

## Severe Obesity in Children and Adolescents: Identification, Associated Health Risks, and Treatment Approaches: A Scientific Statement From the American Heart Association

Aaron S. Kelly, Sarah E. Barlow, Goutham Rao, Thomas H. Inge, Laura L. Hayman, Julia Steinberger, Elaine M. Urbina, Linda J. Ewing and Stephen R. Daniels

on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology

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## Severe Obesity in Children and Adolescents: Identification, Associated Health Risks, and Treatment Approaches A Scientific Statement From the American Heart Association

*Endorsed by The Obesity Society*

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Linda J. Ewing, PhD, RN, FAHA; Stephen R. Daniels, MD, PhD, FAHA; on behalf of the  
American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee  
of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and  
Metabolism, and Council on Clinical Cardiology

**Abstract**—Severe obesity afflicts between 4% and 6% of all youth in the United States, and the prevalence is increasing. Despite the serious immediate and long-term cardiovascular, metabolic, and other health consequences of severe pediatric obesity, current treatments are limited in effectiveness and lack widespread availability. Lifestyle modification/behavior-based treatment interventions in youth with severe obesity have demonstrated modest improvement in body mass index status, but participants have generally remained severely obese and often regained weight after the conclusion of the treatment programs. The role of medical management is minimal, because only 1 medication is currently approved for the treatment of obesity in adolescents. Bariatric surgery has generally been effective in reducing body mass index and improving cardiovascular and metabolic risk factors; however, reports of long-term outcomes are few, many youth with severe obesity do not qualify for surgery, and access is limited by lack of insurance coverage. To begin to address these challenges, the purposes of this scientific statement are to (1) provide justification for and recommend a standardized definition of severe obesity in children and adolescents; (2) raise awareness of this serious and growing problem by summarizing the current literature in this area in terms of the epidemiology and trends, associated health risks (immediate and long-term), and challenges and shortcomings of currently available treatment options; and (3) highlight areas in need of future research. Innovative behavior-based treatment, minimally invasive procedures, and medications currently under development all need to be evaluated for their efficacy and safety in this group of patients with high medical and psychosocial risks. (*Circulation*. 2013;128:1689-1712.)

**Key Words:** AHA Scientific Statements ■ adolescents ■ children ■ obesity ■ risk factors

Despite recent data suggesting that the rate of increase of obesity among children and adolescents has slowed and overall prevalence has possibly begun to plateau,<sup>1,2</sup> a worrisome trend has emerged in the form of severe pediatric

obesity. As the fastest-growing subcategory of obesity in children and adolescents,<sup>1,3,4</sup> severe obesity afflicts between 4% and 6% of all youth in the United States<sup>3-7</sup> and has both immediate and long-term health consequences. Recent data further

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suggest that compared with overweight and obese children and adolescents, youth with severe obesity have a much more adverse cardiometabolic risk factor profile and demonstrate early signs of vascular dysfunction and subclinical atherosclerosis.<sup>6,8-18</sup> Tracking of adiposity from childhood into adulthood is much stronger in the severely obese,<sup>6</sup> and high body mass index (BMI) in childhood is associated with increased risk of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and premature death.<sup>19-29</sup> Unfortunately, many of the treatment approaches commonly used with some success in overweight and obese youth are less effective in those with severe obesity.<sup>30-33</sup> Novel treatment strategies tailored for severe obesity are therefore needed to alter the health trajectory of children and adolescents afflicted with this condition.

The purposes of the present scientific statement are to (1) provide justification for and recommend a standardized definition of severe obesity in children and adolescents; (2) raise awareness of this serious and growing problem by summarizing the current literature in this area in terms of epidemiology and trends, associated health risks (immediate and long-term), and challenges and shortcomings of currently available treatment options; and (3) highlight areas in need of future research. Because various definitions and terms have been used for this condition in the literature and no uniform consensus currently exists, a standardized definition and nomenclature are suggested so that clinical and research efforts can be streamlined, including improved clinical identification and management of severe obesity, as well as assessment of outcomes from research interventions. Severe pediatric obesity demands attention and clinical management, because if left unchecked, it will have a profound effect on those it afflicts and will place a significant economic and clinical services burden on the future healthcare system.

### Definition and Nomenclature

Although various definitions have been proposed to identify severe obesity in children and adolescents, BMI  $\geq 99$ th percentile has been the most commonly used. Freedman et al<sup>6</sup> demonstrated that a BMI  $\geq 99$ th percentile identified a subgroup of obese youth with an especially adverse cardiovascular risk factor profile and showed that tracking of adiposity into adulthood was extremely strong in these individuals. In 2007, expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity recognized an emerging category of severe obesity, and a table was provided that showed BMI values at ages 5 to 17 years that corresponded with the 99th percentile, derived from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 data.<sup>6,34</sup> Use of a percentile allows a uniform metric across all ages such that the excess weight of a 5-year-old boy with a BMI at the 99th percentile should be similar to the excess weight of a 14-year-old boy with a BMI at the 99th percentile, relative to age- and sex-matched peers. However, because the 99th percentile performs poorly from a statistical standpoint, the widespread adoption of this particular BMI percentile cutoff is inadvisable. The same problems arise with use of BMI *z* score.

More recently, Flegal et al<sup>5</sup> have proposed an alternative method by which to calculate extreme values of BMI based on the Centers for Disease Control and Prevention reference

growth charts for the United States, which include smoothed percentiles only up to the 97th percentile<sup>35</sup>; BMI percentiles greater than this are beyond the range of the reference data.<sup>36</sup> Flegal et al<sup>5</sup> suggested that the expression of high BMI values as a percentage above the 95th percentile provides a flexible means by which to evaluate heavier youth. Using this approach, it was found that 120% of the 95th percentile (1.2 $\times$ 95th percentile) of BMI for age was similar to the unsmoothed 99th percentile of the growth chart data set. For example, the 95th percentile BMI for a 7-year-old girl is 19.5 kg/m<sup>2</sup>, and 1.2 $\times$ 95th percentile BMI is 23.4 kg/m<sup>2</sup> (19.5 $\times$ 1.2). Those BMI values are associated with weights of 29 kg (64 lb) and 35 kg (77 lb), respectively, assuming a median height. The 95th percentile BMI and 1.2 $\times$ 95th percentile BMI for a 13-year-old boy, also of median height, would be 25.1 and 30.1 kg/m<sup>2</sup>, respectively, with associated weights of 61 kg (134 lb) and 73 kg (161 lb). For a more comprehensive description of the value of using percent above the 95th percentile and how it is calculated for the clinical tracking of youth with severe obesity, see Gulati et al.<sup>37</sup>

One potential advantage of this approach is that tracking changes in BMI status over time may be easier than attempting to assign a precise percentile or *z* score, which is misleading at the extreme tails of the BMI distribution. In addition, changes are difficult to interpret clinically in these extreme values, because substantial weight fluctuations result in very small changes in percentile and *z*-score values. In a report on the prevalence of severe obesity in California, Koebernick et al<sup>7</sup> used this definition (120% of the 95th percentile) but also included in this category those with an absolute BMI  $\geq 35$  kg/m<sup>2</sup>, using the justification that this is the cutoff for class II obesity in adults. Although an absolute value is acceptable as a cut point in adolescents, a single value in younger children for a range of ages works poorly, because one value would reflect different degrees of excess weight depending on age of the child. Multiple absolute cut points that vary with age are cumbersome.

Two other measures of relative BMI are in use: BMI “sympercent” and percent over BMI. BMI sympercent is the percentage difference from the 50th percentile BMI value for age and sex, based on the natural log scale.<sup>38,39</sup> The equation for sympercent is  $100 \times \ln(\text{BMI}/50\text{th percentile BMI})$ . For a 7-year-old girl of median height, 50th percentile BMI is 15.5 kg/m<sup>2</sup>. Therefore, when BMI is 19.5 kg/m<sup>2</sup>, which is the 95th percentile, sympercent is 23.1%, and it is 41.2% when BMI is 23.4 kg/m<sup>2</sup>. Percent over BMI is the percentage above the 50th percentile BMI for age and sex.<sup>40</sup> Although studies have evaluated these measures for responsiveness to pediatric treatments, they have been used neither to define cut points for severe obesity nor to evaluate severe obesity epidemiology or health risk.

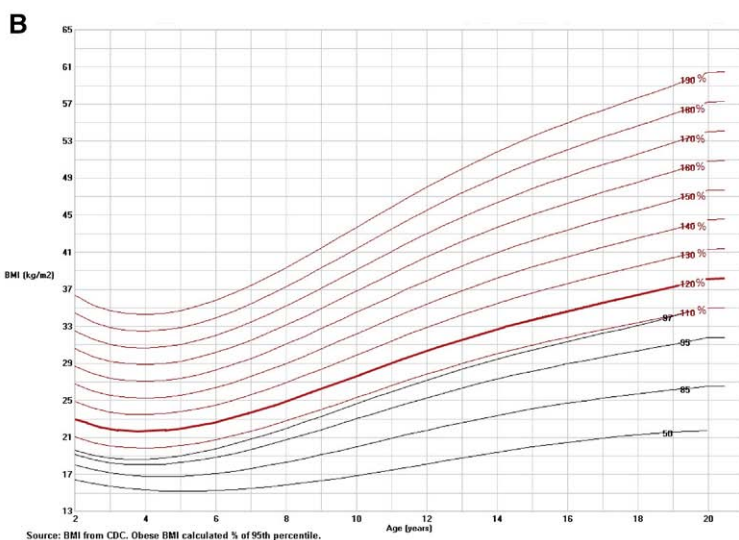
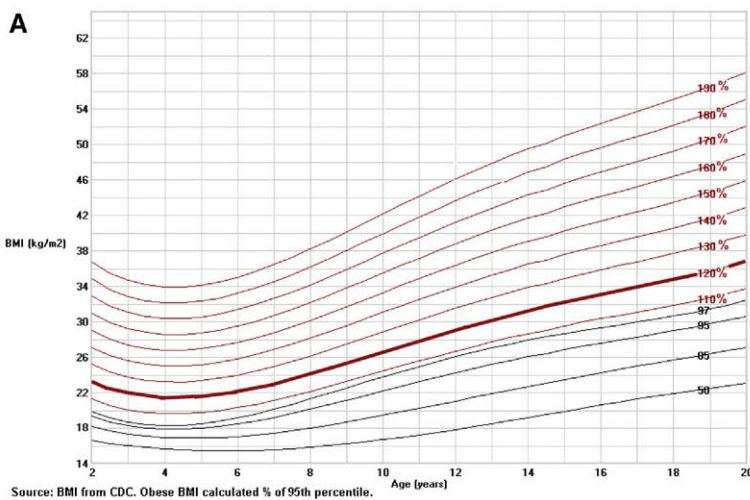
Although high BMI is a fairly good indicator of excess body fatness, other methods have been proposed; however, 2 of the most common, skinfold thickness and waist circumference (including waist-to-height ratio), are not advised to define severe obesity for several reasons. In regard to the use of skinfold thickness, many challenges would likely limit its widespread adoption, especially in the clinical setting, including lack of standardization, the presence of skinfold thickness

in youth with severe obesity that may exceed the capacity of standard calipers, and potentially high variability caused by measurement error. Similar practical challenges would limit the usefulness of waist circumference, including difficulty in properly locating anatomic landmarks such as the umbilicus and superior iliac crest because of the large volume of adipose tissue and high measurement error. Therefore, although skinfold thickness and waist circumference have been proposed as potentially attractive alternatives for quantifying adiposity in overweight and obese children and adolescents, these methods are not recommended in youth with severe obesity.

In consideration of the above issues, the writing group recommends that severe obesity in children  $\geq 2$  years of age and in adolescents be defined as having a BMI  $\geq 120\%$  of the 95th percentile or an absolute BMI  $\geq 35 \text{ kg/m}^2$ , whichever is lower based on age and sex. The inclusion of an absolute BMI threshold ( $35 \text{ kg/m}^2$ ) aligns the pediatric definition with class II obesity in adults, a high-risk category of obesity associated with early mortality in adults.<sup>41</sup> BMI  $35 \text{ kg/m}^2$  is a higher threshold than BMI  $\geq 120\%$  of the 95th percentile among most children, but it is a somewhat lower threshold (and therefore expands the population that is categorized as severely obese) among boys  $\approx 18$  years and older and girls  $\approx 16$  years and older. We recommend

that this definition be used consistently in clinical and research settings to standardize efforts to better characterize the unique features and risk factors associated with severe obesity, particularly compared with less severe categories of adiposity, and to evaluate novel approaches for the management and treatment of youth with severe obesity. Figure 1 shows the BMI curves associated with the newly proposed definition for severe obesity for boys (Figure 1A) and girls (Figure 1B).

In view of the various terms used to describe this condition, the writing group focused on the 2 most common in the literature: *extreme* and *severe*. From an epidemiological/statistical point of view, the term *extreme* accurately describes the condition because it implies an order of magnitude and/or being situated at the farthest possible point from the center. Alternatively, from a clinical standpoint, the term *severe* implies harshness, seriousness, and/or a condition of grave consequence. The writing group considered clinical relevance to be of primary importance in its recommendation of a standardized nomenclature, especially in how this condition is perceived by pediatricians, patients, and their families. Considering the immediate and long-term health risks associated with very high BMI, as detailed in other sections of this scientific statement, the writing group believed that the term *severe* most appropriately



**Figure 1.** Body mass index (BMI) curves from Centers for Disease Control and Prevention (CDC) reference growth charts associated with the newly proposed definition for severe obesity for boys (A) and girls (B). Note that an absolute BMI  $\geq 35 \text{ kg/m}^2$  would qualify as severe obesity, consistent with the definition of class II obesity in adults. This  $35\text{-kg/m}^2$  threshold is lower than the 120% of the 95th percentile benchmark primarily among girls age  $\geq 16$  years. Figures provided courtesy of David W. Kaplan, MD, MPH, Department of Pediatrics, University of Colorado School of Medicine.



described this condition and that the sense of gravity that this term conveys accurately represents the heightened level of risk associated with it.

## Epidemiology

Epidemiological evaluation in severe obesity presents some challenges: Cut points for severe obesity that functionally define a group of children and adolescents with markedly worse healthcare issues lack robust epidemiological data because of the relatively new need for this category and other statistical issues. However, some work has been done to determine whether variations by age, race/ethnicity, and poverty exist in categories of severe obesity (Table 1).

## Overall Prevalence

Using data from NHANES 1999–2004 and defining severe obesity as BMI 99th percentile, Freedman et al<sup>6</sup> reported the prevalence at 4% for children and adolescents aged 5 to 17 years. A subsequent analysis that included a wider range of ages (2–19 years) found a rate of 3.8%.<sup>3</sup> Application of BMI  $\geq 120\%$  of the 95th percentile in an expanded NHANES data

set of 1999–2006 identified a somewhat higher percentage of youth aged 2 to 19 years of age (4.6%).<sup>5</sup> The authors of that article cautioned that although BMI  $\geq 120\%$  of the 95th percentile fit the empirical data, the small sample size used may not have reflected the true prevalence. When expanded to include absolute BMI  $\geq 35$  kg/m<sup>2</sup>, the proportion was 4.9%.<sup>4</sup> This same expanded definition of BMI  $\geq 120\%$  of the 95th percentile was used in a more recent cohort of >700 000 children and adolescents aged 2 to 19 years in an integrated prepaid health plan in southern California between 2007 and 2008. Although not a population-based sample, the distributions of age, sex, and race/ethnicity were similar to the southern California census of 2000. This much larger sample revealed that 6.4% of youth were in the severe obesity category.<sup>7</sup> Use of absolute BMI alone to define severe obesity has been limited to studies of adolescents, most commonly in the context of criteria for bariatric surgery. In NHANES 1999–2004, an estimated 1.3% of 12- to 19-year-olds had a BMI  $\geq 40$  kg/m<sup>2</sup>.<sup>3</sup> The Medical Expenditure Panel Survey, a nonrepresentative sample but one that provides information about comorbidities, found that 2.8% of youth 13 to 17 years

**Table 1. Summary of Epidemiological Data With Application of Different Cut Points to Define Severe Obesity**

	BMI $\geq 99$ th Percentile	BMI $\geq 120\%$ of 95th Percentile	Absolute BMI
Overall prevalence	NHANES 1999–2004: $\approx 4\%$ <sup>6</sup>	NHANES 1999–2006: 4.6% <sup>5</sup> NHANES 1999–2006*: 4.9% <sup>4</sup> California health plan 2007–2008*: 6.4% <sup>7</sup>	No data available
Age	NHANES 1999–2004 <sup>3</sup> : 2–5 y=4.2% 6–11 y=4.0% 12–19 y=3.4% NHANES 1999–2008 <sup>42</sup> : 3–5 y=4.7% HEALTHY middle school study 2006 <sup>43</sup> : Mean 11.8 y=6.9%	NHANES 1999–2006 <sup>5</sup> : 2–5 y=2.2% 6–11 y=4.6% 12–17 y=5.8% NHANES 1999–2006 <sup>44</sup> : 2–5 y=2.2% 6–11 y=4.7% 12–17 y=6.3% California health plan 2007–2008 <sup>7</sup> *: 2–5 y=2.5% 6–11 y=7.4% 12–19 y=7.7%	NHANES 1999–2004 <sup>3</sup> : BMI $>40$ kg/m <sup>2</sup> ; 12–19 y=1.3% MEPS 2000–2004 <sup>44</sup> : BMI $\geq 40$ kg/m <sup>2</sup> or $\geq 35$ kg/m <sup>2</sup> plus comorbidity; 13–17 y=2.8%
Race/ethnicity	NHANES 1999–2004, 2–19 y <sup>3</sup> : H=5.2% B=5.8% W=3.1% NHANES 1999–2008, 3–5 y <sup>42</sup> : H=7.8% B=5.2% W=3.4% HEALTHY middle school study 2006 <sup>43</sup> : H=6.4% F, 8.2% M B=8.7% F, 7.1% M W=4.1% F, 5.8% M	California health plan 2007–2008 <sup>7</sup> *: H=7.9% B=8.2% W=3.8% As=3.4% NHANES 1999–2006 <sup>44</sup> : H=5.1% F, 6.9% M B=9.1% F, 7.1% M W=3.5% F, 4.0% M	No data available
Poverty	NHANES 1999–2004 <sup>3</sup> : PIR $<1$ : 4.3% PIR 1–3: 4.3% PIR $>3$ : 2.5% NHANES 1999–2008 3–5 y <sup>42</sup> : Income level: no difference	No data available	NHANES 1999–2004 <sup>3</sup> : 12–19 y, BMI $\geq 40$ kg/m <sup>2</sup> PIR $<1$ : 2.0%, PIR 2–3: 1.1% PIR $>3$ : 0.8%

As indicates Asian; B, black or African American, non-Hispanic; BMI, body mass index; F, female; H, Hispanic or Mexican American; M, male; MEPS: Medical Expenditure Panel Survey; NHANES, National Health and Nutrition Examination Survey; PIR, poverty-income ratio, the ratio of the midpoint of observed family income category to the official poverty threshold, which is scaled to family size; and W, white, non-Hispanic.

\*Severe obesity category also includes children with BMI  $\geq 35$  kg/m<sup>2</sup>. Starting at age 16 years in girls and 18 years in boys, this BMI level is lower than 120% of 95th percentile BMI, which expands the number of youth included in the category.

of age had a BMI  $\geq 40$  kg/m<sup>2</sup> or a BMI  $\geq 35$  kg/m<sup>2</sup> with a serious comorbidity.<sup>44</sup> Prevalence estimates of more extreme BMI values are elusive; however, using data from NHANES 1999–2010, one can estimate that  $\approx 0.16\%$  (1.6 per thousand) of 12- to 19-year-olds in the United States (or  $\approx 45$  000 adolescents) have a BMI  $\geq 50$  kg/m<sup>2</sup>. Taken together, these studies indicate that  $\approx 4\%$  to  $6\%$  of children and adolescents 2 to 19 years of age have a BMI in the severe obesity range of  $\geq 99$ th percentile or  $\geq 120\%$  of the 95th percentile.

### Prevalence Differences by Age and Sex

Although preschoolers have a lower prevalence of obesity than 6- to 19-year-olds,<sup>1,45</sup> the severe obesity cut point of 99th percentile applied to NHANES 1999–2004 showed a prevalence rate of  $\approx 4\%$  across the age groups (Table 1). An analysis of NHANES 1999–2008 focused on younger children and found a 4.6% prevalence rate of BMI  $\geq 99$ th percentile among ages 3 to 5 years.<sup>42</sup> In contrast to the 99th percentile cut point, BMI  $\geq 120\%$  of the 95th percentile cut point categorizes 2.2% of preschoolers as severely obese.<sup>4</sup> Many analyses of severe obesity have not directly compared rates between boys and girls. The NHANES 1999–2004 analysis, with all age groups combined, estimated 4.6% of boys and 2.9% of girls to have a BMI  $\geq 99$ th percentile.<sup>3</sup> Using the definition of BMI  $\geq 120\%$  of the 95th percentile cut point, the proportions of boys and girls were closer: 5.0% versus 4.3% in NHANES and 7.3% versus 5.5% in the California health plan.<sup>5,7</sup>

### Race and Ethnicity

Regardless of the cut point used to define severe obesity, data consistently have shown higher prevalence among Hispanic or Mexican American children and non-Hispanic black or African American youth.<sup>1,45</sup> Use of the 99th percentile cut point in NHANES 1999–2004 identified a prevalence of 5.2% in Mexican American youth and 5.8% in black youth (non-Hispanic) 2 to 19 years of age in contrast to 3.1% in white youth (non-Hispanic).<sup>3</sup> Among 3- to 5-year-old children, using NHANES 1999–2008, the pattern was similar.<sup>42</sup> This 99th percentile cut point found 6.4% to 8.7% of Hispanic and black boys and girls in the cohort of 6358 middle school students in the 2006 HEALTHY obesity prevention study.<sup>43</sup> Use of BMI  $\geq 120\%$  of the 95th percentile or the BMI  $\geq 35$  kg/m<sup>2</sup> cut point to examine racial/ethnic difference in NHANES data identified a prevalence of 7.1% among black boys 2 to 19 years and 6.9% among Hispanic boys, whereas the prevalence among white boys was 4.0%. Similarly, 9.1% of black girls 2 to 19 years old, 5.1% of Hispanic girls, and 3.5% of white girls had BMI values in this category.<sup>4</sup> This cut point identified comparable racial/ethnic differences in the large, non-population-based sample from the southern California health plan.<sup>7</sup>

### Poverty

Childhood obesity (BMI  $\geq 95$ th percentile) is associated with low income, but interpretation of the data has been difficult because of confounding factors such as race and ethnicity.<sup>46</sup> Data regarding associations of poverty with more severe obesity categories are scarce and inconsistent, varying with the cut point used and cohort examined. When the cut point

of BMI  $\geq 99$ th percentile was applied to data from NHANES 1999–2004, the prevalence of severe obesity was 4.3% in youth with a poverty income ratio (PIR) of  $<1$  and 2.5% in youth with a PIR  $>3$ .<sup>3</sup> PIR is the ratio of the midpoint of observed family income category to the official poverty threshold, which is scaled to family size. PIR  $<1$  identifies individuals who are below the federal poverty level, and PIR  $\geq 1$  indicates relatively higher socioeconomic status. Using the same BMI cut point on data from NHANES 1999–2008 limited to 3- to 5-year-old children, prevalence of severe obesity was not correlated with PIR or with public versus private insurance status.<sup>42</sup> Odds ratio for severe obesity, when defined as 120% of 95th percentile, was higher among low-income girls, but not boys, in a 30-year NHANES sample (1976–2006).<sup>4</sup> When severe obesity in adolescents was defined as BMI  $\geq 40$  kg/m<sup>2</sup> in NHANES 1999–2004, the percentage of severe obesity was higher among those with low income.<sup>3</sup>

### Trends in Prevalence Over Time

Data are limited, but it appears that severe obesity is the fastest-growing subcategory of obesity in youth. Ogden et al<sup>1</sup> reported a continued rise in prevalence of high BMI, defined as  $\geq 97$ th percentile, among boys 6 to 19 years of age between 1999 and 2008, during a period when overweight and obesity prevalence rates were otherwise unchanged. When the cut point of BMI  $\geq 99$ th percentile was applied to 3 cycles of NHANES (1976–1980, 1988–1994, and 1999–2004), a significant trend was identified, from 0.8% to 2.2% to 3.8%, respectively.<sup>3</sup> The trend was observed among males and females, all age categories, and the 3 predominant racial/ethnic categories; however, the small sample size in 1976–1980 made the estimates unreliable. Similar changes were demonstrated using the same 3 NHANES cycles but with severe obesity defined as 120% of 95th percentile or BMI  $\geq 35$  kg/m<sup>2</sup>: 1.2%, 3.0%, and 4.9% among all children 2 to 19 years of age.<sup>4</sup>

## Associated Health Risks

### Immediate Risks

#### Cardiovascular Risks

Substantial research attention has focused on the immediate (during childhood) cross-sectional associations of overweight and obesity and traditional and novel risk factors for CVD in children and adolescents (for comprehensive reviews of pediatric obesity, CVD risk factors, and metabolic syndrome, see the American Heart Association scientific statements<sup>47–49</sup>). Numerous clinical and population-based studies have documented that high BMI and other measures of adiposity are associated with adverse levels of lipids and lipoproteins and blood pressure in childhood and adolescence.<sup>50–55</sup> Similarly, in both school-aged children and adolescents, overweight and obesity have been associated with insulin resistance,<sup>56–58</sup> mediators of inflammatory processes (ie, elevated levels of circulating inflammatory cytokines),<sup>59</sup> and adverse changes in vascular structure and function, including increased arterial stiffness<sup>60,61</sup> and endothelial dysfunction.<sup>62</sup> Results from both clinical and population-based studies have suggested that the number and severity of traditional risk factors for

CVD, as well as nontraditional risk factors, increase with the degree of adiposity in both childhood and adolescence.<sup>11,18,63</sup> Importantly, obesity and CVD risk factors associated with obesity have been linked to early atherosclerosis in pathological studies of the coronary arteries and aorta in adolescents and young adults.<sup>64-67</sup>

More recently, attention has focused on the cardiovascular health risks associated with severe pediatric obesity, with emphasis on how the immediate and long-term risks in this subgroup differ from less extreme forms of obesity. Although severe pediatric obesity has been operationally defined in a variety of ways across studies, available data suggest that children and adolescents in this category have a worse cardiovascular risk factor profile than their less obese counterparts. For example, in one of the first studies designed to address this issue, Freedman and colleagues<sup>6</sup> quantified cardiovascular and metabolic risk factors including dyslipidemia, hypertension, and hyperinsulinemia in a cross-sectional and longitudinal analysis of data from the population-based, biracial Bogalusa Heart Study focused on children and adolescents (5–17 years of age). Of children with a BMI  $\geq$ 95th percentile, 70%, 39%, and 18% had at least 1, 2, or 3 CVD risk factors, respectively. In contrast, among those with a BMI  $\geq$ 99th percentile, which was used to identify severe obesity in the study, 84%, 59%, and 33% had at least 1, 2, or 3 CVD risk factors, respectively. Figure 2 shows the proportion of children and adolescents with  $\geq$ 1 CVD risk factor by age and sex in the Bogalusa cohort according to BMI percentile.<sup>6</sup> Clearly, the number of CVD risk factors increases in a non-linear fashion at the 99th BMI percentile. Results from this study suggest a high level of cardiovascular risk in severely obese children and adolescents.

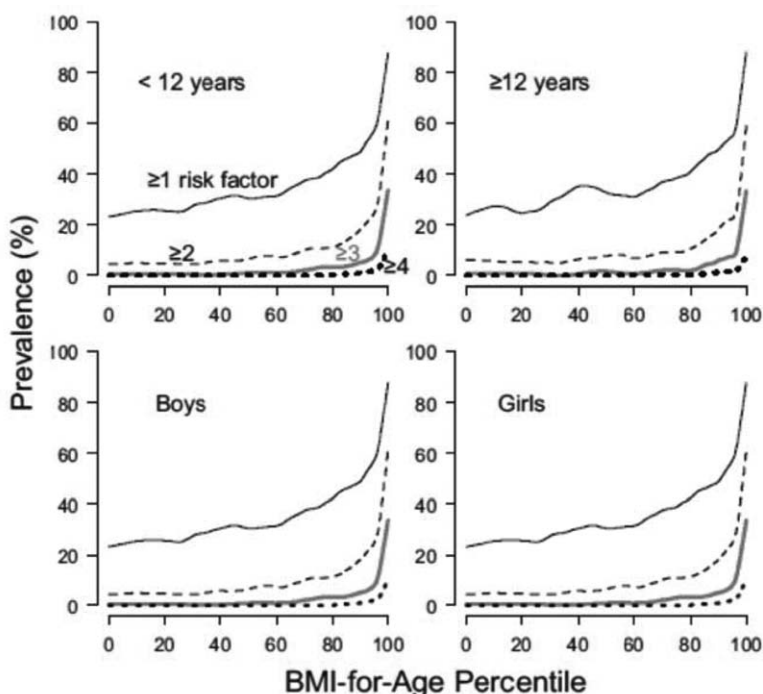
Other studies have reported that severe pediatric obesity, compared with milder forms of adiposity and normal weight, is associated with higher levels of blood pressure,<sup>9,10,12,13,15</sup>

dyslipidemia,<sup>9,10,12,13,15</sup> oxidative stress,<sup>15</sup> inflammation,<sup>11,15,18</sup> cardiorespiratory deconditioning (low fitness level) and poor pulmonary function,<sup>9</sup> clustering of cardiometabolic risk factors,<sup>8,14</sup> arterial stiffness,<sup>17</sup> increased carotid artery intima-media thickness,<sup>11</sup> and endothelial dysfunction/activation.<sup>11,12,16,17</sup> Perhaps most striking are the markedly elevated levels of inflammation that have been demonstrated in severe pediatric obesity. In the studies by Norris et al<sup>15</sup> and Kapiotis et al,<sup>11</sup> mean C-reactive protein levels exceeded 5 mg/L, a level considered to be high risk in adults.<sup>68,69</sup> In addition, oxidized low-density lipoprotein (LDL) is elevated in severe obesity, which likely increases risk of early atherosclerosis because oxidative modification of LDL cholesterol is considered a primary step in the atherosclerotic process.<sup>70</sup> Figure 3 shows mean levels of oxidized LDL, C-reactive protein, and interleukin-6 in severe obesity compared with obesity, overweight, and normal weight.<sup>15</sup>

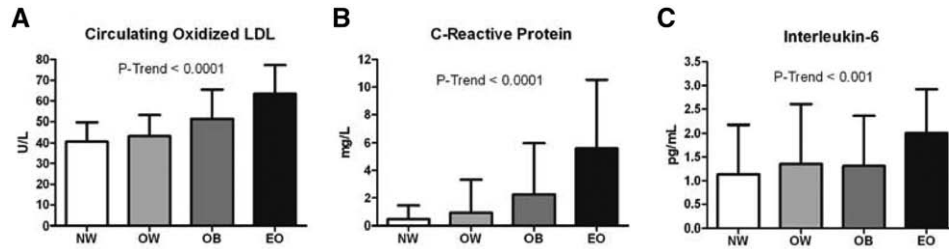
Early cardiac abnormalities have also been demonstrated in severe pediatric obesity. Compared with normal-weight control subjects, adolescents with severe obesity had greater left ventricular mass and reduced systolic and early diastolic tissue Doppler imaging velocities.<sup>71</sup> Youth with hypertension and high BMI had left atrial enlargement, a finding associated with diastolic dysfunction.<sup>72</sup> Diastolic dysfunction has also been shown in adolescent patients evaluated for bariatric surgery who presented with a mean BMI of 60 kg/m<sup>2</sup>.<sup>73</sup> These findings are of great concern, because a secular trend in increased left ventricular mass is seen coincident with the trends in obesity in the United States.<sup>74</sup> Indeed, heart size and mass track significantly over time, which suggests that early abnormalities may have implications for later cardiac health.<sup>75,76</sup>

#### Metabolic Risks

The massive accumulation of body fat observed in severe obesity has been associated with hyperinsulinemia, insulin resistance, and prediabetes.<sup>12,13,15,18,77-80</sup> Impaired glucose tolerance,



**Figure 2.** Body mass index (BMI) percentile and the proportion of children and adolescents with  $\geq$ 1,  $\geq$ 2,  $\geq$ 3, or  $\geq$ 4 cardiovascular disease risk factors. Reprinted from Freedman et al<sup>6</sup> with permission from Elsevier. Copyright © 2007, Mosby, Inc.



**Figure 3.** Oxidized low-density lipoprotein (LDL; **A**), C-reactive protein (**B**), and interleukin-6 (**C**) in normal weight (NW), overweight (OW), obesity (OB), and extreme obesity (EO; body mass index [BMI]  $\geq 120\%$  of the 95th percentile or BMI  $\geq 35$  kg/m<sup>2</sup>). Reprinted from Norris et al<sup>15</sup> with permission of the publisher. Copyright © 2011, North American Association for the Study of Obesity (NAASO).

a strong predictor of future development of T2DM in obese youth, is prevalent among children and adolescents with severe obesity.<sup>77,78,81</sup> In a study of >700 severely obese children of European descent, insulin resistance and insulin secretion were associated with 2-hour postprandial glucose levels.<sup>77</sup> In a multiethnic cohort of 167 children and adolescents referred to a pediatric obesity specialty center, many of whom were severely obese, insulin resistance was the most important risk factor linked to the development of impaired glucose tolerance in severe childhood obesity.<sup>78</sup>

Clustering of cardiometabolic risk factors, often referred to as metabolic syndrome, is highly prevalent in children and adolescents with severe obesity. In a study of 490 children and adolescents, increasing BMI was associated with metabolic syndrome risk factor clustering.<sup>18</sup> Although none of the normal-weight or overweight participants had metabolic syndrome risk factor clustering in that study, 50% of those with severe obesity had this phenotype. Another study reported that 31% of severely obese youth had clustering of metabolic syndrome risk factors and that this group was 3 times more likely to have metabolic syndrome risk factors than moderately obese children and adolescents.<sup>8</sup> In a study of Italian and German youth, metabolic syndrome risk factor clustering was significantly associated with increasing BMI.<sup>82</sup> These findings appear to be consistent across race and ethnic groups in severely obese youth.<sup>14</sup> Moreover, levels of adipokines known to be associated with metabolic risk factor clustering and insulin resistance, such as leptin (secreted from adipocytes, involved in satiety signaling) and adiponectin (secreted from adipocytes, associated with insulin sensitivity), were abnormal in youth with severe obesity.<sup>13,18</sup> In particular, leptin was markedly elevated in severely obese children and adolescents, which suggests problems with satiety signaling and portends increased weight gain over time.<sup>13</sup>

### Other Comorbidities

#### Obstructive Sleep Apnea Syndrome

Severe pediatric obesity is associated with additional comorbidities and conditions, although the information available about their relative prevalence and severity among severely obese compared with obese or overweight children and adolescents in general is limited. Obstructive sleep apnea syndrome (OSAS) is a serious condition characterized by episodes of respiratory obstruction with frequent arousals, sleep fragmentation, intermittent hypoxemia and hypercapnia, nocturnal hypertension, daytime somnolence, and neurobehavioral problems. The association with obesity has been observed

for many years. Estimates of the prevalence of OSAS among obese youth range from 5.7% to 36%, varying considerably depending on the population studied.<sup>83–85</sup> Estimates of the prevalence among all children and adolescents are much lower at roughly 2% to 3%.<sup>86–88</sup> Obese children and adolescents with OSAS are more likely to have excessive daytime sleepiness.<sup>89</sup> Furthermore, OSAS is more likely to persist after treatment with adenotonsillectomy in obese youth than in normal-weight youth.<sup>90</sup>

Only 1 study has addressed the prevalence of OSAS among severely obese youth. Among adolescents with a BMI  $\geq 40$  kg/m<sup>2</sup> referred for bariatric surgery, OSAS prevalence increased with increasing BMI.<sup>91</sup> However, there is additional evidence that the degree of obesity is associated with an increased likelihood of OSAS and with increased severity of OSAS. Mallory et al<sup>92</sup> reported mild polysomnographic abnormalities in a sample of 41 children and adolescents with severe obesity. Another study demonstrated that for each increase of 1 kg/m<sup>2</sup> of BMI above the mean, the risk of sleep-disordered breathing in general (which encompasses a range of conditions from primary snoring to severe OSAS) increased by 12%.<sup>93</sup> In a separate study, the risk of OSAS increased 3.5-fold with each standard deviation unit increase in BMI in adolescents.<sup>94</sup> On the basis of this evidence, it is reasonable to conclude that children and adolescents with severe obesity are more likely to have OSAS and that their disease is likely to be worse than in less obese youth.

#### Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease is strongly associated with visceral adiposity and insulin resistance and is becoming one of the most common liver diseases in the United States and worldwide.<sup>95,96</sup> The spectrum of nonalcoholic fatty liver disease ranges from simple steatosis, believed to be benign and nonprogressive, to more severe, potentially progressive nonalcoholic steatohepatitis, which is characterized by hepatic inflammation, hepatocellular injury, and fibrosis. Reports of pediatric fatty liver disease and steatohepatitis in obese children have been increasing and include cases of cirrhosis<sup>97–100</sup> and liver transplantation.<sup>101</sup> Evidence suggests a strong association with the severity of obesity in children and adolescents,<sup>102,103</sup> with BMI being a significant predictor.<sup>104</sup> In a cross-sectional study of 41 adolescents undergoing gastric bypass with a mean BMI of 59 kg/m<sup>2</sup>,<sup>103</sup> 83% had nonalcoholic fatty liver disease, 24% had steatosis alone, 7% demonstrated isolated fibrosis with steatosis, 32% had nonspecific inflammation and steatosis, and 20% had nonalcoholic steatohepatitis.



### *Musculoskeletal Problems*

Overweight and obese youth are more likely to have a wide variety of musculoskeletal problems than normal-weight individuals, including greater musculoskeletal discomfort such as knee pain, higher rates of fractures, greater impairment in mobility, and a higher rate of lower-extremity malalignment.<sup>105</sup> As in the case of OSAS, studies of musculoskeletal problems among severely obese children and adolescents are lacking. There are, however, some reports of a relationship between serious musculoskeletal problems and the degree of obesity. Blount disease, also known as tibia vara, is a growth disorder characterized by tibial “bowing.” In a retrospective analysis of 890 obese children with a mean BMI of  $\approx 35$  kg/m<sup>2</sup>, higher BMI was associated with increased risk of Blount disease.<sup>106</sup> A recent study of 41 adolescents presenting with Blount disease to a children’s hospital reported a mean BMI of 41 kg/m<sup>2</sup>, which represents severe obesity by any standard.<sup>107</sup> Therefore, the evidence suggests that severe pediatric obesity is a significant risk factor for Blount disease. Severely obese children are also more likely to develop slipped capital femoral epiphysis, displacement of the femoral head from the femoral neck through the growth plate. They are also more likely to develop bilateral slipped capital femoral epiphysis.<sup>108</sup>

### *Psychosocial Problems*

There is mixed evidence related to the prevalence and severity of psychosocial problems among severely obese children and adolescents, and it is unclear whether severe obesity precedes these issues or whether psychosocial issues function as pathogenic factors that contribute to severe obesity. Overall health-related quality of life, which includes aspects of psychosocial functioning, has been reported to be lower in severely obese children than in healthy-weight children. Furthermore, specific measures of emotional, social, and school functioning were significantly lower among severely obese children and adolescents.<sup>109</sup> Another study of severely obese adolescents presenting for bariatric surgery (bariatric surgery is discussed below) reported a high prevalence of clinically significant depression of 30%.<sup>110</sup> By contrast, a community-based study reported a prevalence of depression among severely obese adolescents that was no higher than among normal-weight peers.<sup>111</sup>

### *Disordered Eating*

The population-wide prevalence of eating disorders has not been established, but binge-eating disorder and loss-of-control eating are thought to be common among treatment-seeking obese youth. One metabolic research study that included normal-weight and overweight children (mean age, 10 years) found 9% of all subjects reported loss-of-control eating.<sup>112</sup> Studies that included obese subjects seeking weight treatment have shown rates from 8% to 18%.<sup>113–115</sup> None of these studies examined the association between degree of obesity and prevalence of disordered eating. However, among youth with disordered eating, severe obesity appears to be more common, with one study of 678 teens enrolled in a large T2DM treatment trial finding that 67% of those with clinical binge-eating symptoms had severe obesity (BMI  $\geq 99$ th percentile) compared with 38% of those with no overeating symptoms.<sup>116</sup> Despite the different types of disordered eating examined and the choice of diagnostic or screening questionnaires, the

studies suggest that severe obesity is common among youth with disordered eating.

### **Long-term Risks**

The concept that obesity and levels of risk factors persist over time was first demonstrated by longitudinal studies among children and adolescents, such as the Muscatine and Bogalusa Heart studies.<sup>117–119</sup> Tracking studies suggested that early acquisition of adiposity may increase the risk for adult obesity.<sup>117,119</sup> Even when BMI was measured at a young age (6 years), obese children had the highest prevalence of adult obesity measured 18 years later (nearly 80% prevalence) compared with those in the overweight category.<sup>118</sup> Many international studies have demonstrated greater tracking among the heaviest youth.<sup>120,121</sup> This was seen even in nutritionally insecure countries, such as Indonesia and China.<sup>122,123</sup> The study in China reported that 46% of children in the severely obese group remained in that category after 6 years of follow-up compared with only 31% in the overweight category.<sup>123</sup> Data from the Bogalusa Heart Study demonstrated that of those with severe obesity (BMI  $\geq 99$ th percentile) at a mean age of 12 years, 100% developed an adult BMI  $\geq 30$  kg/m<sup>2</sup>, 88% developed BMI  $\geq 35$  kg/m<sup>2</sup>, and 65% developed BMI  $\geq 40$  kg/m<sup>2</sup>.<sup>6</sup> Results of this study point to the high likelihood of developing severe obesity in adulthood when severe obesity is present in childhood.

Intuitively, the higher levels of risk factors associated with severe obesity and the cumulative length of exposure to these risk factors suggest that the medium- to long-term prognosis of this condition is poor. However, the data are sparse on whether severe pediatric obesity confers greater medium- and long-term disease risk than mild-to-moderate childhood obesity. The scarcity of data is likely a reflection of the low prevalence of severe pediatric obesity a generation ago, which limits the ability to track outcomes in current longitudinal studies. Nevertheless, despite the lack of data on severe obesity per se, it is well established that obese youth (probably because of the strong tracking of adiposity into adulthood) are more likely to have adverse levels of cardiovascular and metabolic risk factors later in life. Higher BMI is associated with tracking in the higher levels of both blood pressure<sup>124–126</sup> and lipids<sup>127–129</sup> in longitudinal pediatric cohort studies. Adolescents with a higher degree of obesity are also much more likely to demonstrate CVD risk factor clustering over time. Rate and degree of obesity development are also important. The Minneapolis Children’s Blood Pressure Study demonstrated that youth with the greatest increase in BMI over a period of 16 years had the highest risk of elevated risk factors, including high insulin, lipids, and blood pressure.<sup>130</sup>

It is also well documented that obese children and adolescents are more likely to demonstrate elevated levels of blood pressure,<sup>131,132</sup> lipids,<sup>133</sup> liver function enzymes,<sup>134</sup> insulin resistance,<sup>135</sup> and manifestations of the metabolic syndrome<sup>136,137</sup> in adulthood. In addition, risk for developing adult metabolic syndrome increases across childhood BMI groups.<sup>138</sup> Inflammation tracks with obesity as well; for every 0.15 U of BMI *z* score measured as a child, the level of high-sensitivity C-reactive protein was 0.02 U greater as an adult.<sup>139</sup> This inflammation leads to higher levels of oxidized LDL, the final common pathway toward development of atherosclerosis.

Therefore, it is worrisome that adolescents with severe obesity demonstrated levels of oxidized LDL 25% higher than the overweight/obese group (44.7 versus 59.3 U/L,  $P \leq 0.0001$ ), even after adjustment for LDL cholesterol.<sup>15</sup> Finally, evidence suggests that the risk of developing T2DM increases greatly with increasing BMI.<sup>140,141</sup> In particular, severe obesity in childhood is strongly associated with future development of T2DM.<sup>81,138,142–148</sup> In one study, severe obesity at baseline was an independent predictor of eventual development of T2DM.<sup>81</sup>

Adiposity in childhood is also known to predict intermediate cardiovascular outcomes in adulthood, including noninvasive measures of target-organ damage. Childhood obesity is correlated with changes in heart size, such as higher left ventricular mass index, left ventricular dilatation, and eccentric left ventricular hypertrophy (increased left ventricular mass with normal relative wall thickness).<sup>149–151</sup> Diastolic blood pressure in childhood, which is affected by obesity, has also been shown to be a significant determinant of concentric hypertrophy (increase in both left ventricular mass and relative wall thickness). These patterns of left ventricular geometry are associated with adverse outcomes in adults.<sup>152</sup> This early acquisition of elevated left ventricular mass is worrisome, because the Bogalusa Heart study<sup>76</sup> has documented tracking of heart size and the Muscatine Heart Study demonstrated a 2-fold increase in the likelihood that a subject would be in the upper tertile for heart size at follow-up if he or she had a heavier heart at baseline.<sup>75</sup>

Risk of adult vascular damage, associated with childhood obesity and tracking of adiposity into adulthood, has also been documented. Longitudinal pediatric cohort studies have demonstrated that risk factors that cluster with obesity during childhood and adolescence are associated with increased thickness of the carotid artery<sup>141,153</sup> and stiffness of the abdominal aorta<sup>154</sup> as an adult. Although data from the Cardiovascular Risk in Young Finns study suggested that the association between obesity during childhood and adolescence and carotid thickness and stiffness is lost after adjustment for adult BMI,<sup>155–157</sup> a later study found that the number of CVD risk factors (including obesity) during childhood and adolescence remained a significant predictor of change in carotid thickness over 6 years as an adult even after adjustment for the number of risk factors a subject possessed as an adult.<sup>158</sup> The independent relationship between obesity during childhood and adolescence and adult carotid intima-media thickness was also confirmed by the Bogalusa Heart Study<sup>159</sup> and the Atherosclerosis Risk in Young Adults study from the Netherlands.<sup>160</sup> Of major concern is the observation that BMI starts to become important in influencing adult carotid intima-media thickness when measured at as young as 10 years of age.<sup>161</sup>

A direct link between obesity during childhood and adolescence and adult cardiovascular morbidity and mortality has been suggested. One study using 3 historical cohorts in Great Britain found no relationship between childhood BMI and risk for adult ischemic heart disease or stroke.<sup>162</sup> However, the subjects had BMI measured before the beginning of the worldwide obesity epidemic (before 1968), and the prevalence of pediatric obesity in these cohorts was extremely low ( $\leq 0.4\%$ ),<sup>162</sup> which makes this study less applicable to the present day (of note, different cut points were

used to define overweight and obesity, which may account in part for the low prevalence). A similar American study examined participants in the Harvard Growth Study of adolescents who were enrolled from 1922 to 1935.<sup>26</sup> Overweight was associated with an increased risk of mortality attributable to coronary heart disease among men (relative risk, 2.3; 95% confidence interval, 1.4–4.1) but not among women.<sup>26</sup> However, morbidity attributable to coronary heart disease and atherosclerosis was increased in overweight adolescents of both sexes.<sup>26</sup> Analyses from a more contemporary cohort, the Princeton Lipid Research Clinic Follow-up Study, extended these observations by linking development of pediatric metabolic syndrome and change in BMI percentile to adult cardiovascular events.<sup>25</sup> Similarly, Native American children in the highest quartile of BMI at baseline had double the rate of death at 24 years of follow-up.<sup>21</sup> The California Teachers Study demonstrated that the relative risk for CVD was 23% higher in subjects who were obese at 18 years of age than in individuals with BMI in the overweight category.<sup>20</sup> To date, the largest study of obesity using the US National Health Interview Survey confirmed these findings and demonstrated that the risk of premature death was much higher in the participants who were severely obese as young adults.<sup>24</sup> A large study from Israel found a similar graded increase in risk for coronary heart disease across childhood BMI percentile, and this risk remained elevated (hazard ratio, 6.85; 95% confidence interval, 3.30–14.21) in youth with a BMI  $\geq 91$ st percentile even after adjustment for adult BMI and other cardiovascular risk factors.<sup>29</sup> In a large study of Danish school children, higher BMI during childhood was associated with an increased risk of coronary heart disease in adulthood, and the strength of the association increased with age.<sup>19</sup> Finally, a systematic review concluded that BMI in childhood was positively related to coronary heart disease risk in adulthood.<sup>27</sup>

Recent data have suggested that much of the increased risk for adult cardiovascular disease can be explained by the tracking of BMI from childhood into adulthood. Indeed, combined data from 4 prospective longitudinal studies demonstrated that overweight and obese children who were also obese as adults had increased levels of cardiometabolic risk factors and carotid artery atherosclerosis.<sup>22</sup> However, the risks of these outcomes among overweight or obese children who were not obese in adulthood were similar to those who were never obese. In addition, 2 separate systematic reviews concluded that the tracking of BMI from childhood to adulthood primarily explained the association of childhood obesity and increased cardiovascular risk in adulthood.<sup>23,28</sup>

## Treatment Approaches

### Lifestyle Modification/Behavioral Therapy

#### *Principles of Lifestyle Modification/Behavioral Therapy for Weight Management*

Derived from principles of classical conditioning and social learning theory,<sup>163</sup> behavioral obesity interventions are based on the assumptions that eating and physical activity are the proximal mediators of body weight and that these behaviors can be modified by changing the environmental cues that precede them and the consequences that follow. Adult and

pediatric behavioral weight management programs incorporate provision of diet and physical activity<sup>164,165</sup> and teach a variety of behavioral skills to help individuals implement and maintain changes. During the past several decades, behavioral obesity interventions have come to include a compendium of behavior change strategies that include but are not limited to self-monitoring, stimulus control techniques, goal setting, positive reinforcement, problem solving, social support, cognitive restructuring, and relapse prevention. Behavioral weight management programs have been used successfully with pediatric populations, most notably by Epstein and colleagues.<sup>166–168</sup> These programs, like evidence-supported behavioral weight management programs for adults, incorporate provision of information, diet, physical activity, and a variety of behavior therapy strategies. However, because parent involvement<sup>168</sup> and parent modeling of healthy behaviors<sup>169</sup> have been identified as crucial components of pediatric weight management, the most successful behavioral weight management programs are family based.

#### ***Role of Lifestyle Modification/Behavioral Therapy in Severe Obesity***

Although aggressive interventions such as medication have been recommended for the treatment of severe pediatric obesity,<sup>6</sup> conservative approaches such as family-based behavioral weight management are indicated as the initial intervention.<sup>170</sup> For example, in their guidelines for the prevention and treatment of pediatric obesity,<sup>171</sup> the Endocrine Society recommended intensive family-based lifestyle modification as a prerequisite for all obesity treatments for children and adolescents. Intensive interventions such as medication or meal replacement should accompany behavioral treatment rather than replace it.<sup>34</sup> However, weight loss and BMI reduction in behavioral weight management programs typically are modest, ranging from 5% to 20% of excess body weight or 1 to 3 U of BMI,<sup>171,172</sup> and relatively high attrition rates have been observed.<sup>173–175</sup> Moreover, because baseline BMI values are often so high, many will remain severely obese even after “successful” (BMI reduction of a few units) lifestyle modification therapy. In many communities, intensive behavior-based programs are not offered or are expensive and not covered by insurance.

To date, relatively few studies of lifestyle modification therapy have focused on youth with severe obesity.<sup>30,31,170,176</sup> Levine et al<sup>170</sup> conducted a family-based behavioral treatment study in 24 children 8 to 12 years old with severe obesity (defined as  $\geq 160\%$  of ideal body weight; mean BMI, 34.5 kg/m<sup>2</sup>) and demonstrated a BMI reduction of 1.7 kg/m<sup>2</sup> at a mean follow-up of  $\approx 8$  months. In a study of children (aged 8–12 years old) with severe obesity (defined as BMI  $\geq 97$ th percentile) and mean baseline BMI at approximately the 99th percentile, Kalarchian et al<sup>31</sup> found that a 6-month comprehensive, family-based behavioral weight management intervention was associated with significantly reduced percent overweight and improved medical outcomes. Specifically, children in the intervention condition decreased their percent overweight by 7.6% compared with 0.7% for children in usual care from pretreatment to posttreatment (baseline to 6 months). There were corresponding significant improvements

in total body fat, blood pressure, waist circumference, and functional health status in children who received intervention versus those who received usual care. However, at 1-year posttreatment follow-up (month 18), there were no differences in percent overweight between the intervention and control children. Thus, the benefits of treatment on weight were promising during the period of intensive intervention but were no longer present 1 year after the intervention ended. Another study conducted by Johnston et al<sup>30</sup> compared the weight loss response to lifestyle intervention in children and adolescents (aged 9–14 years old) in various BMI categories (overweight, obese, and severely obese, defined as BMI  $\geq 99$ th percentile). The intervention focused on eating and physical activity behaviors and behavior modification strategies aimed at weight reduction. Results demonstrated reduced weight loss efficacy in the group with severe obesity at all of the follow-up time points (3, 6, and 12 months). Discouragingly, the mean BMI *z* score returned to baseline in those with severe obesity who completed the 12-month intervention. Promising short-term findings were reported by Savoye et al,<sup>176</sup> who randomized children and adolescents (aged 8–16 years old) with a BMI  $\geq 95$ th percentile to a control group or weight management intervention that consisted of family-based exercise and nutrition counseling and behavior modification. Although not all participants were severely obese, the mean BMI at baseline was  $\approx 36$  kg/m<sup>2</sup>. Significant reductions in BMI, body fat percentage, and the homeostasis model assessment for insulin resistance were reported at 6 months, and these improvements were sustained at 12 months of follow-up; however, at 24 months, a large proportion of the study population was no longer available for follow-up. Evaluation of 44% of the 12-month completers unfortunately showed regain of weight among intervention participants, although less weight gain than in control subjects.<sup>32</sup> A recent study by Danielsson et al<sup>33</sup> investigated whether the degree of obesity at baseline predicted the efficacy of long-term lifestyle modification therapy. This large study included 643 children and adolescents aged 6 to 16 years old who received ongoing lifestyle modification therapy at the National Childhood Obesity Center (Stockholm, Sweden). At baseline, patients were classified as moderately obese (BMI standard deviation score 1.5 to  $<3.5$ ) or severely obese (BMI standard deviation score  $\geq 3.5$ ) based on Swedish pediatric reference standards, and they were followed up for 3 years while lifestyle treatment continued. Results demonstrated that age and obesity status were predictors of response, such that younger versus older children and those with moderate versus severe obesity experienced larger reductions in BMI standard deviation score. Young children (aged 6–9 years old) with severe obesity fared well at each time point (1, 2, and 3 years); however, adolescents (aged 14–16 years) with severe obesity had poor outcomes. In fact, of the latter group, only 2% experienced a BMI standard deviation score reduction of  $\geq 0.5$  at the 3-year time point. Considered together, the behavioral studies conducted among youth with severe obesity to date suggest that lifestyle modification therapy alone results in modest reductions in BMI and body fat and some improvement in cardiometabolic risk factors but that the benefits are not durable over time. Outcomes may be better when lifestyle modification therapy is instituted early in childhood.



Alternative approaches, such as inpatient treatment and meal replacements, have also been assessed. Two studies evaluated inpatient therapy (diet, physical activity, and psychosocial support) and reported relatively large reductions in BMI<sup>177,178</sup>; however, the clinical relevance of this approach is limited, because few such programs exist and most youth with severe obesity will not have access to them. In the largest study of meal replacements in adolescents to date, Berkowitz et al<sup>179</sup> evaluated the effect of meal replacements versus conventional diet, in addition to a structured lifestyle modification program for both groups, in adolescents with BMI 28 to 50 kg/m<sup>2</sup> (mean BMI, 37.1 kg/m<sup>2</sup>). After 4 months, those initially on meal replacements were further randomized to continuation of meal replacements for another 8 months or a group that was transitioned to a conventional diet for the remainder of the study. Individuals randomized to meal replacements achieved significantly greater reductions in BMI (6.3% BMI reduction) than those in the conventional diet group (3.8% BMI reduction). However, BMI increased significantly in all groups between months 5 and 12, which suggests that long-term maintenance of BMI reduction is limited with meal replacement therapy.

In summary, lifestyle modification/behavioral therapy in severely obese children and adolescents appears to have modest short-term efficacy in terms of BMI/weight reduction and cardiometabolic risk factor improvement, and long-term sustainability of these improvements is poor.

## Medications

Although the use of medications to treat pediatric obesity is becoming more common,<sup>180</sup> the number of options is limited, and their safety and efficacy remain uncertain. Many of the medications used to treat obesity in adults, including 2 medications recently approved by the Food and Drug Administration (FDA), lorcaserin (Belviq) and the combination of phentermine and topiramate (Qsymia), along with bupropion and naltrexone, have never been studied in children and adolescents (the latter 2 are not approved by the FDA for the treatment of obesity). To date, the primary medications that have been evaluated for the treatment of pediatric obesity include sibutramine, orlistat, metformin, and exenatide. Metformin and exenatide are not FDA-approved. Sibutramine, the most effective of these medications in terms of weight/BMI reduction, was removed from the US market because of cardiovascular concerns,<sup>181,182</sup> which leaves orlistat as the only medication approved by the FDA for use in adolescents ( $\geq 12$  years).

### Orlistat

Orlistat, a lipase inhibitor that blocks the absorption of fat, is administered orally 3 times per day. It has been shown to have modest weight loss efficacy in obese children and adolescents.<sup>183–187</sup> The largest study (n=539) of orlistat in obese adolescents reported a placebo-subtracted reduction in BMI of 0.86 kg/m<sup>2</sup> (BMI reduction of  $\approx 2.4\%$ ) over a treatment period of 1 year.<sup>183</sup> No cardiometabolic benefits were observed other than a small reduction in diastolic blood pressure. Pooled analyses of orlistat trials have reported reductions in BMI ranging from 0.7 to 0.8 kg/m<sup>2</sup>.<sup>174,188</sup> Although orlistat has a good safety

profile, tolerability issues such as oily spotting, oily evacuation, fecal urgency, and abdominal pain are relatively common and limit the widespread use of this medication in children and adolescents.<sup>183,188</sup> Studies have not examined whether efficacy differs depending on severity of obesity.

### Metformin

Metformin, a biguanide primarily used for glycemic control in T2DM, has been evaluated for its effect on weight loss in a number of pediatric studies but does not have FDA approval for this indication in children and adolescents. Metformin is administered orally and is available in 2 forms, a shorter-acting twice-per-day tablet or an extended-release once-per-day version. Most but not all studies of metformin in children and adolescents have shown modest reductions in body weight and/or BMI.<sup>189–201</sup> However, many of the data should be interpreted with caution, because change in weight or BMI was not identified as a primary end point in the majority of the studies. Only 3 randomized controlled trials specified change in BMI as a primary efficacy end point.<sup>189,201,202</sup> The first study, conducted in adolescents (13–18 years old) with the extended-release formulation (2000 mg once per day), reported a placebo-subtracted reduction in BMI of 1.1 kg/m<sup>2</sup> (BMI reduction of  $\approx 3\%$ ) over a treatment period of 1 year.<sup>189</sup> No improvements in lipid profile, blood pressure, or markers of insulin resistance were observed. The second study, conducted in children (6–12 years old) with the shorter-acting (1000 mg twice per day) formulation, reported a placebo-subtracted reduction in BMI of 1.1 kg/m<sup>2</sup> (BMI reduction of  $\approx 3\%$ ) over a treatment period of 6 months.<sup>201</sup> In that study, metformin treatment also led to a reduction in fasting glucose and the homeostasis model assessment for insulin resistance. The third study, conducted in children and adolescents (8–18 years old) with the shorter-acting (1000 mg in the morning and 500 mg in the evening) formulation, reported a placebo-subtracted reduction in BMI of 1.1 kg/m<sup>2</sup> (BMI reduction of  $\approx 3\%$ ) over a treatment period of 6 months.<sup>202</sup> None of the other cardiometabolic risk factors measured in the study improved at 6 months. A meta-analysis of 5 studies (with treatment periods  $\geq 6$  months) that used metformin in children and adolescents reported a placebo-subtracted reduction in BMI of 1.42 kg/m<sup>2</sup>.<sup>199</sup> Metformin has a strong safety track record, and gastrointestinal side effects (mainly nausea and vomiting), although common, are usually mild in severity. Beyond BMI reduction, metformin has been shown to delay the onset of T2DM in adults.<sup>203</sup> Although similar studies have not been performed in children and adolescents, youth with severe obesity, particularly those at high risk for developing T2DM (eg, those having impaired glucose tolerance, elevated hemoglobin A1c, or family history of diabetes mellitus), may benefit from this medication. Studies focused on adolescents with severe obesity have not been reported.

### Exenatide

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist used for glycemic control in T2DM, has been shown to consistently reduce body weight in adults with and without T2DM. The primary mechanisms responsible for exenatide-associated weight loss appear to be related to increased satiety and suppression of appetite.<sup>204,205</sup> An



open-label pilot study in nondiabetic children and adolescents with severe obesity (BMI  $\geq 120\%$  of the 95th percentile or  $\geq 35$  kg/m<sup>2</sup>) reported a control-subtracted reduction in BMI of 1.7 kg/m<sup>2</sup> (BMI reduction of  $\approx 5\%$ ) with 3 months of exenatide treatment along with improvements in fasting insulin and oral glucose tolerance test–derived markers of insulin resistance and  $\beta$ -cell function.<sup>206</sup> A recent randomized, placebo-controlled trial among adolescents (12–19 years old) with severe obesity (BMI  $\geq 120\%$  of the 95th percentile or  $\geq 35$  kg/m<sup>2</sup>) demonstrated a placebo-subtracted reduction in BMI of 1.1 kg/m<sup>2</sup> (BMI reduction of  $\approx 3\%$ ) with 3 months of exenatide treatment.<sup>207</sup> During the open-label extension phase of the trial (an additional 3 months), BMI was further reduced in those initially randomized to exenatide (cumulative 6-month BMI reduction of 4%). Limitations of exenatide and other GLP-1 receptor agonists include mild to moderate gastrointestinal side effects (mainly nausea and vomiting) and the fact that it is administered as a subcutaneous injection. More studies will be needed to confirm the findings of these initial trials and to further evaluate the safety and efficacy of GLP-1 receptor agonists for the treatment of pediatric obesity.

In summary, only a few medications have been evaluated for the treatment of pediatric obesity, and results have demonstrated that treatment elicits only modest reductions in BMI/weight and has relatively little impact on the cardio-metabolic risk factor profile in obese youth.

## Surgery

Given the limited effectiveness of lifestyle and pharmacological interventions and the severe degree of obesity in many patients, surgical procedures that have proven health benefits for adults are more commonly being considered for severely obese adolescents (for related information regarding adult bariatric surgery, see Poirier et al<sup>208,209</sup>). Indeed, over the past decade, bariatric surgery has become a more broadly accepted approach to treatment of highly selected adolescents

who are suffering from the health and psychosocial effects of severe obesity.

### Types of Bariatric Surgery

Bariatric surgery refers to a variety of different procedures that anatomically alter the gastrointestinal tract and result in restriction of stomach capacity, interference with progression of a meal, or diversion of ingested contents. By far, the most common procedures used for adolescents with severe obesity include roux en Y gastric bypass (RYGB), adjustable gastric banding (AGB), and the more recently introduced vertical sleeve gastrectomy (VSG), which is being used with increasing frequency.<sup>210</sup> Biliopancreatic diversion (BPD), duodenal switch (DS), and VSG combined with massive enterectomy have also been used in adolescent populations but are considered by most surgeons as more complex and potentially less safe than other more commonly used surgical options. In general, published experience with bariatric procedures suggests that weight loss outcomes, comorbidity outcomes, and patient safety are comparable or better for adolescents than those seen in adults.<sup>211–213</sup> Table 2 provides a summary of the adolescent bariatric surgery literature discussed below.

### Roux en Y Gastric Bypass

Use of RYGB for weight loss in the United States dates back to the 1960s for adults and the 1970s for adolescents.<sup>220</sup> Five articles over the past decade reported intermediate- to long-term outcomes of various operations including RYGB,<sup>221–225</sup> whereas fewer reported only RYGB outcomes.<sup>212,214,226</sup> Baseline BMI ranged from 46 to 52 kg/m<sup>2</sup>, with postoperative BMI ranging from 30 to 35 kg/m<sup>2</sup>. Similar to adult studies, adolescent RYGB typically resulted in a significant 35% to 37% reduction in BMI by 1 year after surgery, with the majority of this weight loss occurring in the first 6 months after surgery.<sup>212</sup> By contrast, only a 3% BMI reduction was found when similarly obese (mean BMI 47 kg/m<sup>2</sup>) adolescents were treated in a behaviorally based weight management program.<sup>79</sup> Long-term durability (>14 years) of clinically significant weight reduction in adolescents has been revealed by only 1

**Table 2. BMI Outcomes in Adolescent Bariatric Surgery Studies**

Operation	Study (Year)	Sample Size	Mean Age, y	Baseline BMI, kg/m <sup>2</sup>	Follow-up, mo	Postoperative BMI, kg/m <sup>2</sup>	BMI Change, %
RYGB*	Inge et al (2010) <sup>212</sup>	61	17.2	60	12	37.7	–37
RYGB	de la Cruz et al (2010) <sup>214</sup>	38†	18.2	47.7	12	32	–33
RYGB	de la Cruz et al (2010) <sup>214</sup>	7‡	Not specified	49	12	32	–35
RYGB*	Olbers et al (2012) <sup>215</sup>	81	16.5	45.5	24	30.2	–33.6
AGB*	O'Brien et al (2010) <sup>216</sup>	25	16.5	45	24	32.6	–28
AGB	Nadler et al (2009) <sup>217</sup>	41	16.1	48	24	35.8	–25
VSG	Alqahtani et al (2012) <sup>218</sup>	108	13.9	49.6	12	32.4	–5
VSG	Boza et al (2012) <sup>219</sup>	40	18	38.5	12	25.2	–35
VSG	Boza et al (2012) <sup>219</sup>	34	Not specified	38.5	24	26.3	–32

AGB indicates adjustable gastric banding; BMI, body mass index; RYGB, roux en Y gastric bypass; and VSG, vertical sleeve gastrectomy.

\*Prospective studies.

†Hispanic subset.

‡Non-Hispanic subset.

retrospective study thus far,<sup>225</sup> but the findings are consistent with the larger adult literature that demonstrates the durability of surgery.<sup>227</sup> RYGB has been associated with improvement or resolution of numerous comorbid conditions, including OSAS,<sup>225,228</sup> T2DM,<sup>229</sup> features of metabolic syndrome,<sup>212,225,226</sup> pseudotumor cerebri,<sup>225</sup> and psychosocial functioning.<sup>230</sup>

Olbers et al<sup>215</sup> recently reported results from the largest prospective adolescent bariatric cohort study to date. This group performed a detailed study of 81 adolescents (13–18 years of age, mean BMI 46 kg/m<sup>2</sup>) undergoing laparoscopic RYGB in Sweden. With no one lost to follow-up, BMI was reduced by 32% after 2 years. Hyperinsulinemia, reported in 70% at baseline, was present in 3% at 2 years. Elevated fasting glucose was found in 21% at baseline and in only 5% at 2 years. More favorable lipid profiles were also observed after surgery with hypertriglyceridemia decreasing from 19% preoperatively to 1% after 2 years and elevated LDL cholesterol levels decreasing from 33% at baseline to 16% at 2 years.

When one considers what might be expected in the long-term, it is important to note that controlled, prospective adult studies demonstrate a marked effect of bariatric surgery on mortality,<sup>227</sup> comorbidity reversal,<sup>231</sup> and prevention of comorbidity over ensuing decades; these beneficial effects of bariatric surgery help to inform clinical decision making for severely obese adolescents when no other treatments have demonstrated long-term effectiveness.

After RYGB, no deaths have been reported in the perioperative (within 30 days of operation) period. Several reports of death unrelated to surgery that occurred 9 months,<sup>79</sup> 4 years,<sup>221</sup> and at 2 and 6 years<sup>225</sup> after RYGB have been reported. The typical complications of major gastrointestinal surgery have been seen after RYGB in adolescents, including anastomotic stricture, leak, wound infection, bowel obstruction, bleeding, ulceration, pneumonia, vitamin deficiency,<sup>232</sup> and venous thromboembolism.<sup>225,233</sup> These complications resulted in perioperative readmission rates of 11.5% and reoperation rates of 2.9%.<sup>234</sup> Varela et al<sup>213</sup> used the University Health System Consortium database to compare perioperative risks between >55 000 adults and 309 adolescents cared for between 2002 and 2009. Twice as many adults as adolescents required a postoperative intensive care unit stay (14% versus 7%,  $P<0.05$ ), and adults had higher 30-day morbidity rates (9.8% versus 5.5%,  $P<0.05$ ), which suggests that adolescents may tolerate bariatric procedures better than adults. Olbers et al<sup>215</sup> reported adverse events in 33% of Swedish subjects, and 15% of all study participants required additional abdominal operations over the 2-year period of study. In the Cincinnati, OH cohort, bone mineral density was reduced at 1 year and then normalized between 1 and 2 years after RYGB, but long-term effects on bone health have not been assessed.<sup>235</sup> Thus, based on current literature, RYGB appears to be a safe and effective operation in adolescents, with outcomes similar to, if not more favorable than, those observed in adults, provided measures are taken to prevent vitamin, iron, and calcium deficiency, which can have deleterious effects if uncorrected.<sup>236</sup>

#### **Adjustable Gastric Banding**

The adjustable gastric band, a device that creates a small gastric pouch in the proximal stomach, was approved by the FDA for adults >10 years ago but has not yet been

approved for use in patients <18 years of age. The literature reporting adolescent outcomes of the AGB has continued to grow despite lack of FDA approval, in large part because use of this device does not involve irreversible change in the gastrointestinal tract, the early safety profile demonstrated fewer life-threatening risks, and there are fewer nutritional risks in the long-term. When data from 2002 to 2005 were compared with data from 2007 to 2009, there was an increased use of AGB and decreased use of RYGB in adolescents in the United States,<sup>234,237</sup> although more recent analyses suggest declining use of the band in adolescents.<sup>210</sup> Among the 12 reports reviewed,<sup>212</sup> a total of 482 adolescents were represented (age range, 9–19 years). In these studies, the average mean preoperative BMI was 42 to 50 kg/m<sup>2</sup>, with postoperative BMI mean values ranging from 29 to 41 kg/m<sup>2</sup> during 1 to 7 years of follow-up. A randomized controlled trial by O'Brien et al<sup>216</sup> showed a BMI reduction of 28% in the surgical group, which was significantly more than the 3% reduction in the lifestyle group. Comorbidity changes in adolescents after banding have been inadequately studied. Among the health conditions assessed in the study by O'Brien et al,<sup>216</sup> significant improvements in systolic and diastolic blood pressure, plasma insulin, triglycerides, high-density lipoprotein cholesterol, and prevalence of metabolic syndrome were observed. Zitsman et al<sup>238</sup> found improvements in hypertension in 75%, in dyslipidemia in 88%, in gastroesophageal reflux in 20%, in asthma in 56%, and in irregular menstruation in 60% of patients at  $\approx 1$  year after surgery.

Death in the perioperative period has not been reported for adolescents undergoing AGB. Reoperation rates, including band removal, have been reported in the 8% to 10% range<sup>239,240</sup>; however, in the study by O'Brien et al,<sup>216</sup> the overall adverse event rate was 48%, with 24% of subjects requiring reoperation because of proximal gastric pouch enlargement. When one considers treatment options for pediatric patients with many decades of life expectancy, it is also very important to consider that the adult AGB literature demonstrates that risks of late complications, the need for revisional surgery, and device explantation increase over time. The Belgian experience of a cohort of 151 adults 12 to 15 years after band placement is quite relevant to thinking about use of the AGB in adolescents, because it demonstrates a 39% major complication rate (28% had band erosions), with approximately half of all patients having bands explanted over the period of follow-up.<sup>241</sup> A recent comparison of early risks among 409 RYGB adolescent patients (mean follow-up of 18 months) and 106 who underwent AGB (mean follow-up 12 months) found longer hospital stays after RYGB (2.3 versus 0.6 days) and demonstrated no mortality in either group. There were no statistically significant differences in complication rates between adolescents undergoing RYGB and AGB (pre-discharge complications 5.9% versus 2.8%; readmissions 11.5% versus 4.7%; emergency department visits 9.3% versus 7.6%; reoperations 2.9% versus 4.7%).<sup>234</sup>

On the basis of this evidence, the AGB is more effective than lifestyle intervention for weight loss and cardiovascular risk factor reduction in severely obese adolescents over at

least a 2-year period. It is hoped that the results of an ongoing adolescent FDA trial will provide data from a large US cohort regarding the safety and efficacy of this device.

#### ***Appropriateness of Bariatric Surgery***

In light of the limited effectiveness of lifestyle modification and medical therapy shown to date for severe obesity, surgical procedures that have an evidence base that supports their efficacy and safety should be considered for patients who demonstrate medical necessity and psychosocial readiness. Several groups have suggested guidelines for patient selection, and common themes and differences between selection criteria have been noted. The most recent and authoritative practice recommendations from Pratt et al<sup>242</sup> emphasize the concept that a combination of both severe obesity and the existence of comorbidities should be present to medically justify an operation to treat obesity. There is good evidence that RYGB is reasonably safe and highly effective compared with lifestyle modification for the treatment of severe obesity. Relatively good safety and efficacy data for AGB in adolescents have been reported, although a high rate of reoperation and sparse long-term data, along with a lack of FDA approval for the device, hamper recommendations for usage before adulthood. All adolescents undergoing bariatric surgery should be strongly encouraged to participate in prospective longitudinal outcomes studies to improve the evidence base to evaluate the risks and benefits of operations in this age group.

Overall, data that have been gathered from both adult and adolescent clinical experience and from several prospective clinical research studies among adolescents suggest that bariatric surgery may be the most effective treatment for severe obesity in adolescents. Evidence demonstrates that surgical procedures result in 20% to 35% initial weight loss over at least the first 2 years; sustainability of weight loss for >1 decade has also been shown in one study, and data on complications to be expected with these interventions appear to show such complications to be less severe in adolescents than in adults. However, some questions remain, and prospective studies are ongoing that will more completely examine specific risks of surgery, timing of surgery, mechanisms of the effect of surgery on weight and comorbidity, and long-term effectiveness of specific procedures in this population.<sup>215,243</sup>

In summary, treatment of severe obesity in children and adolescents is challenging. Severe obesity in youth rarely responds to low-intensity or moderately intensive therapy. Although an expert committee suggested a staged approach that starts with primary care-based intervention,<sup>34</sup> clinicians can expect that severely obese youth and their families need the best available intensive behavior-based program (stage 3); however, most will not achieve sustained weight reduction from these programs and would benefit from more intensive interventions that require careful medical oversight (stage 4). Bariatric surgery is the most effective treatment for severe obesity in adolescents; however, surgery is appropriate and available for only some adolescents with severe obesity, and broadening availability will depend on the results of long-term outcome studies, currently in progress.

Clinicians should support the most intensive interventions that are appropriate and available for a severely obese child, but the armamentarium of stage 4 interventions is very limited, especially for preadolescents.

## **Research Gaps and Future Research Needs in Treatment Approaches for Severe Obesity: A Call to Action**

### **Novel Approaches to Lifestyle Modification/Behavioral Therapy**

#### ***Treatment Efficacy in Severe Obesity Versus Obesity and Overweight***

As noted previously, few studies have evaluated the relative efficacy of lifestyle modification approaches for BMI and risk factor reduction in youth with severe obesity compared with overweight and obese peers; however, it seems clear that more effective strategies are needed. Even highly intensive lifestyle interventions generally have left subjects still markedly obese, albeit with modestly improved cardiovascular and metabolic profiles. Alternative approaches are needed for youth who medically qualify for bariatric surgery but are not interested in this option, for youth who lack the family support or emotional maturity for the surgery and resulting change in food intake, and for children too young for surgery but with severe obesity and severe comorbidities. More studies will be needed to better understand the unique underlying physiological, psychological, and environmental factors associated with severe pediatric obesity and how these factors can be adequately addressed within the context of lifestyle modification therapy to maximize treatment outcomes. Additionally, future behavioral intervention studies should be designed to evaluate nonweight outcomes, such as cardiometabolic risk factors, measures of vascular structure and function, and markers of inflammation and oxidative stress, because lifestyle modification may lead to improvements in these factors even without concomitant BMI or adiposity reduction. Indeed, the ultimate goal should be to improve the quality of life and reduce the risk for chronic disease development in children and adolescents with severe obesity.

#### ***Development of a Continuing Care Model for Severe Pediatric Obesity***

As noted in the National Heart, Lung, and Blood Institute's working group report on future research directions in childhood obesity prevention and treatment,<sup>244</sup> the pediatric obesity treatment literature is limited and characterized by methodological shortcomings such as small sample size, which restricts identification of potentially important correlates of outcome, and short intervention and follow-up periods. Moreover, because of its association with medical morbidity and costs, there is growing consensus that severe obesity requires chronic management.<sup>171,245</sup> Data from adult behavioral intervention trials suggest that continuing behavioral weight management is associated with sustained weight loss and health benefits,<sup>246</sup> but pediatric data are limited. Some studies have suggested the potential utility of longer programs in the management of pediatric obesity. Wilfley



et al<sup>247</sup> found that weight loss maintenance programs after a 5-month family-based behavioral intervention had significantly better weight outcomes. Similarly, Savoye et al<sup>176</sup> used a 12-month behavioral lifestyle program with a step down in intensity after 6 months and documented significant differences between intervention and control conditions in weight, body composition, and insulin resistance. These data indicate that ongoing treatment is associated with better outcomes. Nevertheless, the feasibility and acceptability of continuing care over longer periods of intervention are not known, and important questions about sustaining changes in eating and physical activity remain unaddressed.<sup>247,248</sup> Furthermore, challenges such as high rates of attrition within the context of pediatric weight management clinical programs will need to be addressed if a continuing care model is to be successful.<sup>249,250</sup>

**New Medications**

**History of Obesity Pharmacotherapy**

As described previously, options for pharmacotherapy for severe obesity in children and adolescents are extremely limited. In adults, obesity drugs have had an unfortunate track record characterized by initially promising results, followed by concerns about limited effectiveness, and, in some cases, serious side effects. In 1997, the combination drug fenfluramine/phentermine was pulled off the market after reports of serious cardiovascular complications emerged.<sup>251</sup> In 2009, rimonabant, a cannabinoid receptor antagonist available in Europe but never approved in the United States, was withdrawn from the market in Europe because of psychiatric side effects. As noted previously, sibutramine, originally approved for patients ≥16 years of age, was withdrawn in 2010. On the basis of this history and the more stringent standards imposed by the FDA for approval of obesity drugs, it is easy to be pessimistic about the future of drug therapy for severe pediatric obesity; however, 2 new medications have been approved recently, and a growing pipeline of medications is currently in development.

**Medications Recently Approved or in Development for the Treatment of Obesity**

Two new medications for the treatment of obesity have received FDA approval recently, and a number of promising medications are in development or are currently being reviewed by the FDA for treatment of obesity in adults, and eventually children and adolescents. Table 3 provides information on the medications that have been approved recently and another that is in late-stage development. A strategy of using combinations of medications for treatment of obesity is likely to be beneficial. First, combining established medications diminishes the likelihood of unexpected side effects, a phenomenon that has been observed repeatedly with new single agents. When lower doses of each can be administered, the likelihood of side effects is diminished further. Second, a combination of medication can target multiple distinct mechanisms, which would ideally promote greater satiety and appetite suppression. This is particularly important because individuals tend to have varying levels of weight loss responsiveness when only 1 mechanism is targeted. The pipeline of weight loss medications currently in development for adult obesity appears promising. As soon as these medications receive FDA approval for use in adults, studies should be performed to evaluate their safety and confirm their benefits in children and adolescents.

**Other Techniques in Bariatric Surgery**

Although much of the research in adolescent bariatric surgery to date has focused on RYGB and AGB, other procedures are beginning to emerge, such as BPD, DS, and VSG. Initial pediatric studies of these procedures have been completed, but further evaluation will be needed to better characterize their safety and efficacy in children and adolescents.

**BPD and DS**

Limited reports of BPD<sup>224</sup> and DS<sup>259</sup> in adolescents have demonstrated that these procedures result in significant malabsorption. For BPD, a concerning rate of malnutrition (15% of adolescent patients), and high rates (20%) of reoperation

**Table 3. Medications Recently Approved or in Late Stages of Development for the Treatment of Obesity**

Medication	Mechanism of Action	Clinical Trial Data	Status
Phentermine plus topiramate	Phentermine: norepinephrine release in hypothalamus; appetite suppression Topiramate: mechanism of weight loss unknown; reduced food intake	56-wk study in 2487 obese adults demonstrated 9.8% weight loss <sup>252</sup> ; weight reduction was sustained at 2 y in extension study. <sup>253</sup> 56-wk study in 1267 adults with severe obesity demonstrated 10.9% weight loss <sup>254</sup>	Approved by FDA in July 2012
Lorcaserin	Selective 5-HT2C agonist; satiety enhancement; possible appetite suppression	52-wk study in 3182 overweight/obese adults demonstrated ≈6% weight loss. <sup>255</sup> 52-wk study in 4008 overweight/obese adults demonstrated 5.8% weight loss <sup>256</sup>	Approved by FDA in June 2012
Naltrexone plus bupropion	Naltrexone: Opioid antagonist; mitigates the opioid-mediated effect of food on pleasure and palatability of eating. Bupropion: Dopamine and norepinephrine reuptake inhibitor; mitigates dopamine-mediated effect of food on motivation/reinforcement	56-wk study in 1742 overweight/obese adults demonstrated 6.1% weight loss. <sup>257</sup> 56-wk study in 793 overweight/obese adults demonstrated 9.3% weight loss (treatment included intensive behavior modification) <sup>258</sup>	Cardiovascular outcomes trial initiated in 2012; FDA review and approval could take place in 2014

FDA indicates US Food and Drug Administration; and 5-HT2C, 5-hydroxytryptamine (serotonin) receptor 2C.



attributable to the complexity of the procedure were reported, and weight loss results were not distinguishable from that achieved with RYGB.<sup>224</sup> Adolescent data from a single DS series of 13 adolescents followed up for 11 years, by contrast, demonstrated satisfactory weight loss results, but there were concerns about calcium and vitamin A levels.<sup>259</sup> BMI reduction of 47% on average was observed. Preservation of a small region of duodenal absorptive area in DS operations may well be responsible for major differences in nutritional outcome of BPD and DS procedures. However, because of the complexity of the operations and the generally perceived poor compliance for nutritional supplements among adolescents,<sup>260</sup> at present there are insufficient outcome data to support the use of either the BPD or DS procedures in adolescents.

### Laparoscopic VSG

The laparoscopic VSG is a newer operation that produces significant initial weight loss with low operative risk in adult studies. Indeed, important mechanisms of action for weight loss and metabolic improvement may be similar between VSG and RYGB,<sup>261</sup> although risks may be much lower than with RYGB.<sup>262</sup> Current estimates suggest that >12 000 operations have been performed in adults,<sup>263</sup> and controlled trial data support use of this operation.<sup>264,265</sup> Several adolescent case reports and small case series have appeared over the past 4 years,<sup>266,267</sup> and 1 study that described the combination of VSG with a massive enterectomy has been reported,<sup>268</sup> albeit without any cogent rationale for the additional small bowel resection.<sup>269</sup> A recently published series of 108 pediatric patients undergoing VSG in Saudi Arabia (age range, 5–21 years; mean, 14 years), included 7 with Prader-Willi syndrome, 2 with Brader-Biedl syndrome, 3 with mental retardation, and 1 with Down syndrome.<sup>218</sup> This cohort had a median preoperative BMI of 47 kg/m<sup>2</sup> (range, 32–97 kg/m<sup>2</sup>) and a BMI reduction of 37% at 1 year (41 patients) and 38% at 2 years (8 patients). Authors reported no deaths and no major complications (eg, no bleeding, no staple line leak). Minor complications were seen in 4.6%, and only 1 patient (0.9%) required readmission within 30 days. Comorbidities of obesity responded well, with 70% resolution of dyslipidemia, 75% resolution of hypertension, 91% resolution of symptoms of sleep apnea, and 94% resolution of diabetes mellitus. Although this study represents the largest experience to date with VSG, another study of 51 adolescents who underwent VSG with 1-year follow-up essentially confirms these weight loss and safety findings.<sup>219</sup> Although much more research is needed, VSG may prove to be a safer alternative with fewer nutritional risks than RYGB, with no device/foreign body–related complications, while providing weight loss comparable to other modern weight loss operations. Current knowledge gaps remain concerning durability of weight loss, incidence of gastroesophageal reflux induced by the procedure, and long-term nutritional risks.

### Conclusions

Severe pediatric obesity is a significant public health problem because of the high percentage of children and adolescents afflicted (≈4%–6%) and the considerable immediate and long-term health consequences associated with it. Emerging

data suggest that the number of youth in this category of obesity is on the rise, but more data will be needed to more precisely describe the prevalence and trends. Various names and definitions have been used in the literature, but the writing group recommends that this condition be called *severe obesity*, and it should be defined as having a BMI ≥120% of the 95th percentile or an absolute BMI ≥35 kg/m<sup>2</sup>, whichever is lower based on age and sex. Accumulating evidence suggests that severe obesity in childhood is associated with an adverse cardiovascular and metabolic profile, even compared with obesity and overweight. Although the unique characteristics that distinguish severe obesity from less extreme forms of adiposity are beginning to be explicated, more work needs to be done to better understand the pathogenesis and distinct pathophysiology that underlie this condition and the psychosocial/behavioral dynamics that allow it to be perpetuated. A more complete understanding of these factors and their interplay will be needed to appropriately tailor interventions to achieve the maximum impact. Moreover, current treatment approaches using lifestyle modification and medications to reduce BMI and improve chronic disease risk factors are insufficient for most patients, and significant residual risk (unacceptably high BMI and risk factor levels) remains. Although experts recommend stepped intensification of interventions, the “step” after behavior-based and pharmaceutical interventions to the next established alternative, bariatric surgery, is unacceptably large because of its limited applicability and availability. Despite the effectiveness of surgery in terms of BMI and risk factor reduction and its reasonably acceptable safety profile, recommended selection criteria are stringent, and access is limited for most adolescents because of lack of insurance coverage. Therefore, innovative approaches to fill the gap between lifestyle/medication and surgery are urgently needed.

- Generation of additional longitudinal data addressing tracking of severe obesity and risk factors (including measures of vascular structure and function, markers of inflammation and oxidative stress, insulin resistance, and impaired glucose tolerance) from childhood into adulthood and assessment of long-term health outcomes later in life.
- Improved utilization of early-life weight-gain trajectory data that may differentiate young children who are at risk of developing severe obesity to target for preemptive, intensive, family-based intervention that incorporates attention to psychosocial factors that are promoting unhealthy eating and sedentary behavior.
- For younger children for whom medication or surgery will generally be inappropriate, exploration of intensive programs for families, including home-based therapy or short-term residential programs for families.
- Characterization of the origin of severe obesity and identification of distinct behavioral, genetic, pathophysiological, and environmental factors associated with severe obesity, as opposed to overweight or obesity, to inform the design of novel treatment approaches.
- Evaluation of unique approaches to lifestyle modification therapy: intensive dietary (including short-term meal replacement or very low-calorie diets, etc) and physical

activity interventions with innovative strategies to support sustained adherence.

- Assessment of the safety and efficacy of new pharmacotherapies for the treatment of obesity in adolescents (including studies designed to identify “responders” and “nonresponders” by use of clinical characteristics and, potentially, pharmacogenomics); combination of intensive lifestyle modification plus pharmacotherapy (for weight loss maintenance); comparison of outcomes of pharmacotherapy versus surgical approaches.
- Generation of additional safety and efficacy data (especially long-term) on bariatric surgery, including studies describing improvements in vascular structure and function, insulin resistance, and  $\beta$ -cell function.
- Evaluation of non-weight-loss interventions targeting cardiometabolic risk factors with a goal of reducing risk of CVD and T2DM.
- Assessment of the impact of multiple or serial intensive interventions across disciplines.
- A chronic care model for severe pediatric obesity, with the expectation that ongoing care, monitoring, and episodic intensive treatment bouts will likely be needed.

Prevention of severe pediatric obesity is the ultimate goal and ideal outcome; however, widespread prevention is unlikely to be realized in the near future, and the numerous children and adolescents affected by this condition need safe and effective treatments now. Just as a combination of medications offer greater effect with fewer adverse effects than monotherapy, we can expect that various combinations of diet, behavior modification, medical therapy, and minimally invasive procedures will likely be needed. Furthermore, the effectiveness of a given intervention or combination of interventions will vary among individuals, and understanding the best match at a genetic or metabolic level could improve efficacy. Treatment will need to be broad-based and target not only adiposity but also the risk factors associated with it. Increased research funding will be needed from the National Institutes of Health, other funding agencies, and industry. Stakeholders at all levels will need to work together to engage the growing problem of severe pediatric obesity. The task ahead will be arduous and complicated, but the high prevalence and serious consequences of severe obesity require us to commit time, intellectual capital, and financial resources to address it.

**Disclosures**

**Writing Group Disclosures**

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Sarah E. Barlow	Baylor College of Medicine	CDC† (Childhood Obesity Research Demonstration project); NIH/NIDDK† (NASH CRN, starting July 1, 2013)	None	None	None	None	None	None
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person’s gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

\*Modest.  
†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Prabhakaran (Babu) Balagopal	Nemours Children's Clinic	None	None	None	None	None	None	None
Helen Dichek	University of Washington	Takeda Pharmaceutical Company, Inc*	None	None	None	None	None	None
William H. Dietz	Centers for Disease Control and Prevention	None	None	None	None	None	None	None
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Paul Poirier	Quebec Heart and Lungs Institute	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Significant.

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