to evaluate the influence of insulin sensitivity on weight change. Participants were excluded from the study if serum or plasma samples were identified as deteriorated for biochemical analysis.

Body weight and height of the participants were obtained at baseline and after 7 months of intervention. Body weight was measured using a calibrated digital scale with a 150 kg capacity and 100 g precision (Tanita, BC 533 Inner Scan). Height was measured using a calibrated stadiometer with an amplitude of 200 cm and a variation of 0.1 cm. BMI was determined as a ratio between bodyweight (kg) and squared height (m). Nutritional status was estimated using the BMI (BMI = ratio between body weight in kg and squared height in meters) and categorized as underweight if BMI < percentile 5th, eutrophic if BMI ≥ percentile 5th and < percentile 85th; overweight if BMI ≥ percentile 85th and < percentile 95th, and obesity if BMI≥ percentile 95th for age and sex. The adolescents participated in the data collection individually, performed by trained professionals, following standardized procedures (de Onis et al., 2007).

The pubertal stage was self-reported based on Tanner's scale validated for Brazilian adolescents that classifies sexual maturation based on the development of external primary and secondary sex characteristics from stages 1 to 5 (Matsudo & Matsudo, 2008).

Plasma and serum aliquots were isolated from the blood samples, collected at baseline, and frozen at −80°C for further analysis, performed within 1 month after finishing all blood collection. Fasting plasma insulin and blood glucose levels were evaluated by radioimmunoassay (Insulin IRMA KIT, Beckman Coulter, USA) and enzymatic-colorimetric method (Glucose kit, Gold Analisa, Brazil), respectively. Insulin sensitivity was estimated by the homeostatic model assessment for insulin resistance (HOMA-IR), calculated by the following equation: [fasting insulin (μIU/ml) x fasting glucose (mmol/L)/22.5], with greater HOMA-IR values indicating lower insulin sensitivity. The cut-off point >2.5 was considered to determine IR (Andrade et al., 2016; Matthews et al., 1985). Blood samples were collected in schools by trained laboratory technicians, during the morning period, after at least 10 h of fasting.

The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.The ethics committee of the Institute of Social Medicine of the State University of Rio de Janeiro approved the study, and all volunteers signed an informed consent form before the beginning of the study.

Results are presented as means ± standard deviations (SD), or median and interquartile range for

continuous variables, and frequencies and percentages (%) for categorical variables. The normality of the data was assessed with the Shapiro–Wilk test. Student's *t*-test was used to compare means normally distributed, and Chi-square or Fisher's exact tests for categorical variables at baseline. Mann–Whitney test was used to compare continuous variables not normally distributed. Longitudinal BMI changes were evaluated using linear mixed-effect model. The final models for continuous and categorical (IR status) HOMA-IR incorporated the terms *time*, *baseline HOMA-IR*, and *time*× *baseline HOMA-IR*, adjusted for pubertal stage at baseline. An interaction term *time*× *baseline HOMA-IR* × *sex* was included in the model to evaluate an effect modification by sex. Sensitivity analyses were performed to evaluate the influence of outliers. All analyses were performed in SAS (version 9.4, SAS Institute, Cary, NC). Statistical significance was set at $p < .05$ for all analyses.

3 | RESULTS

From the 84 adolescents randomly selected and included in the study, 41 were eutrophic and 43 were overweight/obese at baseline. Of those, three were excluded because of serum or plasma samples deterioration for biochemical analysis. The final population consisted of 81 adolescents with mean age of 10.7 ± 0.6 years old and BMI of 20.5 ± 4.3 kg/m^2. The majority were girls (65.4%), with fasting glucose of 85.3 ± 12.3 mg/dl and fasting insulin of 25.3 ± 22.9 μIU/ml. The frequency of overweight/obesity was 54.7% in girls and 50.0% in boys, and despite the higher frequency of IR observed among girls, no baseline difference in mean HOMA-IR was observed comparing boys and girls (Table 1).

The longitudinal analysis for BMI changes was stratified by sex, considering the effect modification by sex for continuous HOMA-IR ($p = .004$). For boys, baseline HOMA-IR was associated with a decreased BMI over time ($\beta = -0.13$; $p = .03$). In contrast, no association was observed for HOMA-IR at baseline and BMI changes for girls ($\beta = +0.03$; $p = .36$).

Table 2 shows BMI changes according to the IR status at baseline, stratified by sex. IR group did not demonstrate any significant difference for BMI change over time compared to non-IR, both for boys ($\Delta = -0.1$ vs. $+0.4$; $p = .28$) and girls ($\Delta = +0.7$ vs. $+1.0$; $p = .44$; Table 2). We performed additional analysis including BMI at baseline as a confounder variable, and the results did not change. Also, sensitivity analysis showed that the exclusion of three outliers for HOMA-IR did not change the results.

4 | DISCUSSION

The main finding of the present study was a significant association between increased HOMA-IR values at baseline and BMI reduction over time among boys but not girls. Conversely, no significant influence of IR status on BMI changes was observed during the follow-up.

The influence of IR on weight change is still controversial. In a previous study including children with a high risk of obesity in adulthood, no significant association between IR and weight change was evidenced (Sedaka et al., 2017). However, another study including eutrophic children demonstrated a lower weight gain among children presenting IR when compared to those without IR at baseline (Chen et al., 2015), suggesting that IR could act as an adaptative system to counteract the excessive weight gain, as already demonstrated in adults (Chen et al., 2015; Mediano & Sichieri, 2011; Sedaka et al., 2017).

In our study, despite lower insulin sensitivity demonstrating a protective effect against weight gain in adolescents, this effect was not maintained for IR, maybe indicating that this compensatory mechanism is efficient only in the initial stages of glucose metabolism deterioration. Moreover, this protective response seems to occur only in boys, which may be explained by hormonal differences between boys and girls, considering that most of the adolescents (≈85%) included in the study were in puberty (Tanner stage >2; Singh et al., 2013). In this setting, boys have higher levels of testosterone, a steroid hormone that stimulate muscle mass increase and cellular metabolism, increasing the resting metabolic rate that facilitates weight loss (Traish, 2014). Serum insulin levels modulate steroidogenesis, with a greater testosterone production associated with increased insulin levels from decreased insulin sensitivity, resulting in a greater mitochondrial oxidative function and an increased resting energy expenditure, facilitating weight loss. On the other hand, IR state leads to the reduction of testosterone production, probably by the target organ resistance for insulin action (Pitteloud et al., 2005).

The present study has some limitations. First, the greater number of girls participants could restrain the extrapolation of results. Since our sample was obtained from a clinical trial with a greater percentage of overweight/obese girls and that we oversampled overweight/obesity aiming to increase the percentage of insulin resistance adolescents, the greater percentage of girls observed in this secondary study cannot be considered unexpected. Second, since this is a secondary analysis from an experimental study, the sample size was only calculated to detect changes in primary outcome. However, even with a small sample for boys, we observed an association

TABLE 1 Characteristics of participants at baseline stratified by sex

	Total ($n = 81$) mean ± *SD* or *n* (%)	Boys ($n = 28$) mean ± *SD* or *n* (%)	Girls ($n = 53$) mean ± *SD* or *n* (%)	*p*-Value
Age (years)	10.7 ± 0.6	10.7 ± 0.5	10.7 ± 0.6	0.51
Weight (kg)	43.3 ± 11.4	42.2 ± 11.8	43.9 ± 11.3	0.52
Height (m^2)	144.7 ± 6.6	143.4 ± 7.4	145.3 ± 6.1	0.25
BMI (kg/m^2)	20.5 ± 4.3	20.2 ± 3.9	20.6 ± 4.5	0.68
Fasting glucose (mg/dl)	85.3 ± 12.3	88.6 ± 13.8	83.5 ± 11.1	0.10
Serum insulin (μIU/ml)[a]	21.3 (13.7–30.7)	16.0 (10.1–31.0)	22.1 (14.6–30.7)	0.20
HOMA-IR[a]	4.3 (2.8–6.6)	3.3 (2.1–7.4)	4.4 (3.0–6.3)	0.28
Pubertal Stage[b]				
Stage 1	12 (15.2)	5 (19.2)	7 (13.2)	0.69
Stage 2	51 (64.6)	17 (65.4)	34 (64.1)	
Stage 3 or more	16 (20.2)	4 (15.4)	12 (22.6)	
Body Mass Index				
Euthrophic	38 (46.9)	14 (50.0)	24 (45.3)	0.81
Overweight/obesity	43 (53.1)	14 (50.0)	29 (54.7)	
IR	61 (75.3)	17 (60.7)	44 (83.0)	0.02

Abbreviations: IR, insulin resistance; *SD*, standard deviation.
[a]Data showed as median (interquartile range 25%–75%).
[b]Tanner ratings.

TABLE 2 Crude means of body mass index (BMI) and estimated changes (Δ) from baseline stratified by sex

	Girls mean ± *SD*			Boys mean ± *SD*		
	Non-IR	IR	*p*-Value*	Non-IR	IR	*p*-Value*
BMI ($kg\ m^{-2}$)						
Baseline	16.9 ± 2.0	21.4 ± 4.5	0.44	18.8 ± 2.7	21.2 ± 4.4	0.28
Follow-up	17.9 ± 2.4	22.1 ± 4.7		19.2 ± 3.5	21.1 ± 4.3	
Δ	+1.0	+0.7		+0.4	−0.1	

Note: Insulin resistance is defined by the cutoff of HOMA-IR >2.5. Non-IR is defined by the cutoff of HOMA-IR ≤2.5. Model adjusted for pubertal stage at baseline.
Abbreviations: IR, insulin resistance; *SD*, standard deviation.
*p-value of interaction term (time×HOMA-IR).

between increased HOMA-IR at baseline and a reduction on BMI over time, but the lack of effects of IR status at baseline on BMI changes should be interpreted with caution, considering that our study may have been underpowered.

5 | CONCLUSION

In conclusion, our data suggest that increased HOMA-IR values at baseline in boys, but not IR status, were associated with BMI reduction over time. For the development of successful strategies for the prevention of obesity, it is important to identify those individuals who are at risk of increasing body weight or who are less able to lose weight during treatment. Different insulin sensitivity levels across participants in some intervention studies can partially explain the inconsistent findings in the literature. Therefore, future studies are needed for better comprehension of the relationship between insulin resistance and body weight changes over time.

ACKNOWLEDGMENT

The authors thank the Brazilian National Research Council – CNPq for the funding support. Grant number: 500404/2003-8.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Valéria Lima da Cruz: Conceptualization; formal analysis; writing-original draft; writing-review & editing; read and approved the final manuscript. **Mauro Felippe Felix Mediano:** Conceptualization; formal analysis; writing-original draft; writing-review & editing; read and approved the final manuscript. **Vitor Barreto Paravidino:** Formal analysis; writing-original draft; writing-review & editing; read and approved the final manuscript. **Fabiana Alves Neves:** Acquisition of data, writing-review & editing; read and approved the final manuscript. **Tayanne de Oliveira Malafaia:** Acquisition of data, writing-review & editing; read and approved the final manuscript. **Luiz Fernando Rodrigues Junior:** Writing-original draft; writing-review & editing; read and approved the final manuscript. **Anibal Sanchez Moura:** Acquisition of data, writing-review & editing; read and approved the final manuscript. **Rosely Sichieri:** Conceptualization; formal analysis; writing-review & editing; read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

Abdel Rahman, A., Jomaa, L., Kahale, L. A., Adair, P., & Pine, C. (2018). Effectiveness of behavioral interventions to reduce the intake of sugar-sweetened beverages in children and adolescents: A systematic review and meta-analysis. *Nutrition Reviews*, *76*(2), 88–107. https://doi.org/10.1093/nutrit/nux061

Andrade, M. I., Oliveira, J. S., Leal, V. S., Lima, N. M., Costa, E. C., Aquino, N. B., & Lira, P. I. (2016). Identification of cutoff points for homeostatic model assessment for insulin resistance index in adolescents: Systematic review. *Revista Paulista de Pediatria*, *34*(2), 234–242. https://doi.org/10.1016/j.rpped.2015.08.006

Chen, Y. Y., Wang, J. P., Jiang, Y. Y., Li, H., Hu, Y. H., Lee, K. O., & Li, G. W. (2015). Fasting plasma insulin at 5 years of age predicted subsequent weight increase in early childhood over a 5-year period-the Da Qing children cohort study. *PLoS One*, *10*(6), e0127389. https://doi.org/10.1371/journal.pone.0127389

de Onis, M., Onyango, A. W., Borghi, E., Siyam, A., Nishida, C., & Siekmann, J. (2007). Development of a WHO growth reference for school-aged children and adolescents. *Bulletin of the World Health Organization*, *85*(9), 660–667.

Eckel, R. H. (1992). Insulin resistance: An adaptation for weight maintenance. *Lancet*, *340*(8833), 1452–1453. https://doi.org/10.1016/0140-6736(92)92633-q

Heinemann, L. (2002). Variability of insulin absorption and insulin action. *Diabetes Technology & Therapeutics*, *4*(5), 673–682. https://doi.org/10.1089/152091502320798312

Howard, B. V., Adams-Campbell, L., Allen, C., Black, H., Passaro, M., Rodabough, R. J., ... Wagenknecht, L. E. (2004). Insulin resistance and weight gain in postmenopausal women of diverse ethnic groups. *International Journal of Obesity and Related Metabolic Disorders*, *28*(8), 1039–1047. https://doi.org/10.1038/sj.ijo.0802645

Maffeis, C., Moghetti, P., Grezzani, A., Clementi, M., Gaudino, R., & Tatò, L. (2002). Insulin resistance and the persistence of obesity from childhood into adulthood. *The Journal of Clinical Endocrinology and Metabolism*, *87*(1), 71–76. https://doi.org/10.1210/jcem.87.1.8130

Matsudo, S. M. M., & Matsudo, V. K. R. (2008). Validade da auto-avaliação na determinação da maturação sexual. *Revista Brasileira de Ciência e Movimento*, *5*(2), 18–35.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7), 412–419.

Mediano, M. F., & Sichieri, R. (2011). Insulin resistance influences weight loss in non-obese women who followed a home-based exercise program and slight caloric restriction. *Diabetes Research and Clinical Practice*, *92*(3), 361–367. https://doi.org/10.1016/j.diabres.2011.02.031

Mittendorfer, B. (2005). Insulin resistance: Sex matters. *Current Opinion in Clinical Nutrition and Metabolic Care*, *8*(4), 367–372. https://doi.org/10.1097/01.mco.0000172574.64019.98

Pitteloud, N., Hardin, M., Dwyer, A. A., Valassi, E., Yialamas, M., Elahi, D., & Hayes, F. J. (2005). Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *The Journal of Clinical Endocrinology and Metabolism*, *90*(5), 2636–2641. https://doi.org/10.1210/jc.2004-2190

Sedaka, N. M., Olsen, C. H., Yannai, L. E., Stutzman, W. E., Krause, A. J., Sherafat-Kazemzadeh, R., ... Yanovski, J. A. (2017). A longitudinal study of serum insulin and insulin resistance as predictors of weight and body fat gain in African American and Caucasian children. *International Journal of Obesity*, *41*(1), 61–70. https://doi.org/10.1038/ijo.2016.145

Sichieri, R., Paula Trotte, A., de Souza, R. A., & Veiga, G. V. (2009). School randomised trial on prevention of excessive weight gain by discouraging students from drinking sodas. *Public Health Nutrition*, *12*(2), 197–202. https://doi.org/10.1017/S1368980008002644

Singh, Y., Garg, M. K., Tandon, N., & Marwaha, R. K. (2013). A study of insulin resistance by HOMA-IR and its cut-off value to identify metabolic syndrome in urban Indian adolescents. *Journal of Clinical Research in Pediatric Endocrinology*, *5*(4), 245–251. https://doi.org/10.4274/Jcrpe.1127

Traish, A. M. (2014). Testosterone and weight loss: The evidence. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *21*(5), 313–322. https://doi.org/10.1097/med.0000000000000086

Votruba, S. B., & Jensen, M. D. (2011). Insulin sensitivity and regional fat gain in response to overfeeding. *Obesity (Silver Spring)*, *19*(2), 269–275. https://doi.org/10.1038/oby.2010.274

Wedick, N. M., Snijder, M. B., Dekker, J. M., Heine, R. J., Stehouwer, C. D., Nijpels, G., & van Dam, R. M. (2009). Prospective investigation of metabolic characteristics in relation to weight gain in older adults: The Hoorn study. *Obesity (Silver Spring)*, *17*(8), 1609–1614. https://doi.org/10.1038/oby.2008.666

How to cite this article: da Cruz, V. L., Mediano, M. F. F., Paravidino, V. B., Neves, F. A., de Oliveira Malafaia, T., Rodrigues Junior, L. F., Moura, A. S., & Sichieri, R. (2022). Insulin sensitivity as a predictor of longitudinal changes on body mass index in Brazilian adolescents. *American Journal of Human Biology*, e23745. https://doi.org/10.1002/ajhb.23745