Impact of Severe Obesity on Cardiovascular Risk Factors in Youth

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Objective To compare cardiovascular risk factor clustering (CVRFC) in severely obese youth with those with lower degrees of obesity.

Study design We divided a childhood obesity clinic derived cohort into the degrees of obesity (class I, II, and III) and added a "class IV" category corresponding to >160% of the 95th centile of body mass index (BMI) for age and sex. In a cross-sectional analysis, we investigated the presence of CVRFC in 2244 participants; in 621 who were followed longitudinally, we investigated the determinants of endpoint CVRFC.

Results Class IV obesity was associated with increased risk for CVRFC compared with overweight (OR = 17.26, $P < .001$) at a similar magnitude to class III obesity (OR = 17.26, $P < .001$). Male children were at greater risk for presence of CVRFC (OR = 1.57, $P = .03$) compared with female children. Adiponectin (OR = 0.90, $P < .001$) and leptin levels (OR = 0.98, $P = .008$) were protective, independent of degree of obesity. Baseline class IV obesity was associated with increased risk compared with overweight of having CVRFC at follow-up (OR = 5.76, $P = .001$), to a similar extent as class III obesity (OR = 5.36, $P = .001$). Changes in the degree of obesity were significant predictors of CVRFC on follow-up (OR = 1.04, $P < .01$ per percent BMI change).

Conclusions The metabolic risk associated with obesity in childhood is conferred prior to reaching class IV obesity. An individualized risk stratification approach in children with severe obesity should be based on presence of complications rather than simple BMI cutoffs. *(J Pediatr 2018;192:105-14).*

Trial Registration ClinicalTrials.gov NCT01967849.

Although the increase in the prevalence of childhood obesity in the US seems to have recently reached a plateau,[1] the prevalence of severe obesity is still on the rise.[2] In adults the degrees of obesity are classified according to body mass index (BMI) cutoffs (30-34.9 kg/m^2 considered "mild" or class I, 35-39.9 kg/m^2 "moderate" or class II, and BMI >40 kg/m^2 considered "severe" or class III[3-5]); similar definitions of childhood obesity are lacking. Higher obesity categories in adults have been shown to predict mortality.[6] The indications for an intensive approach toward obesity management in adults, namely surgical (bariatric) interventions, are usually based on the presence of severe obesity or moderate obesity with significant comorbidities.[7-10] In contrast, the thresholds for performing such interventions in youth according to most[11,12] but not all[13] authorities are set at higher BMI thresholds representing "extreme obesity" (BMI >50 kg/m^2 with mild comorbidities or BMI >40 kg/m^2 with major comorbidities). This raises the question whether extremely obese children are at greater risk for the presence and/or development of obesity driven metabolic comorbidities justifying reserving intensive surgical interventions only for this high-risk obesity category. In other words, although the presence of obesity-associated morbidity such as prediabetes and cardiovascular risk factor clustering (CVRFC, defined by some as "the metabolic syndrome") is common and has been shown to significantly rise with greater degrees of obesity in childhood,[14-16] it is not clear whether this risk increment plateaus above a certain BMI threshold or continues to rise in cases of extreme obesity. This question is important because this should dictate a strategy for defining the optimal timing for surgical and perhaps pharmacologic interventions in morbidly obese children and adolescents.[17]

We evaluated the presence of obesity associated CVRFC in children and adolescents across the spectrum of obesity. Using a cross-sectional approach, we evaluated whether such risk factors are more prevalent in extremely obese children compared with their counterparts with lower degrees of obesity. In a subsample that was followed longitudinally, we evaluated the dynamics of anthropometric and biochemical cardiovascular risk factors over time in children with various degrees of obesity at baseline. We hypothesized that children and adolescents with extreme obesity will manifest greater CVRFC that will worsen over time than those with milder forms of obesity.

ALT	Alanine aminotransferase
BMI	Body mass index
CRP	C-reactive protein
CVRFC	Cardiovascular risk factor clustering
HDL	High-density lipoprotein
OGTT	Oral glucose tolerance test

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Methods

Between 2005 and 2015, subjects aged 7-20 years were recruited to the Yale Pathophysiology of Type 2 Diabetes in Youth Study, a long-term, multiethnic cohort aimed at studying early alternations in glucose metabolism in obese children (ClinicalTrials.gov: NCT01967849). All were referred to the Yale Pediatric Obesity Clinic and received an intervention based on behavioral modification as previously described.[18,19] None were actively participating in other weight loss oriented programs. Follow-up included bi-annual clinic visits in which behavioral modification was attempted via health monitoring, nutritional guidance, and recommendations for increased physical activity along with family-oriented counseling. Participants of this analysis did not take any medications at baseline or during follow-up that may affect blood pressure, glucose, lipid metabolism, or weight gain/loss and had a normal functioning thyroid at baseline and throughout the follow-up. None of the participants underwent surgical interventions for obesity. Parental written consent was obtained before entering the study as was assent from the children. The Yale University School of Medicine human investigation committee approved the study.

At every clinic visit, anthropometric measurements and biochemical markers were documented and an oral glucose tolerance test (OGTT) was performed at baseline and at 2-year intervals. The OGTT test was performed with the administration of 1.75 g of glucose per kg of body weight (maximal dose 75 g). Baseline blood samples were obtained from the children while they were fasting prior to the OGTT for measurement of levels of glucose, insulin, lipids, adipocytokines, and CRP. Weight and height were measured to the nearest 0.1 cm and 0.1 kg, respectively, and BMI was calculated. Blood pressure was measured 3 times while seated, and the average of the last 2 measurements was used for the analysis. The physical examination included determination of the stage of puberty according to the criteria of Tanner.[20] Participants were defined as prepubertal or pubertal (Tanner stage >1).

Plasma glucose was determined with a YSI 2700 Analyzer (Yellow Springs Instruments, Yellow Springs, OH) and lipid levels (cholesterol, triglycerides, and high-density lipoprotein [HDL] cholesterol) were measured with an AutoAnalyzer (Model 747–200, Roche-Hitachi, Indianapolis, IN). Insulin and total adiponectin levels were measured using double antibody RIAs from Millipore (insulin intra- and inter-assay coefficients of variation are 6.8 and 11.6%, respectively; adiponectin intra- and inter-assay coefficients of variation are 7.1 and 9.5%, respectively). C-reactive protein (CRP) levels were measured using the ultrasensitive assay (Kamiya Biomedical, Seattle, WA) with an intra-assay coefficient of variation that is no greater than 3.0% and inter-assay coefficient lower than 11.6%).

Elevated systolic or diastolic blood pressure was defined as a value that exceeded the 95th percentile for age and sex.[21] Abnormalities in fasting levels of triglycerides and HDL cholesterol were adjusted for age, sex, and race (>95th percentile for triglycerides; <5th percentile for HDL cholesterol).[22] Impaired glucose tolerance was defined as a glucose level greater than 140 mg per deciliter (7.8 mmol per liter) but less than 200 mg per deciliter (11.1 mmol per liter) at 2 hours of the OGTT.[23] The participants were classified as meeting the criteria of CVRFC if they met 3 or more of the following criteria: BMI z score >2.0; triglyceride level above the 95th percentile for age and sex; HDL cholesterol level below the 5th percentile for age and sex; systolic or diastolic blood pressure above the 95th percentile for age and sex; impaired glucose tolerance on the OGTT.[14] This definition of CVRFC has been shown to be associated with intimal medial thickness in obese youth.[24] Insulin sensitivity was determined using the whole body insulin sensitivity index [25] calculated using all glucose and insulin measurements from the OGTT.

For assessment of degrees of obesity in the participants we followed the approach used by Skinner et al who created a classification similar to that used in adults.[15] This defines "overweight" as being between the 85th and 95th centile for age and sex, "mild obesity" (class I) as being between 100% and 120% of the 95th centile for age and sex, "moderate obesity" (class II) as being between 120% and 140% of the 95th centile for age and sex and "severe obesity" (class III) as being above the 140% of the 95th centile for age and sex. To assess the impact of the extremes of obesity in childhood, we defined the "extreme-obesity" category ("class IV") as being greater than the 160% of the 95th centile for age and sex.

Variables are presented as means ± SD. Variables that were not normally distributed were log transformed for the analysis, yet the results are presented as the original values for ease of interpretation. Group comparisons between obesity categories in the analyses were performed using ANOVA with post-hoc Bonferroni corrections for multiple comparisons. Logistic regression models were performed to identify the predictors of the presence of cardiovascular risk clustering in the cross-sectional and longitudinal analyses using the overweight group as a reference. All analyses were performed using SPSS 19.0 for Windows (SPSS Inc, Chicago, IL).

Results

At baseline, there were 2244 participants in the cross-sectional analysis (**Table I**). Subjects were classified into obesity categories with an addition of the class IV obesity (extreme) category. In total, 40% were male and 60% were female. There was a higher prevalence of female subjects in the lower compared with the higher obesity categories ($p\chi^2 < 0.001$). The race breakdown between obesity categories showed a significant predominance of African Americans in the super and severe obesity categories ($p\chi^2 < 0.001$). The overweight participants were slightly older compared with other obesity categories ($P < .01$ vs all other obesity categories).

As expected, weight increased by obesity category from ~59 kg in the overweight group to ~119 kg in the class IV group. Similarly, waist circumference, hip circumference, and waist-to-hip ratio significantly increased across obesity categories (P ANOVA <.001 for all). Diastolic and systolic blood pressure