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Insulin Resistance, Hyperinsulinemia, and Energy Intake in Overweight Children

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Abstract

Objective—To examine the relationship between energy intake during a buffet meal and indices of insulin dynamics in overweight children.

Study design—95 non-diabetic, overweight (BMI $\geq 95^{\text{th}}$ percentile) children (age 10.3 ± 1.4 y) selected lunch from a 9,835kcal buffet eaten *ad libitum* after an overnight fast. The associations between energy intake and measures of insulin dynamics, in the post-absorptive state and during a 2h-hyperglycemic clamp, were determined. Covariates in the statistical model included race, sex, skeletal age, fat-free mass, fat mass, socioeconomic status, and number of foods in the buffet rated as acceptable.

Results—Energy intake was positively associated with the fasting homeostasis model assessment for insulin resistance index (HOMA-IR; $\beta=0.24$, $p=0.042$), fasting insulin/glucose ratio ($\beta=0.24$, $p=0.044$), 1st-phase insulin ($\beta=0.23$, $p=0.032$), and 1st-phase C-peptide ($\beta=0.21$, $p=0.046$); energy intake was negatively associated with clamp-derived insulin sensitivity (SI_{clamp} ; $\beta=-0.29$, $p=0.042$). Each 10% decrease in SI_{clamp} predicted 27 kcal greater energy intake.

Conclusions—Insulin resistance and hyperinsulinemia are associated with greater energy intake after an overnight fast in overweight children. These associations suggest mechanisms whereby insulin resistance may contribute to excessive weight gain in children.

Keywords

Glucose homeostasis; obesity; food intake; hyperglycemic clamp; insulin dynamics

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Clinical Trial Registration: NCT00005669 (<http://www.clinicaltrials.gov/>)

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The association between excess adiposity and insulin resistance is well-established in both children and adults, and excess adiposity is clearly an important antecedent factor in the development of insulin resistance (1,2). However, there is also some evidence to suggest that disordered glucose homeostasis may itself be a factor contributing to subsequent weight gain. In epidemiological studies, some (3,4), but not all (5-7), longitudinal data in adults suggest that greater insulin resistance and higher fasting and post-challenge insulin levels are associated with greater subsequent weight gain and visceral adiposity. Similarly, in children some (8-10), but not all (11,12) studies find that those with the greatest insulin resistance and highest insulin concentrations have the greatest increases in weight and adipose tissue over time. Thus, neither the role nor the mechanisms by which insulin resistance and hyperinsulinemia may influence subsequent weight gain are well understood.

In addition to its primary function in peripheral glucose metabolism, insulin is believed to act within the central nervous system (CNS) to regulate energy homeostasis (13). Peripherally-circulating insulin is thought to cross the blood brain barrier via a saturable receptor-mediated transport mechanism (14,15) to act within the brain in a manner similar to leptin at sites where leptin functions (16,17). Several lines of evidence are consistent with the hypothesis that the anorexigenic effects of insulin are diminished in obese animals and humans, and suggest that resistance to insulin occurs not just peripherally, but also centrally, in obesity. Compared to its actions in those who are not obese, CNS insulin administration decreases food intake to a lesser degree in obese animals (18). Similar results are found in obese humans given insulin intranasally (19). In contrast to normal weight adults, obese adults do not exhibit a correlation between postprandial insulin response and subsequent energy intake, suggesting that insulin-mediated appetite regulation may be dysfunctional in obese adults (20,21). In addition, the chronic hyperinsulinemia that is associated with obesity and insulin resistance may further exacerbate central insulin resistance through downregulation of insulin transport receptors at the blood brain barrier (22).

The literature supports the hypothesis that both insulin resistance and chronic hyperinsulinemia may impair regulation of energy intake. However, there are few studies directly examining this hypothesis in children. We therefore examined the relationship between insulin dynamics and energy consumption in overweight children. We hypothesized that insulin resistance and hyperinsulinemia would be predictors of greater energy intake at meals and provide possible mechanisms whereby insulin resistance and hyperinsulinemia could contribute to excess weight gain in children.

Methods

A convenience sample of overweight children, aged 6-12 years, was recruited through newspaper advertisements and letters mailed to pediatricians and family physicians in the metropolitan Washington, D.C. area for a weight-loss study (<http://www.clinicaltrials.gov> NCT00005669) examining the effects of metformin hydrochloride (23). Children were eligible if they had a BMI $\geq$ 95th percentile for age and sex, were pre-pubertal or early pubertal (breast Tanner I-III for girls; testes $<$ 8 mL for boys), and had hyperinsulinemia (fasting insulin $\geq$ 15 μ U/mL). Children were excluded from this analysis if they were diabetic (fasting glucose $\geq$ 126 mg/dL or HgbA1c $\geq$ 6.5%), had any other significant medical disease, had anorexia use or $>$ 2% body weight loss in the preceding 6 months, or were determined to have binge-eating disorder as assessed by the Questionnaire of Eating and Weight Patterns – Adolescent Version (24).

The study was approved by the National Institute of Child Health and Human Development Institutional Review Board. The children provided written assent, and their parents/legal

guardians provided written consent. Data were collected between October 2000 and April 2007.

Before beginning weight-reduction therapy, subjects were studied during an inpatient admission. After an overnight fast, subjects refrained from eating until 11:30 AM, when they were offered a standardized lunch buffet. On the following day, fasting serum and plasma samples were obtained and a 2-hour hyperglycemic clamp study was performed. Energy intake at all other meals during the admission was not restricted.

Height was measured in triplicate to the nearest 1 mm with a stadiometer. Weight was measured to the nearest 0.1 kg using a digital scale. Body composition was measured as previously described (25), using air-displacement plethysmography (Life Measurement Inc., Concord, CA) to determine body fat mass and fat-free mass. Roentgenogram of the left hand and wrist was obtained to assess skeletal maturation, and interpreted by a single radiologist using standards for age and sex (26). Waist circumference was measured in triplicate to the nearest 1 mm at the level of the umbilicus. Metabolic syndrome categorization was based on criteria suggested by Cruz *et al.* (27)

The method for energy intake testing has been described in detail previously (28). In brief, at 1130 AM, after an overnight fast, subjects ate *ad libitum* from a 28-item lunch buffet meal (Table I; available at www.jpeds.com) consisting of a variety of foods which offered 9,835 kcal for ingestion (28). The amount consumed was calculated by using the difference in weight of each food item before and after the meal. Nutrient composition was determined using ProNUTRA 3.1 (Viocare Technologies, Inc., Princeton, NJ), the US Department of Agriculture Nutrient Database for Standard Reference, and manufacturer-supplied nutrient information.

To determine the number of foods offered in the buffet meal that were considered acceptable by the subject, a food-preference questionnaire was administered to all participants, as previously described (28). Socioeconomic status (SES) was determined using the Hollingshead two-factor index of social status, based on parental education and employment history (29).

After an overnight fast, baseline serum and plasma samples were obtained at 0800 h and a 2-hour hyperglycemic clamp study was performed. A bolus infusion of 50% dextrose (0.19g/kg, max 30g) was given over 2 min, followed by maintenance of plasma glucose levels at 180 – 220 mg/dL by continuous infusion of 20% dextrose for 120 min. The rate of dextrose infusion was adjusted based on plasma glucose levels measured using a bedside glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH) every 2.5 min for 15 min, and then every 5 min thereafter. Additional venous blood samples were also obtained every 5 min for 15 min and then every 15 min thereafter for measurement of insulin, C-peptide, and (laboratory confirmed) glucose. First-phase insulin was derived from the mean of measurements at time 0 – 12.5 min. Steady-state insulin was derived from the mean of measurements at time 60 – 120 min. Values were considered valid for use in steady-state analysis if the standard deviation in bedside glucose values was <15 mg/dL and mean glucose at time 60-120 min >190 mg/dL. Using these criteria, 19 subjects were excluded in analyses of steady-state indices, but they were included for all other analyses. Whole-body glucose uptake was estimated as the metabolic rate (M), defined as the exogenous glucose infusion rate (GIR), adjusted for urinary glucose losses and glucose space correction (30): $M = GIR - \text{Urinary Glucose Loss} - [0.19 \text{ L/kg} \times 10 \times (\text{Glucose}_{120\text{min}} - \text{Glucose}_{60\text{min}} (\text{mg/dL}))] \div 60 \text{ min}$.

Plasma glucose concentrations were confirmed in the clinical laboratory using a glucose oxidase assay (Synchron LX[®], Beckman Coulter Inc., Fullerton, CA) with a sensitivity of 3

mg/dL, and an intra- and inter-assay coefficient of variation (CV) of 2% and 3%, respectively. Serum insulin was measured using a sandwich chemiluminescence immunoassay (Immulite 2000®, Diagnostic Products Corporation, Los Angeles, CA), with a sensitivity of 2 µU/mL, an intra- and inter-assay CV of 6.2% and 11.5%, respectively, and <1% and 8% cross-reactivity with C-peptide and proinsulin respectively. Serum C-peptide was measured using a competitive sandwich chemiluminescence immunoassay (Immulite 2000®), with a sensitivity of 0.5 ng/mL, an intra- and inter-assay CV of 3.4% and 8.3%, respectively, and <1% and 17% cross-reactivity with insulin and proinsulin respectively. Serum leptin was measured using a double antibody RIA (Esoterix, Inc., Calabasas Hills, CA), with a sensitivity of 0.1 ng/mL, an intra- and inter-assay CV of 9.6% and 12%, respectively. Lipid panel was measured using Beckman Coulter Reagent (Fullerton, CA).

Insulin sensitivity was estimated by homeostasis model assessment for insulin resistance index (HOMA-IR) (31) and hyperglycemic clamp insulin sensitivity index (SI_{clamp}) (30): $HOMA-IR = [\text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Glucose } (\text{mmol/L})] \div 22.5$; $SI_{\text{clamp}} = 100 \times (M \div \text{Steady State Insulin})$. Pancreatic β -cell secretory function was estimated by several proxy measures: fasting and clamp C-peptide concentrations, fasting and clamp insulin concentrations, and insulinogenic index (31): $\text{Fasting I/G} = \text{Fasting Insulin } (\mu\text{U/mL}) \div \text{Fasting Glucose } (\text{mg/dL})$. Hepatic insulin clearance was estimated based on the observation that, C-peptide is secreted from the β -cell in equimolar amounts with insulin C-peptide but is primarily cleared by the kidneys with negligible hepatic clearance, thus permitting C-peptide-to-insulin molar ratio (C/I) to serve as a surrogate measure of hepatic insulin clearance (32).

Data were analyzed using SPSS Version 12.0.1 for Windows software. Fat-free mass, fat mass, and all the indices of insulin dynamics were normalized by log-transformation. Pearson correlation coefficient was calculated to assess the simple association between indices of insulin dynamics and energy intake without adjustment for covariates. A univariate general linear model with type III sum of squares analysis was used to evaluate these associations with adjustment for covariates. The covariates in the final statistical model included race, sex, skeletal age, interaction between sex and skeletal age (as a proxy for pubertal status), fat-free mass, fat mass, socioeconomic status, and number of foods in the buffet meal that were rated as acceptable. Analysis after exclusion of the 10 subjects who rated fewer than 50% of the items in the buffet meal as acceptable did not alter the significance or direction of associations (data not shown) and so they were included in the final analyses. Exclusion of the 1 subject with the largest energy intake (4092 kcal) during the buffet meal also did not affect results and so this subject is included in the final analyses. All data are reported as mean $\pm$ SD unless otherwise indicated.

Results

A total of 95 severely overweight children participated in the study, of whom 75 completed the 2-hour hyperglycemic clamp study, 4 had partial clamp studies terminated early due to loss of intravenous access, and 16 had only fasting laboratory values obtained. Subject characteristics and results of laboratory testing and calculated indices of insulin dynamics are shown in Table II. Criteria for metabolic syndrome were met by 28.4% of study subjects.

Mean energy intake was 1345 ± 608 kcal at the buffet meal (Table II), and macronutrient content was approximately 44% of energy from carbohydrate, 41% from fat, and 15% from protein. The associations between indices of insulin dynamics and energy intake after adjustment for covariates are shown in Table III. The β -coefficient corresponds to the predicted SD unit change in energy intake for each SD unit change in the index analyzed. Energy intake was positively associated with HOMA-IR ($p=0.042$), fasting I/G ($p=0.044$),

1st-phase insulin ($p=0.032$), and 1st-phase C-peptide ($p=0.046$), and was negatively associated with SI_{clamp} ($p=0.042$). Correction of SI_{clamp} with division by mean plasma glucose concentrations during time 60 to 120 min of the clamp study yielded similar values ($\beta = -0.29$, $p=0.048$).

Based on the model with the above covariates (which yielded adjusted $r^2 > 0.3$ for all analyses), each 10% increase in HOMA-IR was associated with 29 kcal greater energy intake and each 10% increase in fasting I/G was associated with 31 kcal greater energy intake. Each 10% decrease in SI_{clamp} was associated with 27 kcal greater energy intake. Each 10% increase in 1st-phase insulin was associated with 19 kcal greater energy intake, and each 10% increase in 1st-phase C-peptide was associated with 31 kcal greater energy intake.

A trend toward negative association was observed for fasting leptin and energy intake ($\beta = -0.20$, $p=0.069$). No statistically significant associations between indices of insulin dynamics and macronutrient composition of the meal were observed.

Discussion

In this cohort of overweight children, we found, after accounting for appropriate covariates, that indices of insulin resistance and hyperinsulinemia were associated with greater energy intake at a lunchtime buffet meal after an overnight fast. Each 10% decrease in insulin sensitivity (SI_{clamp}) predicted 27 kcal greater energy intake, and each 10% increase in 1st-phase insulin predicted 19 kcal greater energy intake. These data are compatible with two divergent explanations: the observed derangements in insulin dynamics could be one of the causes of increased energy intake or could represent one of the consequences of excessive consumption.

The possibility that insulin resistance and consequent hyperinsulinemia may be a cause of greater energy intake is corroborated by several prior studies on the role of insulin in the regulation of energy homeostasis (14-21). Peripheral insulin resistance may signify central resistance and loss of appropriate negative feedback regulation of appetite as well as downregulation of insulin transport into the hypothalamus (22). Chronic hyperinsulinemia might also impact body weight regulation through its action to induce expression of SOCS-3, a negative regulator of both insulin and leptin receptor signaling (33,34). Thus, chronic hyperinsulinemia not only antagonizes insulin's own actions, but may also diminish the central actions of leptin (35).

The alternative hypothesis is that insulin resistance and hyperinsulinemia are a consequence of increased energy intake and weight gain. Habitually greater energy intake may induce obesity and thus insulin resistance, and potentially condition the pancreas to have a larger insulin secretory capacity to maintain euglycemia. Greater insulin secretion, in turn, may promote insulin-mediated deposition of consumed energy in the form of adipose tissue, which leads to the development of an even greater degree of muscle insulin resistance. Further hyperinsulinemia would then ensue and perpetuate this vicious cycle of fat accumulation and derangements in insulin dynamics. Given the cross-sectional nature of the study design, we are unable to exclude this possibility. Longitudinal follow-up of patients to relate baseline insulin sensitivity to subsequent weight gain could perhaps determine the direction of the association, but both positive and negative longitudinal studies exist in the pediatric and adult literature. Although insulin concentrations and insulin resistance were significant predictors of energy intake even after body composition was taken into account in the statistical model, this conceptualization seems somewhat less likely to explain the relationship between insulin resistance and consumption observed during the buffet meal.

In either scenario, pharmacotherapies aimed at ameliorating hypothalamic insulin resistance and peripheral hyperinsulinemia would seem logical choices for controlling energy intake and weight gain in obesity. Metformin decreases hepatic glucose production, thereby diminishing peripheral hyperinsulinemia, and has also been found to alter muscle and hypothalamic AMP-activated protein kinase activity in a fashion expected to improve insulin-independent glucose uptake in muscle and decrease appetite (36). Octreotide is a somatostatin agonist that, among its many effects, decreases pancreatic insulin secretion and has been reported to help stabilize body weight in children with hyperinsulinemia and hypothalamic obesity (37). One pediatric study has suggested that weight loss in response to metformin or octreotide therapy may be predicted by the degree of baseline insulin resistance and glucose-induced insulin secretion, respectively (38). Further studies are needed to investigate this mechanistic approach to therapy and at present no recommendations regarding pharmacotherapy for pediatric overweight can be made on the basis of the extant data on insulin resistance and hypersecretion.

There are several limitations to this study that should be recognized. Because all subjects had fasting hyperinsulinemia as a study inclusion criterion, no lean, or non-hyperinsulinemic obese, subjects were studied. Thus, the generalizability of the associations observed remains uncertain and the power to detect some associations may have been diminished. For example, the trends toward negative association of energy intake with leptin might have become statistically significant had we included non-overweight, non-insulin resistant subjects in this study. We included both pre-pubertal and early-pubertal subjects in these analyses in order to increase sample size and to allow for a broader range of insulin sensitivity as well as application of the findings to a wider age range. Insulin sensitivity decreases during puberty and pubertal status could therefore be a potential confounder for the result presented. However, we included bone age and the interaction of bone age and sex as covariates in our models, so that the influence of pubertal status is unlikely to explain the observed phenomena. Although we attempted to account for appropriate covariates, the effects of unmeasured variables, such as physical activity, may also potentially explain the observed relationships between food intake and indices of insulin secretion and action.

The lunch buffet used for meal testing, selected to have foods preferred by children, may not have been uniformly representative of the typical foods normally consumed by the study subjects. However, food likes and dislikes were incorporated as a covariate in statistical analysis to account for food preferences, and analysis after exclusion of the 10 subjects who rated fewer than 50% of the items in the buffet meal as acceptable did not alter the significance or direction of associations. Because of the nature of the protocol design, excessive energy intake on the first day of admission could have potentially affected the baseline and hyperglycemic clamp results on the following day. The lack of statistically significant correlation between percentage carbohydrate intake and indices of insulin dynamics, however, suggests that “carbohydrate loading” did not significantly influence the following day’s testing results. Furthermore, “carbohydrate craving” did not appear to be associated with insulin resistance or hyperinsulinemia, although it is possible that this study lacked power to observe such an association.

The indices employed in this study also have limitations in their use as proxies for insulin dynamics. Although SI_{clamp} is potentially a better measure of whole body insulin sensitivity, we also chose to report HOMA-IR because a portion of our subjects lacked steady-state clamp results and we wished to have a confirmatory surrogate measure. Although we assessed degree of hyperinsulinemia, we did not directly measure insulin secretion or clearance. In steady-state conditions, insulin secretion can be calculated as the product of the peripheral concentration of C-peptide and its metabolic clearance rate (39). We did not measure C-peptide metabolic clearance rate in our subjects. However, the measures for C-

peptide kinetics are very similar in heterogeneous populations when sex, age, and volume of distribution are taken into account (40). Therefore, we used C-peptide concentrations, adjusted for these covariates, in the basal fasting steady-state and hyperglycemic clamp steady-state as proxies for insulin secretion, and found no significant correlation with energy intake. Peripheral insulin has been shown to parallel changes in insulin secretion after administration of intravenous glucose bolus (41). Therefore, we used 1st-phase insulin as a proxy for insulin secretion in initial response to intravenous dextrose challenge, and found a positive association with energy intake. The discrepancy between the 1st-phase and steady-state results suggests that, in these overweight subjects, it is higher pancreatic β -cell storage of pre-formed insulin rather than higher insulin synthesis rate that is associated with greater energy intake in overweight children. The positive association between the insulinogenic index (I/G ratio) and energy intake also supports this hypothesis. Finally, C/I ratio in steady-state (fasting and clamp) and 1st-phase served as proxies for hepatic insulin clearance (39). Although not statistically significant, a trend was observed for an association between greater energy intake and lower steady-state C/I, an indicator of slower hepatic insulin clearance, which may reflect hepatic insulin resistance and contribute to chronic hyperinsulinemia. This finding would be consistent with our hypothesis that derangements in insulin dynamics, primarily insulin resistance with secondary hyperinsulinemia, are associated with defective appetite regulation by insulin and, therefore, greater energy intake.

More data are required to confirm and elucidate the association of insulin resistance and hyperinsulinemia with energy intake and to determine if greater energy intake at meals may provide the mechanism whereby insulin resistance and hyperinsulinemia may contribute to excessive weight gain in children.

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Abbreviations

BMI	body mass index
HOMA-IR	homeostasis model assessment for insulin resistance index
SI _{clamp}	hyperglycemic clamp-derived insulin sensitivity index
HgbA1c	hemoglobin A1c

M	metabolic rate
GIR	glucose infusion rate
C/I ratio	C-peptide-to-insulin molar ratio
I/G ratio	insulin-to-glucose ratio

TABLE 1

Items presented at the buffet meal¹

Item	kcal
12 Slices white bread	801.0
180 g Ham	216.0
180 g Turkey	282.6
240 g American cheese	901.1
200 g Chicken nuggets	550.8
120 g Peanut butter	711.6
120 g Grape jelly	339.6
200 g Tomatoes	42.0
50 g Lettuce	6.0
3 Medium bananas	325.7
250 g Grapes	177.5
3 Medium oranges	184.7
12 Oreo cookies ²	566.4
12 Vanilla wafer cookies	206.3
90 g Mayonnaise	645.1
90 g Mustard	59.4
90 g Light ranch dressing	240.0
90 g Barbeque sauce	67.5
250 g Mild salsa	70.0
200 g Baby carrots	76.0
120 g Tortilla chips	601.2
150 g Pretzels	571.5
120 g Jellybeans	440.4
120 g M&M's candy ³	590.4
850 g Bottled water	0.0
850 g 2% Milk	422.2
850 g Apple juice	400.0
850 g Lemonade	340.0

¹The total energy content was 9,835 kcal.²Kraft Foods, Northfield, IL³Mars, Inc, Masterfood USA, Hackettstown, NJ

TABLE 2

Characteristics of study participants (n=95)

Age (y)	10.3 ± 1.4
Sex (% Female)	60.0
Race	
White (%)	48.4
Black (%)	36.8
Other (%)	14.7
Metabolic syndrome (%)	28.4
BMI (kg/m²)	34.3 ± 6.6
BMI-SDS (CDC 2000)	2.6 ± 0.2
Fat mass (%)	48.5 ± 6.1
Fasting leptin (ng/mL)	32.8 ± 20.1
Fasting glucose (mg/dL)	88.1 ± 6.3
Fasting insulin (μU/mL)	21.4 ± 11.4
Fasting C-peptide (ng/mL)	3.8 ± 1.4
Fasting I/G ratio (μU/mL/mg/dL)	0.24 ± 0.12
HOMA-IR (μU/mL × mg/dL)	4.77 ± 2.70
First-phase insulin (μU/mL)	163.0 ± 101.5
Steady-state insulin (μU/mL)	221.1 ± 120.7
SI_{clamp} (mg/kg-min/μU/mL)	4.87 ± 2.95
First-phase C-peptide (ng/mL)	9.6 ± 3.8
Steady-state C-peptide (ng/mL)	13.6 ± 3.6
Fasting C/I molar ratio	9.1 ± 3.6
First-phase C/I molar ratio	3.5 ± 2.1
Steady-state C/I molar ratio	3.3 ± 1.3
Energy intake (kcal)	1345 ± 608

Mean ± SD shown unless otherwise indicated. SI unit conversion factors: glucose (mg/dL) × 0.0555 to obtain mmol/L; insulin (μU/mL) × 7.175 to obtain pmol/L; C-peptide (ng/mL) × 0.3310 to obtain nmol/L; leptin (ng/mL) × 0.0625 to obtain nmol/L. I/G ratio: insulin/glucose ratio; HOMA-IR: homeostasis model assessment of insulin resistance index; C/I ratio: C-peptide/insulin ratio; SI_{clamp}: insulin sensitivity estimated during hyperglycemic clamp.

TABLE 3

Associations between indices of insulin dynamics and energy intake

	Association with Energy Intake	
	β -coefficient	P-value
Fasting Indices		
Insulin	0.164	0.097
I/G ratio	0.241	0.044
HOMA-IR	0.244	0.042
C-peptide	0.061	0.552
C/I ratio	-0.118	0.213
Hyperglycemic Clamp Indices		
First-phase insulin	0.228	0.032
First-phase C-peptide	0.207	0.046
First-phase C/I ratio	-0.163	0.125
Steady-state insulin	0.244	0.053
Steady-state C-peptide	0.188	0.175
Steady-state C/I ratio	-0.205	0.108
SI_{clamp}	-0.286	0.042

Covariates for analysis included race, sex, skeletal age, interaction between sex and skeletal age (a proxy for pubertal status), fat-free mass, fat mass, socioeconomic status, and number of foods in the buffet meal that were rated as acceptable. I/G ratio: insulin/glucose ratio; HOMA-IR: homeostasis model assessment of insulin resistance index; C/I ratio: C-peptide/insulin ratio; SI_{clamp}: insulin sensitivity estimated during hyperglycemic clamp.