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Differences in Cardiometabolic Risk between Insulin-Sensitive and Insulin-Resistant Overweight and Obese Children

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Abstract

Background: It is known that 15–30% overweight/obese adults do not suffer cardiometabolic consequences. There is limited literature examining factors that can be used to assess cardiometabolic health in overweight/obese children. If such factors can be identified, they would aid in differentiating those most in need for aggressive management.

Methods: Baseline data from 7- to 12-year-old, overweight, and obese children enrolled in a weight management program at an urban hospital were analyzed. Homeostatic model assessment for insulin resistance (HOMA-IR) <2.6 was used to define insulin-sensitive and HOMA-IR ≥ 2.6 was used to defined insulin-resistant participants. Demographics, physical activity measures, and cardiometabolic risk factors were compared between the two phenotypes. Odds ratios (ORs) examining the association between intermediate endpoints (metabolic syndrome [MetS], nonalcoholic fatty liver disease [NAFLD], systemic inflammation, and microalbuminuria) and the two metabolic phenotypes were evaluated.

Results: Of the 362 overweight/obese participants, 157 (43.5%) were insulin sensitive and 204 (56.5%) were insulin resistant. Compared to the insulin-sensitive group, the insulin-resistant group was older (8.6 ± 1.6 vs. 9.9 ± 1.7; $p < 0.001$) and had a higher BMI z-score (1.89 ± 0.42 vs. 2.04 ± 0.42; $p = 0.001$). After multivariable adjustment, compared to the insulin-sensitive group, the insulin-resistant group had higher odds of having MetS (OR, 5.47; 95% confidence interval [CI]: 1.72, 17.35; $p = 0.004$) and NAFLD (OR, 8.66; 95% CI, 2.48, 30.31; $p = 0.001$), but not systemic inflammation (OR, 1.06; 95% CI: 0.56, 2.03; $p = 0.86$) or microalbuminuria (OR, 1.71; 95% CI, 0.49, 6.04; $p = 0.403$).

Conclusions: Using a HOMA-IR value of ≥ 2.6, clinical providers can identify prepubertal and early pubertal children most at risk. Focusing limited resources on aggressive weight interventions may lead to improvement in cardiometabolic health.

Introduction

Adult literature shows that 15–30% overweight/obese individuals are ''metabolically benign,'' that is, they fulfill the criteria of clinical obesity by BMI or waist circumference, but compared to their ''at-risk'' counterparts, do not suffer cardiometabolic consequences of their obesity in cross-sectional and longitudinal studies.[1–4] Adult studies use presence of metabolic syndrome (MetS) components, including high blood pressure (BP), impaired fasting glucose (FG), abdominal obesity, and dyslipidemia, to categorize the at-risk phenotype. However, overweight and obese children may not have developed enough components to diagnose MetS. Given that insulin resistance (IR) is a critical mediator in the association between obesity and cardiometabolic health,[5,6] pediatric studies have used the presence of IR to define these phenotypes.[7]

In the absence of clinical endpoints of cardiometabolic morbidity and mortality (such as diabetes, heart disease, and stroke) in the pediatric population, intermediate endpoints that are strongly associated with cardiometabolic health can serve as cardiometabolic risk factors. MetS, nonalcoholic

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fatty liver disease (NAFLD), systemic inflammation, and decreased renal function have all been associated with an increase in cardiometabolic risk factors in adults and their presence in childhood has been associated with adverse cardiometabolic health in adulthood.[8,9] If phenotypes based on IR are able to assess intermediate endpoints that are associated with cardiometabolic health, categorizing children by phenotypes could help in differentiating the children most in need for aggressive management and closer follow-up.

We therefore aimed to examine the association between metabolic phenotypes (as defined by IR) and intermediate endpoints (MetS, systemic inflammation, NAFLD, and microalbuminuria) in a group of overweight/obese 7- to 12-year-old children.

Methods

The present study used baseline data obtained from a randomized, controlled trial (The Family Weight Management Study) evaluating the effectiveness of a multidisciplinary weight loss program called *Fun Healthy Families* at an urban, municipal hospital. From July 2009 to December 2011, 7- to 12-year-old children identified by pediatricians at Jacobi Medical Center (Bronx, NY) as being either overweight (BMI 85th–94th percentile for age and sex) or obese (BMI $\geq$95th percentile for age and sex) were recruited. Exclusion criteria included: major physical, cognitive or emotional impairment that would affect ability or safety in following the study protocol; treatment with medications that affect body weight, intention of the family to move beyond commuting distance, already enrolled in other weight management programs, and unwillingness or inability of the child or parents to provide assent and consent, respectively. Patients with chronic illnesses (*i.e.*, diabetes or human immunodeficiency virus) were not eligible to participate in the study. The study was approved by the Albert Einstein College of Medicine Institutional Review Board committee (Bronx, NY).

Measures

Anthropometric measures. Height and weight were measured in light clothing and without shoes using a stadiometer and a digital scale. Using an inelastic tape, waist circumference was measured at the iliac crest and recorded to the nearest centimeter. Scales and stadiometer were calibrated and anthropometry tapes were examined for signs of wear on a weekly basis using standardized protocols.[10]

Systolic (SBP) and diastolic BP (DBP) were measured three times using appropriate cuff size with a manual sphygmomanometer after sitting for 5 minutes. Diagnosis of high BP was made using the sex and height percentile-based tables in the fourth report on the diagnosis, evaluation, and treatment of high BP in children and adolescents.[11]

Sexual maturation. Participants were examined by one of the two pediatricians who were responsible for clinical assessments for the study. For girls, breast maturation was documented, and for boys, genital maturation was documented using Marshall and Tanner's sexual maturity rating.[12]

Physical activity. Objective physical activity (PA) was measured using the Actigraph GT3X (Actigraph LLC, Pensacola, FL) accelerometer. Participants were instructed to wear the activity monitor for 5 days on their hip at the waistline at all times, except for when they went to bed at night, bathed, or went swimming. Data from the accelerometer were downloaded, processed, and screened for wear time. Nonwear periods were defined as 60 minutes of consecutive zero counts with an allowance for up to 2 minutes of nonzero counts. A valid wear day included at least 10 hours of wear time. Accelerometer data were calculated for participants with $\geq$3 valid days of wear time. Average total activity counts per day were calculated using summed daily counts detected over all valid wear periods. Time in minutes spent in different activity intensities was calculated by using age-specific formulas for count cutoffs corresponding to sedentary, light (1.00–3.99 metabolic equivalents [METs]), moderate (4.00–6.99 METs), and vigorous ($\geq$7.00 METs). These intensity levels were derived from a published age-specific energy expenditure prediction equation developed by Freedson and colleagues[13] and used by others.[14,15]

Blood tests. Fasting blood specimens were obtained to assess lipid panel, glucose and insulin, and liver transminases. Fasting glucose, triglyceride (TG) levels, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein (HDL) cholesterol were measured spectrophotometrically using a Beckman-Coulter LX-20 autoanalyzer (Beckman-Coulter, Brea, CA). Serum insulin concentration was measured with an immunometric assay using an Immulite 2000 analyzer (Bio-DPC; Siemens Medical, Gywneed, UK). High-sensitivity C-reactive protein (hs-CRP) was measured using latex-enhanced immunoturbidometry on the COBAS INTEGRA 800 analyzer (Roche Diagnostics, Mannheim, Germany). The lowest CRP concentration that could be reproducibly measured with an interassay coefficient of variation of $<$10% was 0.3 mg/L (functional sensitivity). The homeostatic model (HOMA) was used to calculate IR using the formula [HOMA-IR = insulin (μU/ml) $\times$ glucose (mmol/L)/22.5].

Definitions

Obesity phenotypes. With no consensus on the definition of metabolic phenotypes in the pediatric population,[16] and a growing recognition of wide interindividual variation in IR at any given BMI or percent body fat,[17] we based our definition of metabolic phenotypes on level of IR. HOMA-IR has been validated with euglycemic clamp data and glucose tolerance tests in children and adolescents.[18–20] HOMA-IR values HOMA-IR $\geq$2.6 have been associated with presence of MetS, with 0.65 sensitivity and 0.87 specificity.[21] We therefore chose to use this value to define metabolic phenotypes for our primary analysis.

In addition to the cutpoint of HOMA-IR ≥2.6, we performed sensitivity analyses, using different values of HOMA-IR to categorize IR: (1) a value of HOMA-IR ≥4.39, which is >2 standard deviations above the National Health and Nutrition Examination Survey population for normal-weight adolescents[22]; (2) we used the lowest tertile of the present cohort's HOMA-IR. This value was 2.7, which was very close to the primary analysis. Because results were similar regardless of the cutpoint used in our largely prepubertal cohort, we present here phenotypes that use the HOMA-IR cutpoint of 2.6 only.

Intermediate endpoints. We used the following as surrogates of increased CMR.

1. MetS: Presence of MetS in childhood is associated with increased subclinical atherosclerosis in children[23] and predictive of an increased risk of cardiovascular disease (CVD) and diabetes during adulthood.[24] We defined MetS using the commonly used pediatric/adolescent adaptation of the Adult Treatment Panel III criteria. A participant was considered to have MetS if he or she fulfilled three of the following five criteria: (1) HDL <40 mg/dL; (2) waist circumference ≥90th percentile for age and sex; (3) TG ≥110 mg/dL; (d) BP ≥90th percentile; and (5) FG ≥100 mg/dL.[25]
2. Systemic inflammation: Of the inflammatory markers, hs-CRP shows a strong association with CVD risk in adults,[26] as well as with subclinical atherosclerosis in adults[27] and children.[28] Elevated levels of hs-CRP are now considered an independent risk factor for CVD in adults.[26,29] A participant with CRP levels ≥3.0 mg/dL was considered to have high levels of systemic inflammation given that this value is associated with increased cardiometabolic risk.[30]
3. NAFLD: Approximately 38% of obese children in the United States have some degree of NAFLD,[31] with males and Hispanics being at a higher risk. Because liver enzyme elevation is not universal,[32] early identification of fibrosis becomes particularly important in children given that they have the potential to have the longest exposure to the disease and are at particular risk of complications and poor prognosis.

   Mathematical equations have been constructed to predict NAFLD and those with a high likelihood of fibrosis. In our clinical sample, we used the pediatric NAFLD fibrosis index (PNFI) to diagnose severe NAFLD. Using age, waist circumference, and TGs, the PNFI predicts presence of liver fibrosis, as well as necessity of a liver biopsy. Confirming liver fibrosis by liver biopsy, a PNFI ≥9 shows a positive likelihood ratio of 28.6, (95% confidence interval [CI]: 4.0–201.0) and a positive predictive value of 98.5 (95% CI, 91.8–100.0).[33] Only those participants with a PNFI ≥9 were considered to have NAFLD.
4. Microalbuminuria: Microalbuminuria is an independent predictor of CVD and all-cause mortality in both diabetic and nondiabetic men and women[34,35]; and by some, is considered a stronger indicator for future cardiovascular events (CVEs) than SBP or serum cholesterol.[36] Detecting microalbuminuria is an important screening tool to identify people who are at high risk for CVEs and progression of kidney disease. According to the American Diabetes Association (ADA), a random urine specimen can be used to detect microalbuminuria by calculating the albumin (_g)/creatinine (mg) ratio (ACR).[37] As per the ADA and the National Kidney Foundation guidelines, we defined microalbuminuria as an ACR ≥30 g/mg.[38]

Statistical Analysis

After categorizing participants as insulin sensitive (HOMA-IR <2.6) and insulin resistant (HOMA-IR ≥2.6), each group was further divided into overweight (BMI 85th–95th percentile for age and sex) and obese (BMI >95th percentile for age and sex) categories.

Demographic, anthropometric, PA, and laboratory measures were compared among the four groups using one-way analysis of variance analysis with Bonferroni's post-hoc multiple comparison test for continuous variables and the chi-square test for categorical variables. For skewed data, nonparametric alternatives were used.

Prevalence of components of the intermediate endpoints was compared between the insulin-sensitive and -resistant groups using chi-square analysis.

To examine the association between insulin-resistant obesity and the intermediate endpoints of increased cardiometabolic risk (MetS, systemic inflammation, NAFLD, and miroalbuminuria), we constructed separate logistic regression models for each endpoint, using the insulin-sensitive overweight/obese group as the reference category. Each model was initially adjusted for age, sex, and race/ethnicity. To examine the potential confounding effects of degree of obesity and PA, BMI *z*-score and moderate-to-vigorous PA (MVPA) were also added to the models sequentially.

Analyses were performed using Stata software (version 11.0; StataCorp LP, College Station, TX). For all analyses, a p value of <0.05 was considered statistically significant.

Sensitivity Analysis

In addition to using different values of HOMA-IR to categorize the phenotypes (see *Methods* above), we adjusted each multivariable model for tanner stage, rather than age, to examine differences between pubertal maturity and chornological age. Also, because PA data were available for 259 (72%) participants, models were reconstructed using only participants for whom additional adjustment for PA could be performed.

Results

Of the 362 overweight/obese study participants, 157 (43.5%) were categorized as insulin sensitive (HOMA-IR <2.6) and 205 (56.5%) as insulin resistant (HOMA-IR ≥2.6). Table 1 shows the differences between the two groups. The at-risk groups were older and had a higher

Table 1. Demographic, Anthropometric, and Laboratory Differences Between Metabolic Phenotypes in Overweight and Obese Children

	Insulin sensitive overweight/obese (HOMA-IR <2.6) $N=157$	Insulin resistant overweight/obese (HOMA-IR ≥ 2.6) $N=205$	p value
Age, years	8.6 ± 1.6	9.9 ± 1.7	< 0.001
Sex (% females)	72 (46)	115 (56)	0.05
Race/ethnicity, *n* (%)			0.201
Non-Hispanic black	27 (17)	38 (18.5)	
Hispanic	122 (77.7)	147 (71.7)	
Other[a]	8 (5.1)	20 (9.8)	
Pubertal maturity[a], *n* (%)			< 0.001
Prepubertal (Tanner stage 1)	80 (79)	52 (43)	
Earlypuberty (Tanner stage 2 and 3)	19 (19)	66 (55)	
Late puberty (Tanner stage 4&5)	2 (2)	2 (2)	
Height, cm	135.3 ± 10	145 ± 10.8	< 0.001
Weight, kg	43.4 ± 10.6	57.4 ± 15	< 0.001
BMI, kg/m^2	23.45 ± 3.31	26.86 ± 4.35	< 0.001
BMI z-score	1.89 ± 0.42	2.04 ± 0.42	0.001
Waist circumference, cm	76.5 ± 8.4	86.8 ± 10.8	< 0.001
SBP, mm Hg	103 ± 9	109 ± 11	< 0.001
DBP, mm Hg	57 ± 6	59 ± 6	< 0.001
Light PA, min	436 ± 97	420 ± 112	0.22
MVPA, min	82 ± 50	59 ± 38	< 0.001
Sedentary activity, min	436 ± 113	470 ± 114	0.02
TG, mg/dL[b]	61 (45, 86)	85 (59, 114)	< 0.001
HDL-C, mg/dL	48 ± 10	45 ± 9	< 0.001
Fasting plasma glucose, mg/dL	81 ± 9	88 ± 8	< 0.001
Fasting insulin, u/L[b]	9.0 (6.8, 11.1)	19.6 (16, 26.9)	< 0.001
CRP, mg/dL[b]	1.3 (0.5, 3.0)	1.8 (0.8, 4.5)	0.07
HOMA-IR[b]	1.86 (1.36, 2.25)	4.3 (3.4, 5.93)	< 0.001
ALT, U/L	25 ± 20	27 ± 15	0.34
PFNI	4.92 ± 3.05	7.2 ± 6.81	< 0.001
Albumin/creatinine ratio	13.2 ± 61.9	16.1 ± 47.3	0.634

[a]Pubertal staging was available for 221 (61%) participants.

[b]Median (interquartile range).

SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, physical activity; MVPA, moderate-to-vigorous physical activity; TGs, triglycerides; HDL-C, high-density lipoprotein-cholesterol; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; ALT, alanine aminotransferase; PNFI, pediatric NAFLD fibrosis index.

BMI *z*-score. The at-risk groups also had higher levels of all components of MetS, NAFLD, and hs-CRP. However, the difference in albumin/creatinine ratio was not statistically significant. Interestingly, in diagnosing NAFLD, PNFI scores were significantly higher in the insulin-resistant phenotype, regardless of the degree of overweight. Differences based on further differentiation of the groups by overweight and obese subjects are shown in Supplementary Table 1. (see online supplementary material at http://www.liebertpub.com).

Table 2. Differences in Intermediate Endpoints Between Metabolic Phenotypes in Overweight and Obese Children

	Insulin sensitive overweight/obese (HOMA-IR <2.6) *N*=157	Insulin resistant overweight/obese (HOMA-IR ≥2.6) *N*=205	*P* value
BMI ≥95th percentile, *n* (%)	109 (69)	164 (80)	0.021
Components of MetS			
Waist circumference >90th percentile, *n* (%)	111 (71)	175 (85)	0.001
TGs >150 mg/dL, *n* (%)	6 (4)	22 (11)	0.014
HDL-C <40 mg/dL, *n* (%)	28 (18)	73 (36)	<0.001
Elevated BP ≥90th percentile, *n* (%)	18 (11)	43 (21)	0.017
Elevated glucose >100 mg/dL, *n* (%)	1 (0.6)	11 (5)	0.013
MetS, *n* (%)	8 (5)	47(23)	<0.001
Systemic inflammation			
Elevated CRP ≥3.0 mg/dL, n (%)	40 (25)	74 (37)	0.022
NAFLD			
PNFI ≥9, *n* (%)	22 (14)	78 (38)	<0.001
Microalbuminuria			
Albumin/creatinine ratio >30, *n* (%)	6 (4)	17 (9)	0.071

MetS, metabolic syndrome; TGs, triglycerides; HDL-C, high-density lipoprotein-cholesterol; CRP, C-reactive protein; BP, blood pressure; NAFLD, nonalcoholic fatty liver disease; PNFI, pediatric NAFLD fibrosis index; PNFI, pediatric NAFLD fibrosis index; HOMA-IR, homeostatic model assessment for insulin resistance.

Table 2 compares the presence of intermediate endpoints between the insulin-sensitive and at-risk overweight/obese groups. Again, we found a higher prevalence of all endpoints in the at-risk group. However, prevalence of early renal dysfunction (defined by an elevated albumin/creatinine ratio) did not reach significance. Presence of intermediate endpoints in overweight and obese participants is presented in Supplementary Table 2. (see online supplementary material at http://www.liebertpub.com).

Table 3 shows separate multivariable logistic regression models, each using one of the intermediate endpoint of cardiometabolic risk as the dependent variable. After adjusting for age, sex, and race/ethnicity, we found that, compared to the insulin-sensitive group, the insulin-resistant group had a 4-fold higher odds of having MetS (odds ratio [OR], 4.48; 95% CI, 1.94, 10.35). Although the ORs were attenuated once adjusted for BMI *z*-score (OR, 3.0; 95% CI, 1.28, 7.31), the association strengthened after

Table 3. Multivariable-Adjusted Odds Ratios of Intermediate Endpoints Associated With Metabolically At-Risk Overweight/Obesity

	Model 1 (*N*=362)		Model 2 (*N*=362)		Model 3 (*N*=259)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
MetS, ATP criteria	4.48 (1.94,10.35)	<0.001	3.06 (1.28, 7.31)	0.012	5.47 (1.72, 17.35)	0.004
Systemic inflammation (CRP ≥3.0 mg/dL)	1.83 (1.1, 3.03)	0.02	1.24 (0.72, 2.13)	0.44	1.06 (0.56, 2.03)	0.86
NAFLD (PNFI ≥9)	10.03 (4.61 21.80)	<0.001	6.94 (2.49, 19.34)	<0.001	8.66 (2.48, 30.31)	0.001
Microalbuminuria (albumin/creatinine ratio ≥30)	1.95 (0.71, 5.37)	0.20	2.66 (0.91, 7.82)	0.07	1.71 (0.49, 6.04)	0.403

Model 1: adjusted for age, sex and race/ethnicity. Model 2: model 1 + adjusted for BMI z-score. Model 3: model 2 + adjusted for moderate/vigorous activity. Model 3 includes only participants with valid accelerometer data.

MetS, metabolic syndrome; ATP, the National Cholesterol Education Program's Adult Treatment Panel; CRP, C-reactive protein; NAFLD, nonalcoholic fatty liver disease; PNFI, pediatric NAFLD fibrosis index; PNFI, pediatric NAFLD fibrosis index; OR, odds ratio; CI, confidence interval.

further adjustment for MVPA (OR, 5.47; 95% CI, 1.72, 17.35). Insulin-resistant phenotype was also associated with higher odds of NAFLD. Although elevated levels of CRP were noted in the insulin-resistant group, the association was no longer significant after adjusting for BMI *z*-score. We found no significant association between metabolic phenotypes and microalbuminuria.

Sensitivity Analysis

Using different values of HOMA-IR to categorize insulin-resistant overweight/obesity yielded similar directions of associations (results not shown). Using pubertal staging instead of age in the models yielded similar associations, with no difference in significance of the models (results not shown). Finally, using data from participants who had all variables, including PA measures, did not alter the direction of the association in models 1 and 2 (see Supplementary Table 3). (see online supplementary material at http://www.liebertpub.com).

Discussion

In our cohort of overweight and obese children, predominantly belonging to ethnic minorities, we found that insulin-resistant children are at significantly higher odds of having MetS and NAFLD, and that these associations persist even after adjusting for their degree of obesity and MVPA. Thus, our study confirms that metabolic phenotypes based on level of IR have an independent effect on CMH, and that the adverse effects of having the insulin-resistant phenotype can be observed as early as childhood. By using IR to define metabolic phenotypes and the direct association with intermediate endpoints of CMR, we add to the scant knowledge of metabolic phenotypes in the pediatric population.

Despite similar body fatness, metabolically benign obese adults not only carry a lower cardiometabolic risk factor burden,[4,39,40] but also a lower prevalence of subclinical atherosclerosis[3,41] and clinical CVD, compared to at-risk obese adults.[1,2,42] In our cohort, insulin-resistant subjects were significantly heavier than their insulin-sensitive peers in both the overweight and obese categories. However, adjustment for BMI *z*-score did not alter the increased odds of having MetS and NAFLD in the at-risk group. Other studies have suggested an independent effect of IR on cardiovascular risk in children.[43] Over an 8-year period of observation, the Bogalusa Heart Study showed a strong relation between persistently high fasting insulin levels during childhood and the development of CVR factors in young adults.[44] Our study shows that, at the HOMA-IR level of ≥ 2.6, CMR factors can be found even during childhood. Although our results do not fully reproduce Sinaiko and colleagues' findings of an independent association of both body fatness and IR with cardiovascular risk,[45] these differences could be owing to the difference in pubertal maturity between our cohorts. Physiologically, peak pubertal development is marked with a significant increase in IR[46] and thus a more marked effect of IR may have been apparent in Sinaiko and colleagues' cohort. Our cohort was made of younger children, the majority of whom were prepubertal or in early puberty, making the effect of IR and body weight more striking and concerning.

Interestingly, when examining the association of metabolic phenotypes with NAFLD, we found that the association was much stronger with IR, as evidenced by a higher prevalence of PNFI >9 in children with insulin-resistant phenotype, regardless of their degree of overweight (Supplementary Table 1). (see online supplementary material at http://www.liebertpub.com). In regression models, both at-risk phenotype and BMI *z*-score were strongly associated with NAFLD. Thus, our study corroborates the association between NAFLD and IR reported in the literature.[47]

Pathophysiologically, in the setting of excess weight, IR is considered to play a pivotal role in accumulation of TGs in the liver, leading to increased oxidative stress and inflammation. In addition, certain genetic alleles have been associated with an increase in the progression to fibrosis in both adult and pediatric populations.[48,49] Although studies report a preponderance of NAFLD in Hispanic children, compared to non-Hispanic blacks and white children,[50] we did not observe these race/ethnic differences in our predominantly Hispanic population. Our lack of spotting these known race/ethnic differences could be owing to our using predicting equations, rather than liver biopsies. However, even with the lack of specificity of these equations, the strong associations between insulin-resistant phenotype and NAFLD cannot be ignored.

The healthier metabolic profile of insulin-sensitive obese adults has been postulated to be owing to a lower accumulation of fat within ectopic sites,[51,52] differences in visceral fat deposition,[40,53] lower levels of inflammation,[39] and, possibly, genetic protective mechanisms.[54] We did not find a significant difference in CRP levels between the two phenotypes and in regression models; once adjusted for BMI *z*-score, the association between metabolic phenotypes and systemic inflammation was lost. We used CRP because of its known predictive ability for CVD risk. However, other inflammatory markers may show stronger associations with IR.

Our results should be seen in light of certain limitations. As a cross-sectional study, we cannot comment on the cause and effect of IR and the intermediate endpoints of increased cardiometabolic risk factors. In the absence of liver biopsy, the gold standard to confirm the degree of NAFLD, we used a mathematical equation for diagnosis. However, by using the PNFI, we are identifying only those subjects who have a high likelihood of NAFLD. It is possible that we have not identified participants with mild-to-moderate fatty infiltration who may also benefit from early counseling for weight loss. As medical treatment options for NAFLD become available, the rationale for identifying all patients with early stages of NAFLD will become stronger. Finally, our participants were recruited from a clinical weight loss program, and the results may not be generalizable to the entire pediatric population.

Despite these limitations, our study adds to the existing literature of the presence of metabolic phenotypes in the overweight and obese pediatric population and the strong association with cardiometabolic health. By using a fasting insulin and glucose to calculate HOMA-IR values of ≥ 2.6, clinical providers can identify prepubertal and early puberal children most at risk of developing CMR factors and focusing limited resources on aggressive weight interventions may lead to improvement in cardiometabolic health.

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Author Disclosure Statement

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