In 1998, the World Health Organization (WHO) designated obesity as a global epidemic affecting adults and children. In general, obesity is defined as the degree of somatic overweight that affords detrimental health consequences. This definition does not contemplate a specific cutoff point, but it allows health care providers to consider individual predisposition when assessing at-risk children, including underlying conditions, family history, medications, and lifestyle. Within the scientific community, the discovery of leptin and the elucidation of disorders affecting various neuroendocrine pathways and the genetic linkages of obesity have promulgated the notion that obesity is a disease.

BMI is the accepted measure of obesity in children and adolescents. In childhood, comparison of BMI to normal curves for age and sex allows for categorization of BMI above the 85th percentile as overweight and above the 95th percentile as obese.

In the United States, the most recent estimates of obesity prevalence are based on data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES IV).\(^1\) NHANES IV demonstrated that 20.6% of 2- to 5-year-old children in the United States were overweight. In older children, this prevalence was even higher, with 30.3% of 6- to 11-year-old children and 30.4% of adolescents (12–19 years of age) being overweight. The prevalence of obesity among children aged 0–23 months, 2–5 years, 6–11 years, and adolescents was 11.4, 10.4, 15.3, and 15.5%, respectively.

This epidemic equally affects both sexes, and its prevalence has increased compared to data from the previous NHANES reports in all age ranges and racial groups. However, minorities are over-represented in this epidemic.\(^1\) For instance, the prevalence of obesity among African-American (23.6%) and Hispanic (23.4%) adolescents is twice that among white adolescents (12.7%), and the rate of increase in the prevalence of obesity among African-American and Hispanic adolescents almost doubled between the periods 1988–1994 and 1999–2000, from 13.4 to 23.6% in African Americans and from 13.8 to 23.4% in Hispanics.

Obesity has overtaken AIDS and malnutrition as the top health problem in the world.\(^2\) Obesity markedly reduces life expectancy, especially among younger individuals. Severely obese (BMI > 45 kg/m\(^2\)) young adults have a reduced life expectancy of 5–20 years. Childhood obesity often persists into adulthood and has been independently associated with subsequent morbidity and mortality in adulthood. However, the sequelae of obesity are not limited to adulthood,
as evidenced by the increased incidence of concomitant comorbidities seen in overweight youth (Table 1). It has been suggested that because of the health impact of obesity, this generation may be the first to live a shorter average lifespan than the preceding generation.

It has been well demonstrated that cardiovascular risk factors frequently occur in obese youth and that these risk factors tend to cluster. Obesity and insulin resistance are hypothesized to be the underlying mechanism for this clustering of risk factors, known as the metabolic syndrome. Central adiposity, atherogenic dyslipidemia, hypertension, insulin resistance, glucose intolerance, and a prothrombotic, pro-inflammatory state characterize the metabolic syndrome.

Clinical criteria for defining the metabolic syndrome in adults have been developed by the WHO and the National Cholesterol Education Program Adult Treatment Panel III. In adults, specific cut-off points have been delineated for these clinical criteria of waist circumference, systolic and diastolic blood pressure, serum triglycerides and HDL cholesterol, and fasting glucose. Several studies have examined the frequency of the metabolic syndrome in youth based on components of the adult criteria. The lack of standardized criteria and cutpoints for defining the metabolic syndrome in youth makes comparisons across studies difficult. Despite the use of diverse criteria and cutpoints, results from these studies substantiate that the metabolic syndrome is already highly prevalent among obese children and adolescents.

Population-based data suggest that the epidemic of pediatric obesity is being followed by an increase in type 2 diabetes, particularly in adolescents of minority groups. The American Diabetes Association estimates that between 8 and 45% of children newly diagnosed with diabetes have type 2 diabetes. In the greater Memphis, Tenn., area, the authors have reported a fivefold increase in childhood type 2 diabetes between 1990 and 2001, with type 2 diabetes accounting for 43% of the newly diagnosed cases in 2000 and overweight African-American adolescents accounting for nearly 86% of the new cases.

As a consequence of this epidemic, annual hospital costs for obesity and obesity-associated conditions in youth (6–17 years of age) increased from $35 million during the period from 1979 to 1981 to $127 million during the period from 1997 to 1999. A relationship has been found between BMI in young adulthood and middle age to subsequent health care expenditures at ages ≥ 65 years. Age- and race-adjusted cardiovascular disease (CVD)-related, type 2 diabetes–related, and total charges were significantly higher for overweight and obese adults. Total charges for severely obese men and women were $6,192 more (84% higher) and $5,618 more (88% higher), respectively, than for nonoverweight subjects. If the trend in obesity-associated type 2 diabetes and cardiovascular risk factors continues in children, national expenditures for health care are likely to escalate.

Based on the current set of evidence, we speculate that in genetically susceptible populations, the interaction of racial, sociocultural, and biological factors, triggered or exacerbated by concomitant obesity, ultimately leads to early development of type 2 diabetes and increased risk for CVD in youth. In this review, we hope to provide useful information to assist health care providers in identifying those individuals more vulnerable to becoming obese and developing associated comorbidities.

Identifying Children at High Risk for Obesity, Type 2 Diabetes, and CVD

Prevention of childhood obesity is critical because obesity is associated with the development of unfavorable health outcomes during childhood and adulthood. It has been overemphasized that the major etiopathogenic factors contributing to obesity result from an imbalance in the energy equation produced by either increased energy intake or decreased energy expenditure or both. This notion has led health providers to develop a simplistic perception that societal and nutritional changes (i.e., “the toxic environment”) are the chief parameters that foster the current epidemic of obesity, type 2 diabetes, and CVD in children.

However, this imbalance in the energy equation does not explain differences in fat distribution, individual susceptibility to develop obesity-associated comorbidities, or the dissimilar weight loss response to lifestyle and pharmacological interventions. Compared to that in adults, the energy balance in children is more affected by the intrauterine environment, metabolic abnormalities, racial and genetic predisposition, underlying conditions, medications, and other factors. The interactions of these factors with social and environmental forces clearly denote differences between children and adults.

How and when to intervene to prevent obesity in childhood is a challenging question. The rapid increase in the prevalence of childhood overweight and its potential effect on morbidity and mortality in childhood and adulthood underscores the importance of identifying critical periods for the prevention of overweight in vulnerable populations and of developing an understanding of factors that cause excess weight gain. A critical period for overweight or obesity is defined as a time when the risk of onset, complications, or persistence of overweight or obesity is increased.

Risk factors associated with the

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<td>Hypertension</td>
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<td>Cancer</td>
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<td>Polycystic ovarian disease</td>
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<td>Gout</td>
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<td>Gallbladder disease</td>
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<td>Hypercoagulability</td>
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<th>Mechanical</th>
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<td>Sleep apnea/hypventilation</td>
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<td>Kidney structural abnormalities</td>
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<td>Cardiomyopathy</td>
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<td>Degenerative arthritis</td>
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<td>Flat feet</td>
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<td>Blunt disease</td>
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<td>Respiratory disease</td>
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<td>Depression</td>
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<td>Deterioration of social interactions</td>
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antnatal environment, the early postnatal years, adiposity rebound (5–6 years of age), and puberty have been identified within different critical periods for the development of obesity (Table 2). Health providers should recognize these critical periods in the development of children during which interventions may successfully prevent obesity.

Factors associated with the antenatal environment and the fetus appear to be important components in the development of childhood obesity, type 2 diabetes, and CVD. Effects of the intrauterine environment on cell numbers, satiety centers in the brain, and endocrine function represent mechanisms that may logically account for the apparent prenatal channeling of either restricted or exuberant growth. The fetal origins hypothesis, as proposed by Barker et al., suggests that antenatal stress or placental insufficiency “programs” metabolic alterations in β-cell function and insulin sensitivity that persist into adult life and promote the development of the metabolic syndrome. Third-trimester amniotic fluid insulin and serum lipids, lipoprotein apolipoprotein (apo) B100, and apo (A-1).12

Children with at least one overweight parent at the age of adiposity rebound have a four- to fivefold greater chance of becoming obese adults.13 Lean children ≤ 5 years of age have a 13-fold risk of adult obesity if both parents are obese, suggesting that genetic influences predominate in childhood weight gain. Obesity, type 2 diabetes, and CVD often run in families, particularly in minorities with lower socioeconomic backgrounds.

Postnatal factors, including infant overnutrition, play an extremely important role in the future development of obesity. A pattern of rapid weight gain during the first 4 months of life also has been associated with an increased risk of overweight status at age 7 years, independent of birth weight and weight attained at age 1 year. Early overnutrition has been correlated with elevated leptin concentrations, a marker of adiposity in later life. Differences in both volume and composition of commercial formula compared to breast milk have also been proposed as etiological factors of childhood obesity. Some evidence suggests that the rate of weight gain during the first few months of life and related determinants, such as type of infant feeding, may influence weight status later in childhood as well as the later development of adult CVD. The prevalence of obesity in children who were never breastfed was 4.5%, compared to 2.8% in breastfed children, and a clear time-response effect was identified for the duration of breastfeeding on the decline in prevalence of obesity. The age of adiposity rebound, the point of the BMI nadir before body fatness begins to increase (between 5 and 6 years of age) is also an important predictor for adult obesity.13 Children with early adiposity rebound have a fivefold greater chance of becoming obese as adults, compared to those with late adiposity rebound. At the age of adiposity rebound, children who are already overweight have a sixfold greater risk for adult obesity compared to lean children. Therefore, the earlier the onset of childhood obesity, the greater the risk of adult obesity.

Of special consideration are children with pre-existing diseases, who often require the use of medications that may stimulate weight gain. The recognition of medications that induce weight gain may be an efficient measure to identify children at risk of obesity. Medication-induced weight gain is often overlooked and may be associated with an increased risk of complications, such as diabetes, asthma, hypertension, and depression. Although not every patient will gain weight while receiving treatment with drugs known to promote weight gain, many will. Health care providers should monitor weight as part of routine assessment. They should be aware of the impact of even a small increase in weight and make appropriate adjustments to the medication regimen or lifestyle. Drugs that have been associated with weight gain and that are often used in children with underlying conditions are listed in Table 3.

The BMI chart is a valuable predictive device and should be used with all children. The higher the BMI during childhood, the more likely adult obesity will manifest. In general, children with a BMI ≥ the 95th percentile have a high risk for adult obesity. Children and adolescents with BMI ≥ the 95th percentile have a 62–98% chance of being obese at 35 years of age. This risk increases as the child becomes older. Change in BMI during and after adolescence is the most important predictive variable for adult obesity.17 Obese adolescents (15–17 years of age) have 17.5 times greater odds of becoming obese adults compared to normal-weight peers, whereas obese 1- to 2-year-olds have a 1.3 times greater odds of becoming obese adults compared to normal-weight toddlers.

<table>
<thead>
<tr>
<th>Table 2. Risk Factors Associated With the Development of Obesity</th>
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<tr>
<td><strong>Antenatal Factors</strong></td>
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<tr>
<td>• Placental insufficiency</td>
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<td>• Elevated insulin levels in amniotic fluid</td>
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<td>• Food deprivation in early pregnancy</td>
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<td>• Gestational diabetes</td>
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<td>• Maternal overweight pre-pregnancy</td>
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<td>• Maternal weight gain during pregnancy</td>
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<td>• Parental history of overweight</td>
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<td>• Smallness for gestational age</td>
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<td>• Largeness for gestational age (macrosomic baby)</td>
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<tr>
<td><strong>Postnatal Factors</strong></td>
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<td>• Infant overnutrition</td>
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<td>• Bottle feeding</td>
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<td>• Type of infant formula</td>
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<td>• Rapid weight gain during first 4 months of life</td>
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<td>• Early adiposity rebound</td>
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<td>• Drug-induced weight gain</td>
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<td>• Overweight in adolescence</td>
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Diabetes Spectrum Volume 18, Number 4, 2005
Elevated levels of FFAs alter the and enhanced platelet aggregation. Through alterations in protein C, plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein (CRP) and inhibitory and thrombotic markers, such as C-reactive protein (CRP) and fibroblast growth factor-2 (FGF2) may promote hypercholesterolemia. Macrophages and arterial smooth muscle cells more readily take up LDL cholesterol, especially small dense LDL particles, contributing to the development of atherosclerotic lesions. An LDL particle linked to an apo(a) polypeptide chain, lipoprotein(a), may inhibit endogenous fibrinolysis and be a marker for thromboembolic disease, particularly in youth.

Several cross-sectional studies have examined established cardiovascular risk factors in overweight and lean youth. Compared to lean peers, overweight youth are more likely to have lipid abnormalities and elevated blood pressure. Both overweight severity and central (abdominal) adipose distribution are associated with cardiovascular risk factors and development of glucose intolerance in adults, with abdominal adiposity, particularly visceral fat mass, considered to be more deleterious than peripheral fat mass. In youth, central fat distribution, whether measured by waist circumference or waist-to-hip ratio, is related to adverse lipid and lipoprotein levels and higher blood pressure. Greater intra-abdominal fat mass has also been shown to correlate with higher basal insulin, higher triglyceride levels, higher blood pressure, and lower HDL cholesterol and apo (A-1) levels in adolescents. However, the lack of age- and sex-specific normative values for waist circumference or waist-to-hip ratios among children makes it difficult to identify which youth are at greater risk for developing these obesity-associated conditions.

Physical inactivity is recognized as a risk factor for obesity, CVD, and type 2 diabetes. In a predominantly white group of 610 9- to 18-year-olds, higher levels of cardiorespiratory fitness and habitual physical activity were associated with more favorable levels of triglycerides, LDL and HDL cholesterol, fasting glucose, and blood pressure. In contrast, a study of 82 African-American sixth graders found no significant relationships between blood pressure and physical activity or adiposity. However, others have reported modest associations between blood pressure and cardiorespiratory fitness in African-American youth, with the percentage of overweight and cardiorespiratory fitness accounting for 34% of the variance in the cardiovascular risk profile.

Defects of insulin secretion, insulin action, hepatic glucose production, or combinations of these mechanisms characterize childhood type 2 diabetes. These defects are likely triggered or exacerbated by concurrent obesity, sedentary lifestyle, unhealthy eating habits, and hormonal changes (puberty) in genetically susceptible populations that ultimately could lead to β-cell failure and the appearance of glucose intolerance and diabetes. Decreased insulin sensitivity (insulin resistance) has been shown to precede the development of type 2 diabetes and CVD. Several mechanisms link excess of adiposity with insulin resistance, including insulin signaling abnormalities, adipokines, sedentary behavior, nonesterified fatty acids, and ectopic fat infiltration. In vulnerable individuals, transient changes associated with puberty, including increase in fat mass, insulin resistance, leptin, growth hormone, and IGF-I.
overweight above the ideal BMI per-
clinical estimation of the percentage of
LeBonheur Children's Medical Center
adult BMI values (~18 years of age).
progressively increase until reaching
BMI cutoff points are constantly
longitudinally follow overweight in
they provide a comprehensive way to
comparison of severity of overweight
across age and sex groups, nor do
of childhood obesity and associated
comparisons. Efforts to identify the
negative impact of obesity at its incipi-
ent stages may justify early and more
aggressive treatment intervention to
prevent the progression and develop-
ment of complications.

Health providers taking care of
obese children require a practical and
objective way to assess the severity
and progression of overweight in chil-
dren who are still growing. The cur-
cent consensus is that BMI is a valid
and feasible indirect measure of body
fatness. The BMI cutoff points are
linked to adult cutoff points for over-
weight and obesity, which are good
indicators of risks for adverse health
outcomes. They correlate with mark-
ers of obesity-related complications,
including blood pressure, lipid profile,
and insulin resistance, as well as with
long-term mortality.37

BMI is simple to use, consistent for
children and adolescents, and very
useful in clinical practice and in epi-
demiological studies. However, it suf-
fers from a number of limitations.
BMI cutoff points do not permit com-
parison of severity of overweight
across age and sex groups, nor do
they provide a comprehensive way to
longitudinally follow overweight in
youth. In children and adolescents,
BMI cutoff points are constantly
changing, and they are expected to
progressively increase until reaching
adult BMI values (~18 years of age).

The team at the Lifestyle Clinic at
LeBonheur Children's Medical Center
in Memphis, Tenn., has validated the
use of the relative BMI (RBMI) as a
clinical estimation of the percentage of
overweight above the ideal BMI per-
centile. RBMI is an objective way to
assess and compare changes to any
intervention in our overweight popu-
lation. RBMI is calculated using the
following equation: BMI ÷ BMI at
50th percentile for age and sex × 100.

We have found that both BMI and
RBMI are similarly associated with
indexes of glucose metabolism and
insulin dynamics and cardiovascular
risk factors in our population. RBMI
transforms BMI into a continuous
variable relative to the ideal reference
value (50th percentile on age- and
sex-specific BMI charts) that reflects
the severity of overweight, allowing a
comparison across age and sex groups
based on severity of overweight and
facilitating longitudinal follow-up.

Our experience supports the notion
that estimating the severity of over-
weight by RBMI could aid clinicians
assessing the magnitude and progres-
sion of overweight at different time-
points of the growing period in an
objective and practical way.

Presently, the lack of clinical indi-
cators to identify youth at higher risk
of developing impaired glucose toler-
ance (IGT) or type 2 diabetes pre-
cludes clinicians from early interven-
tion to stop its progression. Com-
monly, referrals for glucose tolerance
testing in severely obese children are
triggered by the development of symp-
toms rather than geared toward iden-
tification of children at risk who
could benefit from early intervention.

Using a standardized screening proto-
col for high-risk groups, we have
found a fourfold higher prevalence of
abnormalities in glucose metabolism
in youth with BMIs between the 85th
and 95th percentiles,38

There is not definitive agreement
about which screening tests best
reflect the negative impact of
increased adiposity on glucose metabo-
lim in adolescents. Screening rec-
ommendations favor fasting blood
glucose (FBG) as the ideal screening
method in subjects at risk for IGT or
type 2 diabetes because of its low cost
and greater convenience. However,
we agree with a growing set of evi-
dence suggesting that a single FBG
may not reflect the early impact of
increasing adiposity on glucose home-
ostasis nor discriminate between
youth with and without IGT/type 2
diabetes until significant deterior-
ation in glucose metabolism has
occurred.39,40 Abnormalities in post-
prandial blood glucose typically pre-
cede deterioration in FBG.39 It has
been shown that FBG is a poor pre-
dictor of diabetes in obese adolescents
and subjects with polycystic ovarian
syndrome.41 In agreement with these
investigations, we have reported that
~ 66% of severely overweight adoles-
cents with IGT during the oral glu-
cose tolerance test (OGTT) and have
an FBG value < 100 mg/dl at the time
of their initial evaluation. Therefore,
the opportunity for earlier interven-
tion in these adolescents will be
missed.

Simple methods of assessing
insulin sensitivity and secretion are
important in the evaluation and fol-
low-up of youth with obesity and risk
factors for type 2 diabetes. The
OGTT is a clinically and widely used
procedure originally developed to
classify carbohydrate tolerance. The
effectiveness and reliability of the
OGTT to establish the diagnosis of
IGT/type 2 diabetes have been
demonstrated in children. Plasma glu-
cose and insulin response during the
OGTT reflect the ability of pancreatic
β-cells to secrete insulin and the sensi-
tivity of tissues to insulin. Therefore,
many investigators have studied and
validated simple surrogate indexes of
β-cell function and insulin resistance
in children and adults based on values
obtained during the OGTT39,42-48
(Table 4). The OGTT-derived indexes
provide clinically useful information
that allows the estimation of insulin
secretion capacity and insulin sensi-
tivity, both of which are essential for
defining the treatment approach.

Indexes reflecting β-cell secretion
capacity clearly help clinicians to
demonstrate that β-cell workload
increases with overweight. However,
these β-cell indexes are not good pre-
dictors for type 2 diabetes because
overweight adolescents with glucose
intolerance show insulin secretion
capacity at a level that is at least
equivalent to those with normal glu-
cose tolerance.

We agree with other investigators
that the accuracy of surrogate esti-
mates of β-cell function may be
diminished once IGT is present.48

Conversely, indexes reflecting insulin
sensitivity clearly support the notion
that deterioration of insulin sensitivity
with increasing overweight could be
the most important pathogenic factor
leading to IGT among adolescents.49

We have found that adolescents at
even moderate levels of overweight
have already experienced a pro-
ounced reduction in insulin sensitiv-
The best predictors of IGT and type 2 diabetes has been shown to be one of the traditional lipoprotein analysis; however, these measures may underestimate insulin sensitivity in adolescent minorities. Fasting levels of insulin and glucose do not reflect the hyperinsulinemia that occurs during adolescence or the racial differences reported during stimulated glucose tolerance testing. Despite having a higher incidence of CVD, African Americans may not exhibit the same magnitude or frequency of traditional lipid abnormalities as their white counterparts. In severely obese African-American youth, we found that established cardiovascular risk factors of elevated total and LDL cholesterol occurred, respectively, in 48 and 33% of the youth. Hypertriglyceridemia and low HDL cholesterol, components of the metabolic syndrome, occurred less frequently (13 and 24%, respectively), whereas hypertension (values > the 95th percentile based on norms for age, sex, and height) was present in 50% of the youth.

Chronic, subclinical inflammation has been identified as one mechanism explaining the increased risk of obesity-related CVD and diabetes. This awareness has lead to an increased interest in emerging markers of cardiovascular risk, such as CRP, fibrinogen, and PAI-1. A number of studies have examined relationships between obesity and these emerging cardiovascular risk factors in children. In youth, severity of obesity assessed by fat mass was associated with increased levels of fibrinogen and CRP. We found that 43% of obese youth had elevated CRP, and 38% had elevated fibrinogen, despite having normal LDL cholesterol levels.

These findings suggest that the current screening recommendations may underestimate risk for CVD and diabetes in severely overweight youth, particularly adolescent minorities. We recommend assessment of glucose tolerance by OGTT and determination of insulin sensitivity using OGTT-derived indexes.

Accurate comparison of resting blood pressure to normative values based on age, sex, and height resulted in identification of hypertension in 50% of youth who were referred to our clinic as “healthy” children for weight management. Emerging risk factors for CVD may provide helpful information beyond that provided by the lipid profile in overweight minority youth.

Summary
Greater body weight predisposes children to many of the medical complications of obesity found in adults, in particular components of the metabolic syndrome: hypertension, dyslipidemia, and impaired glucose metabolism. As these children age, the obesity epidemic will lead to epidemics of diabetes, hypertension, and CVD. However, not all overweight adolescents have the same risk of developing these complications. Appropriate risk stratification could guide clinicians to recognize overweight youth who are at higher risk of developing type 2 diabetes or CVD and lead to prompt intervention. Stratification of adolescents based on 1) severity of overweight (RBMI), 2) estimates of β-cell activity and insulin resistance (OGTT-derived indexes), and 3) cardiovascular risk profile may be useful for the longitudinal follow-up of overweight youth. Health care providers of overweight children need to pursue efficient screening procedures earlier in the progression of overweight in order to prevent adolescents from developing these diseases.

Acknowledgments
The research data presented in this article were supported by the Children’s Foundation Research Center of Memphis at Le Bonheur Children’s Medical Center and Le Bonheur Health Systems. The authors...
would like to thank the staff of the Lifestyle Clinic at Le Bonheur Children’s Medical Center and the Health Evaluation and Lifestyle Promotion (HELP) Center for technical assistance and their assistance in the care of our patients.

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