Examining Metabolic Syndrome Definitions in Overweight Hispanic Youth: A Focus on Insulin Resistance

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Objective   To examine the prevalence of the metabolic syndrome in overweight Hispanic youth according to 3 published pediatric definitions. Furthermore, the relationship of each definition to directly measured insulin resistance was examined.

Study design   We conducted a secondary data analysis of 218 overweight Hispanic youth with a family history of type 2 diabetes mellitus. The metabolic syndrome was defined as ≥3 of these criteria: elevated triglyceride level, low high-density lipoprotein cholesterol level, elevated blood pressure, abdominal obesity, and hyperglycemia. The cutoff points were derived from updated definitions of Cook et al,[1] Cruz et al,[2] and Weiss et al.[3] Insulin sensitivity was determined with the insulin-modified frequently sampled intravenous glucose tolerance test.

Results   Prevalence of the metabolic syndrome ranged from 25.7% to 39%, with moderate to substantial agreement between definitions (kappa = 0.52-0.70). Regardless of definition, an inverse relationship between metabolic risk and insulin sensitivity was noted such that children with the metabolic syndrome had 51% to 60% lower insulin sensitivity compared with children without any risk factors ($P ≤ .001$ for all definitions).

Conclusion   The metabolic syndrome is prevalent in overweight Hispanic youth and may provide pediatricians with additional clinical insight for identifying the most metabolically at-risk children. Working toward a uniform and practical definition of the metabolic syndrome may improve its clinical implementation. *(J Pediatr 2008;152:171-6)*

The metabolic syndrome is a clustering of cardiovascular disease and type 2 diabetes mellitus risk factors, which includes central obesity, hypertension, dyslipidemia, and glucose intolerance.[4] Collectively, these risk factors cluster around a common pathophysiolgy related to insulin resistance and thus may be an early indicator of chronic disease risk.[5] In adults, the metabolic syndrome is predictive of future diabetes mellitus, cardiovascular disease, and all-cause mortality.[6] Although the predictive value of the metabolic syndrome has not been established in younger populations, evidence indicates that the individual risk factors in children track into adulthood.[7,8] Several recent reports have demonstrated that 30% to 50% of overweight youth exhibit the metabolic syndrome phenotype.[1-3] These estimates are suggestive of dramatically increased risk for long-term obesity-related health consequences in this population.

To this end, the American Academy of Pediatrics has identified the prevention of pediatric obesity and its metabolic co-morbidities as a critical priority for clinicians, with the hopes of improving the current and future health status of overweight youth.[9] The pediatric growth charts have provided pediatricians and researchers with a standardized, population-based tool to assess for overweight and track adiposity changes with time.[10] Unlike the pediatric growth charts, there is no accepted reference for the metabolic syndrome in children. As such, clinicians and researchers are left with the challenge of how to appropriately ascertain the level of metabolic risk in overweight children with multiple cardiovascular disease and diabetes mellitus risk factors.

Our research group has examined the relationship between the metabolic syndrome and insulin sensitivity in overweight Hispanic youth.[2] We used age-appropriate cutoff points to establish a pediatric definition of the metabolic syndrome on the basis of criteria from the National Cholesterol Education Panel Adult Treatment Panel III (ATP III).[4]

ATP III	National Cholesterol Education Panel Adult Treatment Panel III	IFG	Impaired fasting glucose
		IGT	Impaired glucose tolerance
HDL	High-density lipoprotein	USC	University of Southern California

Other studies have used varying pediatric cutoff points of the ATP III definition to establish prevalence rates of the metabolic syndrome in adolescents[1] and its relationship to obesity.[3] However, comparing data across studies is problematic because of the lack of congruency between definitions. Recently, the National Institute of Child Health and Human Development sponsored a workshop to initiate dialogue among researchers and clinicians about a pediatric definition of the metabolic syndrome. Collectively, the group was asked to analyze existing data cohorts against various published definitions of the metabolic syndrome in youth. We summarize the data presented to the Pediatric Metabolic Syndrome Working Group, for which the purpose was: 1) to compare the prevalence of the metabolic syndrome phenotype with various published definitions and 2) to examine the association between the metabolic syndrome definitions and insulin sensitivity in a cohort of overweight Hispanic youth who are at extremely high risk for cardiovascular disease and type 2 diabetes mellitus.

METHODS

Participants

Data from 218 children from the University of Southern California (USC) SOLAR (Study of Latino Adolescents at Risk) Diabetes Project were analyzed. The study was designed to explore risk factors for the development of type 2 diabetes mellitus in at-risk youth.[11] Participants were recruited from greater Los Angeles County through community health clinics, health fairs, and word of mouth. They were required to meet these inclusion criteria at baseline: 1) Latino ethnicity (all 4 grandparents of Latino descent), 2) age 8 to 13 years; 3) a family history of type 2 diabetes mellitus (sibling, parent, or grandparent), and 4) age and sex BMI ≥85th percentile on the basis of the standards of the Centers for Disease Control and Prevention. Children were excluded when they had an earlier major illness, including type 1 or type 2 diabetes mellitus, took medications, or had a condition known to influence body composition, insulin action, or insulin secretion. This study was approved by the USC Institutional Review Board. Written informed consent and assent were obtained from all parents and children before any testing procedures. Data from this cohort have been reported.[2,12]

Protocol

Children arrived at the USC General Clinical Research Center in Los Angeles County Hospital at approximately 8:00 a.m. after an overnight fast. Physical maturation was assessed by a pediatrician according to the criteria of Marshall and Tanner.[13] Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer, and weight was measured to the nearest 0.1 kg with a medical balance beam scale. Subjects ingested 1.75 g of oral glucose solution/kg body weight (to a maximum of 75 g). Blood samples were taken via antecubital vein catheter for measurement of glucose before and 2 hours after glucose load.

At least 7 days after the initial visit, children were admitted for an overnight stay to the General Clinical Research Center, where they underwent a brief physical examination, completed body composition (see below), and anthropometric measures. At aproximately 7:30 the next morning, flexible intravenous catheters were placed in both arms. Fasting blood was drawn for analysis of plasma lipid, insulin, and glucose concentrations. At time zero, glucose (25% dextrose, 0.3 g/kg body weight) was administered intravenously. Blood samples were then collected at these points: 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes. Insulin (0.02 U/kg body weight; Humulin R regular insulin for human injection; Eli Lilly, Indianapolis, IN) was injected at 20 minutes. Plasma was analyzed for glucose and insulin levels, and values were entered into the Minmod Millenium 2003 computer program (version 5.16) for determination of insulin sensitivity.

Anthropometry and Blood Pressure

Waist circumference (at the umbilicus) was recorded to the nearest 0.1 cm by a trained technician. Sitting blood pressure was measured on 2 separate days by using the right arm after the subject had rested quietly for 5 minutes. On each occasion, 3 readings of blood pressure were obtained, and the average of the 6 measures was recorded and used for analysis.[14]

Body Composition

Total body composition (fat mass and fat-free mass [ie, soft lean tissue mass]) was determined with a whole-body dual-energy x-ray absorptiometry scan by using a Hologic QDR 4500W (Bedford, MA).

Definition of the Metabolic Syndrome

In adults, the presence of the metabolic syndrome is defined as having at least 3 of these risk factors: abdominal obesity measured via waist circumference, triglyceride level ≥150 mg/dL, high-density lipoprotein (HDL) cholesterol level <40 mg/dL in men and <50 mg/dL in women, blood pressure ≥130/85 mm Hg, and a serum fasting glucose level ≥100 mg/dL.[15] Three pediatric variations (Cook et al,[1] Cruz et al,[2] and Weiss et al[3]) based on the ATP III definition were used. All defined metabolic syndrome as ≥3 risk factors, but incorporated different cutoff points depending on age, sex, and ethnicity (Table I). The original manuscripts used either available pediatric criteria for each risk factor or, in the case of Cook et al,[1] cutoff points derived from the dataset. The original manuscripts were published in 2003 to 2004, and since that time, revised cutoff points for several of the individual metabolic syndrome risk factors have been released. To incorporate the most up-to-date evidence, our analyses used current cutoff points rather than what was available at the time of original publication. For example, Cook et al used a fasting glucose level ≥110 mg/dL to define impaired fasting glucose (IFG). Since the original publication, the American Diabetes Association has redefined IFG as a fasting glucose

Table I. Metabolic syndrome definitions

Feature	Cook et al	Cruz et al	Weiss et al
Elevated triglyceride level	≥110 mg/dL	≥90th% for age and sex*	≥95th% for age, sex and ethnicity*
Low HDL cholesterol level	≤40 mg/dL	≤10th% for age and sex	≤5th% for age, sex, and ethnicity*
Abdominal adiposity	≥90th% for age and sex†	≥90th% for age, sex, and ethnicity‡	BMI-z ≥2
Hyperglycemia	IFG§	IGT	IGT
Elevated blood pressure	≥90th% for age, sex and height¶	≥90th% for age, sex, and height¶	≥95th% for age, sex, and height¶

IGT, impaired glucose tolerance (post-challenge glucose ≥140 <200 mg/dL).[16]
*Hickman et al.[24]
†Cook et al used original dataset to define waist circumference cutoff point.
‡Cruz et al originally used unpublished data, which have since been published. The published data have been used in this manuscript.[17]
§Cook et al originally used fasting glucose level ≥110 mg/dL to define IFG. The criteria for IFG has been updated by the American Diabetes Association as a fasting glucose level ≥100 mg/d.[16] The revised cutoff point has been used.
¶All 3 variations for defining elevated blood pressure have been updated.[14]

level ≥100 mg/dL[16]; thus the current value was used. Other notable updates included the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents[14] and the publication of waist circumference percentiles in a nationally representative sample of children and adolescents.[17]

Assays

Blood samples taken during the oral glucose tolerance test were separated for plasma and immediately transported on ice to the Los Angeles County-USC Medical Center Core Laboratory, where glucose was analyzed with a Dimension clinical chemistry system by using the in vitro hexokinase method (Dade Behring, Deerfield, IL). During the overnight stay, fasting blood samples were taken and centrifuged immediately to obtain plasma, and aliquots were frozen at −70°C until assayed. Fasting triglyceride and HDL cholesterol levels were measured with the Vitro chemistry DT slides (Johnson and Johnson Clinical Diagnostics, Rochester, NY).

Statistics

Sex differences in physical and metabolic characteristics were examined with independent sample t tests. Variables that were not normally distributed were log transformed (insulin sensitivity, total fat mass, total fat-free mass, body mass index percentile, systolic blood pressure, diastolic blood pressure, waist circumference, triglycerides, HDL cholesterol, and fasting glucose). Descriptive characteristics were presented as untransformed data for ease of interpretation. Agreement among cutoff points of definitions for prevalence of individual risk factors and the metabolic syndrome was examined by using χ^2 analysis and Kappa statistics. Interpretation of Kappa scores was taken from Landis and Koch[18] and were as follows: 0 to 0.19 = poor agreement; 0.20 to 0.39 = fair agreement; 0.40 to 0.59 = moderate agreement; 0.60 to 0.79 = substantial agreement; and 0.8 to 1.0 = almost perfect agreement. Analysis of variance was used to establish differences in insulin sensitivity according to definition across children who exhibited 0, 1, 2, or ≥3 risk factors of the metabolic syndrome. Results are presented as estimated means plus or minus SE for insulin sensitivity. All analyses were performed

with SPSS software version 14.0 (SPSS, Chicago, IL), with a type I error set at 0.05.

RESULTS

Physical and metabolic profiles of the children are presented in Table II. Girls had significantly lower fasting glucose levels and diastolic blood pressure, but had significantly higher percent fat compared with boys. Data from both sexes were combined for further analyses.

The prevalence of the individual features of the metabolic syndrome by the 3 definitions is presented in Table III. In general, the definitions showed substantial to almost perfect agreement (Kappa statistic between 0.6 and 1.0). However, the measure of hyperglycemia from the Cook et al definition showed poor agreement (Kappa = 0.13) with both the Cruz et al and the Weiss et al definitions. Furthermore, the Cook et al definition of the metabolic syndrome (≥3 features) showed only moderate agreement with either the Cruz et al or Weiss et al definitions (both Kappa = 0.52). The Cruz et al definition of the metabolic syndrome and the Weiss et al definition showed substantial agreement with each other (Kappa = 0.7).

The Figure displays the mean insulin sensitivity ± SE according to the number of abnormal features for each definition. Regardless of definition, insulin sensitivity was significantly lower in children with either 2 or 3 abnormal features compared with those with 0 features. Moreover, children with the metabolic syndrome (≥3 features) had very similar insulin sensitivity levels across the definitions (metabolic syndrome via Cook et al = 1.6 ± 0.15, via Cruz et al = 1.6 ± 0.16, via Weiss et al = 1.6 ± 0.17 × 10−4 min−1/μU/mL).

DISCUSSION

Obesity has become the most prevalent chronic disorder affecting today's youth.[19] Furthermore, pediatricians are diagnosing and treating several obesity-related conditions (eg, type 2 diabetes mellitus and dyslipidemia) that were once thought to be exclusively adult disorders. Several recent reports have described a large proportion of overweight youth with multiple metabolic derangements in the form of the metabolic syndrome.[1-3] Unfortunately, variations in the def-

Table II. Descriptive and metabolic characteristics of sample

Characteristic	Boys	Girls	Total
N	123	95	218
Age (years)	11.2 ± 1.6	11 ± 1.8	11.1 ± 1.7
Height (cm)	149.5 ± 11	148.7 ± 11.7	149.3 ± 11.2
Weight (kg)	64.0 ± 18.9	63.6 ± 20.6	63.9 ± 19.6
BMI (percentile)	96.9 ± 4.4	96.7 ± 4.6	97.8 ± 4.5
Total fat mass (kg)	24.1 ± 10.2	25.6 ± 10.4	24.8 ± 10.3
Total lean tissue (kg)	37.6 ± 9.9	35.7 ± 10.4	36.7 ± 10.2
Percent fat (%)	37.2 ± 6.9	39.9 ± 5.5†	38.4 ± 6.5
Systolic blood pressure (mm Hg)	110 ± 10	110 ± 10	110 ± 10
Diastolic blood pressure (mm Hg)	64 ± 6	62 ± 5*	63 ± 6
Triglycerides (mg/dL)	114.4 ± 66.7	99.6 ± 42.3	108 ± 57.9
HDL cholesterol (mg/dL)	37.4 ± 8.8	37.8 ± 8.3	37.6 ± 8.6
Waist circumference (cm)	88.9 ± 13.4	86.9 ± 13.8	88 ± 13.6
Fasting glucose (mg/dL)	92.9 ± 6.3	89.8 ± 6.7†	91.5 ± 6.6
2-hour glucose (mg/dL)	125.4 ± 17.4	128.3 ± 17.8	126.7 ± 17.6
Insulin sensitivity (×10−4 min−1/ μU/mL)	2.2 ± 1.5	2.1 ± 1.5	2.1 ± 1.5

Data are means ± SD.
*P < .05.
†P < .01.

inition and the cutoff points used have hindered comparison across studies. These findings suggest that despite differences in cutoff points, the 3 definitions examined have substantial to almost perfect agreement for most of the metabolic syndrome risk factors. However, when clustered together, the metabolic syndrome defined by Cook et al only showed moderate agreement with either the Cruz et al or Weis et al definition (kappa = 0.52). This is most likely a function of the poor agreement (kappa = 0.13) noted between the IFG and impaired glucose tolerance (IGT) criteria for hyperglycemia. We did note that, regardless of definition, children with the metabolic syndrome consistently had lower insulin sensitivity compared with children with no risk factors. Therefore, the metabolic syndrome may represent a useful clinical indicator of youth who are at greatest risk for the development of obesity-related chronic diseases such as cardiovascular disease and type 2 diabetes mellitus.

This population represents a comparatively understudied minority group with one of the highest lifetime risks for developing type 2 diabetes mellitus.[20] All our participants had a family history of type 2 diabetes mellitus. Although we cannot determine the impact of family history on our results, other studies have shown that adults with a family history of type 2 diabetes mellitus are more likely to exhibit multiple metabolic risk factors.[21] Whether the same holds true for younger populations has not been determined.

Recent guidelines recommend that overweight youth undergo an in-depth medical evaluation for the metabolic co-morbidities associated with increasing levels of adiposity.[22] A comprehensive examination including a fasting blood draw would provide clinicians with sufficient information to identify youth with the metabolic syndrome and potentially refer these youth for appropriate care or counseling. However, a recent report showed that clinicians routinely fail to adequately screen for obesity in youth, let alone for the metabolic syndrome.[23] Perhaps the challenges of implementing current guidelines in pediatric providers is an indication that a complex algorithm for defining the metabolic syndrome is clinically impractical and is thus less likely to be executed.

The 3 definitions we examined represented varying levels of complexity. For example, all used an age-, height-, and sex-adjusted cutoff point for defining elevated blood pressure,[14] but only the Cruz et al and Weiss et al definitions used an age- and sex-adjusted cutoff point for dyslipidemia (elevated triglyceride or low HDL cholesterol levels).[24] Although Cook et al used age and sex data to establish their criteria for dyslipidemia, they extrapolated those data to come up with a universal cutoff point for all ages and both sexes (Table I). Perhaps the most dramatic difference in the definitions and arguably the cutoff point that would be most difficult to implement in the clinic was the criteria for hyperglycemia. Both Cruz et al and Weiss et al defined hyperglycemia with IGT (2-hour glucose level ≥140 mg/dL),[16] and Cook et al used IFG. To ascertain whether a child has IGT, a provider must administer a 2-hour oral glucose tolerance test initiated with fasting conditions. Establishing IFG can be accomplished with a simple fasting glucose measure. Although very little is known about the metabolic differences in risk between youth with IGT and youth with IFG,[25] we have shown that both forms of pre-diabetes (IFG and IGT) convey similar diabetes risk via reduced pancreatic beta cell function.[11,26] Because our findings that the metabolic syndrome (regardless of criteria) seemed to identify the most at-risk youth and the overwhelming need for clinicians to identify and track these youth, it stands to reason that a clinically practical definition of the syndrome be established (ie, similar to that of Cook et al).

The epidemic of pediatric obesity and related metabolic disorders will dramatically impact the future of our healthcare system. Although longitudinal data are lacking, it is likely that cardiovascular disease and type 2 diabetes mellitus will develop in a high proportion of youth with the metabolic syndrome. In adults, lifestyle interventions have been shown to improve the metabolic syndrome phenotype[27] and prevent the progression from impaired glucose tolerance to frank type 2 diabetes mellitus.[28] A growing body of literature in the pediatric population suggests that similar improvements in cardiovascular disease and type 2 diabetes mellitus risk factors can be achieved via lifestyle modification.[29,30] Therefore, establishing a unified definition of the metabolic syndrome will allow clinicians to appropriately identify youth at high risk

Table III. Prevalence of metabolic syndrome phenotype by definition

Feature	Cook et al	Cruz et al	Weiss et al	Average un-weighted kappa
Elevated triglycerides (%)	85/218 (39%)	45/218 (20.6%)	53/218 (24.3%)	0.68
Low HDL cholesterol (%)	145/218 (66.5%)	125/218 (57.3%)	132/218 (60.6%)	0.8
Abdominal adiposity (%)	157/218 (72%)	153/218 (70.2%)	138/218 (63.3%)	0.74
Hyperglycemia (%)	26/218 (11.9%)	55/218 (25.2%)	55/218 (25.2%)	0.42
Elevated blood pressure (%)	44/218 (20.1%)	44/218 (20.1%)	27/218 (12.4%)	0.86
Metabolic syndrome ≥3 features (%)	85/218 (39%)	67/218 (30.7%)	56/218 (25.7%)	0.58
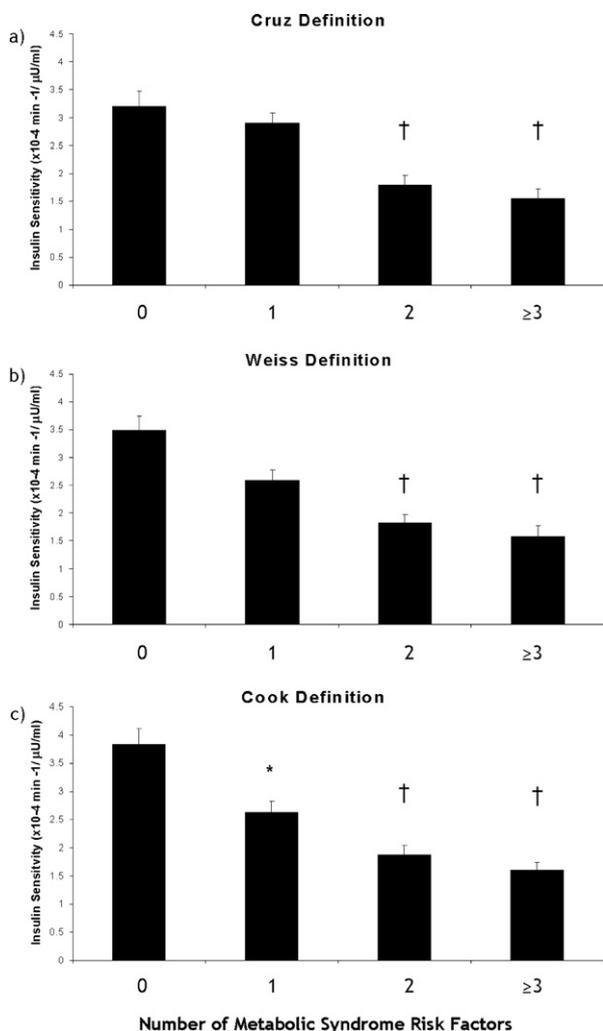
Figure. Insulin sensitivity and the metabolic syndrome: Mean insulin sensitivity ± SE according to pediatric adapatations by **A,** Cruz et al, **B,** Weiss et al, and **C,** Cook et al of the ATP III definition of the metabolic syndrome in overweight Hispanic youth with 0, 1, 2, or ≥3 risk factors. Youth with 0 risk factors for each respective definition serve as reference for comparisons. $*P <.05$; $†P <.01$.

who may benefit from intensive therapeutic lifestyle modifications or pharmacologic treatments. Because we have yet to determine all the factors associated with increased disease risk in youth (eg, obesity, insulin resistance, family history, phys-

ical activity, dietary intake, etc.) and it is almost certainly multi-factorial in nature, it is likely that no one intervention may be ideal. Ultimately, the goal of a pediatric definition of the disorder may provide for improvements in the quality of care and eventual quality of life of overweight youth.

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50 Years Ago in *The Journal of Pediatrics*

REFLECTIONS ON INFANTILE GASTROENTERITIS AND ITS TREATMENT

Levin S. J Pediatr 1958;52:227-44

At the beginning of the 20th century, gastroenteritis and its consequent dehydration were a major cause of childhood mortality. Not surprisingly, investigations into the causes and management of diarrheal dehydration consumed many of the founders of our specialty.

By the middle of the 20th century, mortality from diarrhea had plummeted, and many of the management principles on which we base current practice had been established. In this extensive review, Levin, from Johannesburg, South Africa, provides us with a glimpse into the "state of the art" 50 years ago. A few things have changed, but much of what Levin stressed then remains useful advice today.

The review begins with a discussion of "medication" for childhood diarrhea. Levin's general dismissal of most agents should ring true today, although we still see children being treated with kaolin and opiate preparations, both of which were singled out for avoidance. Interestingly, in light of our current interest in "probiotics," he noted that yogurt was frequently used despite the lack of "really good evidence" of its efficacy. The modern reader may find his discussion of oral antibiotics quite dated; however, keep in mind that the viral etiology of most childhood gastroenteritis had yet to be established.

Levin next moves to a discussion of intravenous therapy for dehydration, an intervention just coming into its own at the time of the review. Unfortunately, this section reflects the somewhat obfuscated state of this particular topic in 1958. The commentary recognizes the possibility of seizures occurring during the course of treatment, yet equivocates on the optimal initial fluid for rehydration. In balance, however, Levin stresses the body's remarkable homeostatic ability to correct metabolic derangements, given the adequate provision of substrate. He also reminds the reader that no fluid plan for a severely dehydrated child can be written with a long time horizon; frequent reevaluations and recalculations are necessary.

Finally, Levin reminds us that "starvation" and "bowel rest" are inappropriate strategies in the management of childhood diarrhea. Although this concept is now a part of widely accepted practice guidelines, it needs frequent reinforcement.

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10.1016/j.jpeds.2007.09.023