Risk Factors in Adolescent Hypertension

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Hypertension is a complex and multifaceted disease, with many contributing factors. While diet and nutrition are important influences, the confounding effects of overweight and obesity, metabolic and genetic factors, racial and ethnic predispositions, socioeconomic status, cultural influences, growth rate, and pubertal stage have even more influence and make diagnosis quite challenging. The prevalence of hypertension in adolescents far exceeds the numbers who have been diagnosed; studies have found that 75% or more go undiagnosed. This literature review summarizes the challenges of blood pressure classification in adolescents, discusses the impact of these confounding influences, and identifies actions that will improve diagnosis and treatment outcomes.

**Keywords:** hypertension | adolescents | metabolic syndrome | diabetes | obesity | extreme obesity | bariatric surgery | polymorphisms | immigrant youth

**Article:**

***Note: Full text of article below***
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D. Rose Ewald1 and Lauren A. Haldeman PhD1

Abstract

Hypertension is a complex and multifaceted disease, with many contributing factors. While diet and nutrition are important influences, the confounding effects of overweight and obesity, metabolic and genetic factors, racial and ethnic predispositions, socioeconomic status, cultural influences, growth rate, and pubertal stage have even more influence and make diagnosis quite challenging. The prevalence of hypertension in adolescents far exceeds the numbers who have been diagnosed; studies have found that 75% or more go undiagnosed. This literature review summarizes the challenges of blood pressure classification in adolescents, discusses the impact of these confounding influences, and identifies actions that will improve diagnosis and treatment outcomes.

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Introduction

For many children, hypertension is only diagnosed when it is severe, or once they reach adulthood. However, the importance of early and accurate diagnosis cannot be overstated, given the long-term health consequences of untreated hypertension and the fact that pediatric hypertension is a diagnostic indicator for some serious underlying medical conditions. For the purposes of this article, the words pediatric and youth refer to both children (aged 2-18 years) and adolescents (aged 13-18 years).

Obesity has been posited as the cause of hypertension, but the fact that there are metabolically obese normal weight (MONW) people, as well as overweight and obese people who are metabolically normal, would argue that there may not be a simple cause-and-effect relationship between them. The fact that they can appear independently as well as together would indicate that they might both be signs that something has gone wrong metabolically, and therefore perhaps both of them are effects. Moreover, the obesity and hypertension epidemics have arisen concurrently with significant changes in family structures that have resulted in increased consumption of fast foods and prepared foods, and therefore sodium, trans-fats, and high-fructose corn syrup, as well as more automation of activities that formerly required physical labor to accomplish, and a more fast-paced and deadline-driven environment in almost every facet of life.

This literature review (a) examines the various factors that contribute to hypertension in adolescents as illustrated in Figure 1, (b) summarizes the findings of researchers in various disciplines who are studying these factors, and (c) identifies the barriers to progress and the interventions that have been proposed by them.

The Challenges of Blood Pressure Classification

Diagnosing Pediatric Hypertension

Untreated pediatric hypertension has long-term serious health consequences. Sustained hypertension in children is often caused by a serious underlying health problem affecting the heart, kidneys, or endocrine system.1-3 This type of hypertension is known as secondary hypertension, because it develops due to the medical condition. Mild to moderate hypertension with no known underlying disease process is classified as primary or essential hypertension. This is the type of hypertension that many older children and most adults have. In children with hypertension, 30% to 60% have secondary hypertension, while 40% to 70% have primary hypertension.4 In children, the prevalence of hypertension is estimated at

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between 2% and 5%, and the prevalence of prehypertension is estimated at between 4% and 15%, but studies in both the United States and Europe have found that only 13% to 26% of childhood hypertension is properly diagnosed. Children with primary hypertension may be asymptomatic or the symptoms may be mild and seemingly unrelated, such as changes in behavior or school performance, nosebleeds, headaches, or shortness of breath.

The upper limit for "normal" blood pressure (BP) in adults is well known, and the same threshold is used for both men and women: the systolic blood pressure (SBP) should be less than 140 mm Hg, and the diastolic blood pressure (DBP) should be less than 90 mm Hg. A diagnosis of high BP in children aged 3 to 18 is more challenging, because children grow so rapidly and BP changes with height. Standardized height-for-age tables have been developed for children, based on gender, with different thresholds for every combination of incremental age and height. This height percentile is then used to determine where SBP or DBP falls within given BP percentiles for healthy children of the same age and gender. When a valid office blood pressure (OBP) reading is taken (using the correct cuff size and a calibrated device, by a properly trained professional) but the height of the child is not measured on the same visit, the practitioner cannot use the reference tables to determine whether that reading places the child in an elevated risk category.

The standardized tables are quite cumbersome and time-consuming and there are too many data points to memorize "normal" parameters. Therefore, attempts have been made to enable rapid preliminary assessment of possible prehypertension or hypertension by simplifying the diagnostic process, but it is not clear how widely these tables are used. In addition, there are different parameters for different nationalities and ethnicities, which further complicates diagnostic efforts. Clearly, without the use of reference tables of some kind it is virtually impossible to correctly identify hypertension in most children unless it is significantly elevated.

In children, prehypertension is persistent BP that equals or exceeds the 90th percentile for a normotensive child of the same age, sex, and height, or is below the 95th percentile but exceeds 120/80 mm Hg (either SBP or DBP)
exceeds 120 mm Hg, or DBP exceeds 80 mm Hg, or both). Hypertension is persistent BP that equals or exceeds the 95th percentile for a normotensive child of the same age, sex, and height. Documentation of elevated BP readings at 3 or more well-child visits has been found to greatly improve the chances of a correct diagnosis, by nearly double for children with hypertension, and more than triple for those with prehypertension.

With repeated testing, one study found that approximately 9% of adolescents had a change in BP classification, with 6.2% decreasing from prehypertension to normotensive, and 2.9% increasing from prehypertension to hypertension.

Failure to recognize elevated BP occurs most frequently when the patient’s SBP and DBP are less than the adult thresholds, the patient appears to be of normal weight for their height, and there is no family history of cardiovascular disease (CVD). One study found that the children most often missed were those who were older, male, and/or those whose BP was taken by nurse-practitioners or less experienced providers. Only 13% of children with elevated BP in this study were actually diagnosed, and the children with the lowest rate of recognition—just 7%—were those of healthy weight. Another study reported that just 11% of prehypertensive and 26% of hypertensive children were diagnosed, even when their health record included a positive family history of hypertension.

These results are consistent with another study, which found that only 25% of pediatric physicians routinely measured BP in their patients, while 71% measured it only when risk factors for hypertension were present, such as obesity or positive family history of hypertension. Of those who measured BP, 65% did not use the reference tables unless they suspected the BP reading was elevated. However, of the pediatric physicians in this study, 14% could not correctly define prehypertension and 17% could not correctly define hypertension in children. Perhaps not surprisingly, a full 47% of pediatricians who participated in this study underestimated the BP category of patients when presented with pediatric case studies.

Both United States and European guidelines recommend obtaining BP readings at each well-child visit, and studies have shown that repeated BP measurements are an effective way to ensure proper classification and tracking of BP in children. Despite this, some claim that individual variability makes screening for elevated BP a less-than-useful tool for predicting CVD, and that there is insufficient evidence to determine whether BP screening in asymptomatic children is harmful or beneficial.

Among those who advocate for diagnostic screening, there is debate about the best method for monitoring BP in children. Ambulatory blood pressure (ABP) monitoring has been proposed by some as a better gauge than OBP of whether the patient’s BP warrants concern. Rather than a health care professional taking a one-time measurement during what can be a stressful experience in an unfamiliar environment, which can lead to an incorrect diagnosis of hypertension due to “white-coat” effect, ABP monitors are worn for 24 hours and periodically measure BP during that time. These results are then analyzed for overall cardiovascular impact.

Although ABP monitoring in children may reduce “white-coat” hypertension diagnoses, it is not without its own complexities and limitations. A 2004 review of several ABP studies expressed concerns about the validity of reference data for children, the lack of monitors specifically designed for children, and the relative lack of familiarity with interpreting the many data points generated during ABP monitoring. However, this review also noted that recent and ongoing studies were addressing these issues and pointed out the usefulness and benefits of ABP monitoring in some research settings. The American Heart Association also affirmed the benefits of ABP monitoring as a diagnostic tool, but emphasized that it should be done by trained staff and experts in pediatric hypertension.

ABP monitoring plays a crucial role in the diagnosis of persistent masked hypertension, which cannot be diagnosed by conventional BP measurements alone. Persistent masked hypertension is diagnosed when 2 or more ABP readings are hypertensive but conventional BP readings are normotensive. ABP monitoring has revealed that the prevalence of persistent masked hypertension is between 10.9% and 14% in adults, and is associated with increased risk of developing sustained hypertension and type 2 diabetes mellitus (T2DM), organ damage, and CVD. Children who have hypertensive parents or a family history of hypertension are at high risk for developing these same conditions and should have ABP monitoring for proper diagnosis and early treatment.

One 2013 retrospective study found that using 24-hour mean arterial pressure (MAP), which is recorded by ABP monitoring devices, increased the number of hypertension diagnoses. MAP is calculated by taking one third of the difference between SBP and DBP and adding it to DBP; this is seen as a measure of the effect of BP on the cardiovascular system over time. Another 2013 retrospective study found that daytime ABP tends to be higher than OBP in children (especially younger children) and can result in incorrectly classifying them as hypertensive. The authors’ recommendation was to continue using OBP in clinical practice until more research has been done and the results have been reviewed.
These academic disagreements about the need for and usefulness of pediatric BP screening and the best method for obtaining reliable data, plus the failure to consistently use reference tables to interpret the readings that are obtained, likely contribute to the low diagnostic rates noted previously. However, in contrast to obesity screening, hypertensive screening cannot be done simply by looking at the children, so pediatric health care providers should follow the consensus guidelines for measuring and documenting BP percentile at every visit. Without this information, an important diagnostic and predictive tool is lost.

Causes of Hypertension

The degree of persistent hypertension, the age of the child, the symptoms found during physical examination, and the risk factors documented in a thorough patient history will determine the next steps taken by the physician. For example, a child with low birth weight, family history of hypertension, and/or obesity has an increased probability of developing pediatric hypertension. Undiagnosed hypertension results in measurable organ damage in children, and overweight and obese children have a significantly increased risk of developing hypertension as adults.

Risk factors for hypertension that cannot be modified include a family history of hypertension or CVD, low birth weight, gender, race, genetic inheritance, socioeconomic status (SES), premature birth, and use of umbilical artery catheters. Risk factors that can be modified include decongestants, nose/eye drops, oral contraceptives, (OC) antidepressants, bronchodilators, dietary habits, salt intake, excess adiposity, physical activity level, secondhand smoke, and poor sleep quality and/or short sleep duration.

Sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA) have both been associated with pediatric hypertension and should be ruled out or treated. The prevalence of OSA in all children is estimated at less than 3%, but estimates in obese youth range from 5.7% to 36%, with prevalence and severity positively correlated with the degree of obesity. The risk of SDB in general increases by 12% for every 1 kg/m² above mean body mass index (BMI), and for each standard deviation above mean BMI, the risk of OSA is 3.5-fold greater.

Typically, older children and adolescents are more likely to present with primary hypertension, while younger children are most likely to have secondary hypertension. Low renin and abnormal sodium transport in the kidneys are characteristics of secondary hypertension with an underlying genetic basis, which should be further investigated. For all children with persistent elevated BP, a baseline evaluation to exclude secondary causes should include certain blood and urine tests, a kidney ultrasound, and an echocardiogram. If these are found to be abnormal, the child should be referred to a pediatric nephrologist or pediatric cardiologist for further evaluation; if the baseline evaluation is normal and no medical condition has been found, primary hypertension is diagnosed.

Hypertension Is Highly Correlated With Overweight and Obesity

Although not all overweight or obese people develop hypertension, weight gain is usually associated with a corresponding increase in BP. It is widely recognized that overweight and obesity are closely associated with hypertension in children. The prevalence of pediatric hypertension is estimated to be 3% to 14% for normal weight children and 11% to 30% for obese children. The degree of overweight or obesity and hypertension manifested during childhood directly correlates with the risk of developing hypertension, stroke or other CVD, and kidney disease in adulthood. Childhood obesity rates have risen alarmingly during recent decades, and not surprisingly, rates of childhood hypertension and T2DM have risen right along with them. Since each of these conditions can exist independently of the other 2 conditions and cannot be accurately diagnosed by a child’s appearance alone, these conditions must be screened for on a regular basis by the child’s healthcare provider.

Studies have found that most physicians can diagnose moderate to severe obesity simply by the appearance of their patients, but they are less likely to visually identify overweight children thus, overweight children are at high risk of progressing to obesity before being diagnosed. BMI is recommended as an objective way to estimate the relative degree of adiposity based on weight and height (kg/m²), and its documentation is recommended at least once per year or at every well-child visit. Repeated BMI documentation has been shown to increase both rates of overweight diagnosis and obesity prevention efforts.

Again, as with pediatric BP tracking, compliance with the consensus guidelines for BMI tracking has been inconsistent. One survey found that 72% of surveyed pediatricians indicated they were not familiar with BMI recommendations, 91% of those physicians relied on visual assessment to diagnose overweight, and BMI percentile was calculated in just 52% of patients aged 3 or older. Another survey of United States pediatric providers found that just 31% could correctly define both
overweight and obesity in children, while only 46% routinely calculated BMI and only 43% made a correct visual diagnosis of overweight and obese children. These findings are consistent with other surveys of pediatricians, which found that 86% of obese patients but only 27% of overweight patients were diagnosed, and that 31% of surveyed physicians said they never used BMI while only 11% said they always did.

Part of the resistance to BMI tracking is that it must be calculated from weight and height and, as with BP, “normal” BMI in children changes with gender and age. Reference tables must therefore be used to determine the BMI percentile for each child. In addition, “normal” BMI is different for each nationality and ethnicity. For children aged 5 to 17, age-, sex-, and race-specific BMI percentile tables have been published, and at least 4 different reference tables are in common use. The reference table that is used matters, because children are classified as underweight, healthy weight, overweight, or obese based on their BMI percentile. Since BMI calculation is time-consuming, a simplified table has been published that uses just height and weight to identify children requiring actual BMI calculation, but it is not known how widely it is used. Even with electronic medical records that automatically calculate BMI percentiles, unless practitioners regularly incorporate these results into their screening practices, overweight children will continue to be underdiagnosed, and obesity prevention efforts will continue to be hampered.

With that said, however, BMI by itself does not accurately indicate body composition, that is, the “fatness” or adiposity of a child. BMI is intended to estimate excess adiposity (not excess weight) in those who are presumed to have a normal amount of lean body mass. Calculated BMI does not directly measure the actual muscle mass or amount of fat in an individual, which can result in misclassification of those who are very muscular. An athlete with a high percentage of muscle mass and very low body fat percentage could be classified as obese based strictly on BMI percentage. In addition, children with low birth weight have reduced lean muscle mass when they are younger and an increased risk of abdominal adiposity when they grow older. Research has shown that children who become obese in infancy are generally taller than average as they mature, while those who have excess adiposity are generally taller than other children of the same sex and age. Clearly, there is not a one-for-one relationship between height and adiposity in children, and variation in degree of fatness is more common than variation in height. Because of these issues, researchers have explored ways to derive a height-adjusted adiposity index that removes this relationship.

From the 2007 Expert Committee recommendations for children, an age- and gender-specific BMI below the 5th percentile is considered underweight, and a BMI at or above the 85th percentile but less than the 95th percentile is classified as overweight. Healthy weight is defined as a BMI that falls at or above the 5th percentile but less than the 85th percentile, while the threshold for obesity is either a BMI greater than or equal to the 95th percentile, or a BMI greater than or equal to 30 kg/m², whichever is lower. In recognition of the greater medical risks faced by those with extreme obesity, the Expert Committee also proposed an additional category of severe obesity for children at or above the 99th percentile. This equates to a BMI of between 30 and 32 kg/m² for children 10 to 12 years old or a BMI of at least 34 kg/m² for children 14 to 16 years old. The American Heart Association defines severe obesity as an absolute BMI greater than or equal to 35 kg/m², or greater than or equal to 120% of the 95th percentile, whichever is lower based on age and sex.

The American Academy of Pediatrics estimates that the risk of childhood obesity continuing into adulthood increases from about 20% at age 4 to about 80% by adolescence, and is associated with medical problems that affect cardiovascular, endocrine, and mental health, in addition to pulmonary, orthopedic, hepatic, and gastrointestinal complications. Severe obesity is more prevalent in those with lower SES and in Hispanic, Mexican-American (MA), non-Hispanic Black (NHB), and Native American (NA) youth. Severe obesity is the fastest-growing classification of obesity, with 4% to 6% of children and adolescents in the United States having a BMI in the severe obesity category.

Among adolescents in the highest BMI quintile, non-Hispanic Whites (NHW) had the highest DBP and rates of hypertension, but at all other BMI quintiles, there were greater rates of high DBP and hypertension in NHB. In all BMI quintiles, SBP was higher for NHW than for NHB, except for older girls, where the opposite relationship was found. In adolescent males, BMI had a significantly greater influence on SBP in NHW than in NHB. A multiethnic study found that higher waist circumference (WC) in NHB and NHW children was significantly associated with a higher BP classification, but Hispanic children, who had the highest measurements of WC, BMI percentile, and fat mass, had the lowest BP classification. NHB racial heritage was independently associated with hypertension; more NHB children were found to have hypertension or hypertension when compared to Hispanic and NHW children, and although NHB children had less body fat and lower BMI than Hispanic children, nearly 20% had elevated BP.
In addition to genetic causes, such as Prader-Willi syndrome, Bardet-Biedl syndrome, and Cohen syndrome, risk factors for childhood obesity include high birth weight, maternal diabetes, a family history of obesity, families with migration background, formula feeding during infancy, eating disorders, racial/ethnic predisposition, low physical activity, high television/computer usage, low income, poor diet, and depression or anxiety. Risk of obesity and hypertension are inversely related to the extent and duration of breastfeeding and to SES, and risk of obesity is possibly influenced by food insecurity.

Excess adiposity is the single most powerful risk factor for higher BP and contributes to more than half of the risk for developing hypertension. However, since body composition changes rapidly during adolescence, an increase in BMI should not automatically be interpreted as an indication of increased adiposity. Increased muscle mass is the primary driver of the increases in BMI which occur in boys between the ages of 12 and 17 years and in girls between the ages of 10 and 16 years. In addition, care must be taken to distinguish adolescents who have a larger BMI due to excess adiposity from those who are tall for their age and therefore may have a larger BMI due to stature. Likewise, the degree of adiposity may be underestimated in those who are at the lower height percentiles.

Several studies have shown that adiposity change in a child over time can best be measured by using actual BMI (kg/m²) or BMI (%) units instead of BMI centiles or z-scores. BMI distribution is skewed in the higher and lower centiles of BMI tables, because the centile curves are farther apart; in effect, the tails of the distribution are biased relative to the median. Z-scores are best for standardizing one-time measurements across a population, but are not designed to measure within-child changes in adiposity over time. In an overweight or obese child, actual BMI (kg/m²) or BMI (%) units tracked over time will identify whether that child is remaining in the same percentile category or crossing percentile categories.

Hypertension and the Adiposity Effect

An accurate assessment of adiposity is very important when determining hypertensive status. A recent study evaluated the effect of adiposity on BP in overweight and obese children and found that when the BMI exceeded the 85th percentile, 14% of overweight and obese children had BP measurements in the prehypertensive or hypertensive range. In contrast, just 5% of normal weight children had BP above the normotensive range. This study also looked at the adiposity effect by race and gender and found that overweight NHB females had a 33% increase in risk of elevated BP for every 5% increase in BMI percentile; for every other group, the risk was nearly doubled for every 5% increase in BMI percentile. The intensification of risk was observed in all race and sex groupings and was similar for all ages of the children in the study. Importantly, for children with a BMI over the 85th percentile, the effect of BMI percentile on BP was 4 to 5 times greater than for children with a BMI below the 85th percentile, and for children with a BMI over the 90th percentile, the effect on BP was more than 6-fold. These findings are significant because they show that elevated BP in children is directly correlated with the degree of adiposity, and the effect on BP escalates dramatically as the degree of adiposity increases. This study echoes the findings from an earlier study, which reported a greater than 4-fold increased risk of future elevated BP when childhood adiposity was above the 85th percentile. However, the more recent study found that elevated BP due to the adiposity effect is not just a future risk once adulthood is reached, but exists as a clear and present risk during childhood.

Hypertension, Metabolic Syndrome, and CVD

There is strong evidence that elevated BMI during adolescence, even within the normal BMI range, is associated with increased risk of developing hypertension and/or CVD as an adult. Elevated BMI in both adolescence and young adulthood is significantly and independently associated with the risk of developing CVD and is predictive for it; there is a 12% increase in risk of CVD for every 1-unit increase in adolescent BMI. Future risk of hypertension can be predicted independently by either BMI at age 17 or BP at age 17, and males have a 3- to 4-fold higher risk than females, while the risk of hypertension is higher for obese adults who were overweight or obese as children than for those who had normal weight as children. One study of children and adolescents found that 35.6% with elevated BP still had elevated BP 6 years later, nearly 20% of those who had been normotensive crossed into an elevated BP category during that time, and an increase in BMI was correlated with a change in BP classification from normotensive to a higher category. Unfortunately, adiposity as measured by BMI does not indicate the distribution of fat, that is, overall subcutaneous fat, centralized abdominal or visceral fat, or a combination of both. Visceral fat has different metabolic characteristics from subcutaneous fat, and those with centralized obesity are at greater risk of developing hypertension, insulin resistance (IR), dyslipidemia,
atherosclerosis or other CVD, and inflammatory responses.\textsuperscript{27,28} The World Health Organization defines centralized obesity as WC greater than the 75th percentile or a waist-to-height ratio greater than or equal to 50%.\textsuperscript{29} Although the 2007 Expert Committee recommended using BMI as a measure of adiposity in children, it did not recommend using WC as a predictor of CVD risk because no reference values were available for children.\textsuperscript{32} However, reference tables have been published for children of varying ethnicities and nationalities.\textsuperscript{53-56}

Recent research suggests that WC should be used along with BMI because it is a reliable measure of visceral adiposity in children and can therefore indicate associated conditions that may be otherwise overlooked. In children with normal BMI, larger WC has been found to be a predictor of increased risk for hypertension.\textsuperscript{28,57} An evaluation of the relationship between measures of fatness (BMI, fat mass, and WC) and stratification of BP (normotensive, prehypertensive, and hypertensive) in children found that when these measures were adjusted for height, only central adiposity and WC were positively associated with elevated BP.\textsuperscript{30}

In adults and children who are overweight or obese, WC as a measure of centralized obesity is highly correlated with increased risk for hypertension, CVD, and metabolic syndrome (MetS).\textsuperscript{27,57}

Metabolic syndrome is the name used to describe a combination of hypertension, abdominal obesity, dyslipidemia, glucose intolerance and/or IR, and proinflammatory or prothrombotic states.\textsuperscript{38} When 3 or more of these conditions occur together, a diagnosis of MetS is made.\textsuperscript{59} Another term for this constellation is metabolically obese. It is important to distinguish between metabolic obesity and physical obesity, because studies have consistently reported that MONW people are quite common.\textsuperscript{40,61}

A recent study of generalized, centralized, and combined adiposity distribution in children found that some overweight and obese children are metabolically normal and some children are MONW.\textsuperscript{57} This study reported that CVD risk factors such as MetS, dyslipidemia, and hypertension were highest in children with combined visceral and subcutaneous adiposity, lower in children with just centralized adiposity, and lowest in children with generalized subcutaneous adiposity. Children who were physically obese but metabolically normal were most often found to have generalized fat distribution but not centralized or visceral adiposity.

In tandem with obesity rates, the prevalence of MetS is rising among children and adolescents,\textsuperscript{55} but there is not always a one-for-one correlation between MetS and adiposity. MetS develops in some children who are of normal weight, while some overweight and obese children do not develop it.\textsuperscript{57,59} MetS is a risk factor for developing CVD and/or T2DM.\textsuperscript{59} Pediatric patients with T2DM may not have symptoms; risk factors include family history of diabetes, NHB, Hispanic, or NA heritage, and BMI at or above the 85th percentile.\textsuperscript{32} The distribution of adiposity is therefore a critical factor in the development (or not) of dyslipidemia, hypertension, and MetS.\textsuperscript{27,57}

In addition to the type of adiposity, ethnicity and gender are also factors that need to be considered when assessing risk of developing MetS with its associated cardiovascular effects. For example, when compared to NHW children, NHB and Hispanic children have a higher frequency of IR, and South Asian and Middle Eastern children have a higher prevalence of MetS.\textsuperscript{59} Studies have found that WC predicts and is significantly correlated with IR,\textsuperscript{62} hypertension, and dyslipidemia\textsuperscript{63} in children with excess abdominal fat, independent of race or BMI percentile. WC may be particularly relevant as a predictor of MetS in non-Hispanic Asian (NHA) children, since several studies have found this ethnicity to have higher visceral adiposity despite lower obesity.\textsuperscript{64-66}

A study in China found that 15.5% of normal weight boys and 18.8% of normal weight girls had MetS, while 63.1% of normal weight adolescents had at least one marker for CVD.\textsuperscript{67} Among normal weight, overweight, and obese children in this study, the prevalence of MetS was found to be 1.5%, 18.3%, and 38.1%, respectively.\textsuperscript{57} In contrast, a similar study of NHB, NHW, and MA children in the United States reported that the prevalence of MetS among normal weight, overweight, and obese subjects was just 0.1%, 6.8%, and 28.7%, respectively.\textsuperscript{68} It is therefore important for all children to be regularly screened for high BP, dyslipidemia, and altered glucose metabolism, regardless of their weight status.

In addition to serious long-term health consequences from delayed diagnosis and treatment of hypertension, obese adolescents often experience discriminatory behavior, leading to social and economic consequences later in life.\textsuperscript{69} Unfortunately, disadvantaged youth are most at risk for these consequences, partly due to socioeconomic factors, partly because of psychosocial stressors that are unique to this population, and partly from racial or ethnicity predispositions.

**Confounding Influences**

**Ethnicity/Racial/Socioeconomic Influences**

Retrospective analyses of several longitudinal studies\textsuperscript{48,69,70} found distinct racial and ethnic differences
among adolescents. NHB boys had lower obesity rates than Hispanic or NHW boys, but adolescent boys were generally more likely to be obese than girls, except among NHB, where obesity was more prevalent in girls. Hispanic adolescents had a greater probability of higher WC, and experienced increased obesity rates over time. Among Hispanic adolescents of both genders, obesity was highest among Puerto Ricans and MA, whereas Central and South American youth and Cuban American females had much lower obesity rates. Among NHA, Chinese and Filipinos had the lowest obesity rates, while Korean, Japanese, Southeast Asian, and Indian-American adolescents were most likely to be overweight. NHW had lower obesity rates than all other adolescent groups except Chinese and Filipino youth. The highest rates of adolescent obesity were found among NHB females, Hispanic males, and NHA who were neither Chinese nor Filipino, and among NA youth, who had significantly higher obesity rates than all other adolescent groups.69,70

First-generation NHA and Hispanics who were not born in the United States had lower obesity levels than children born to immigrant parents in the United States. Except for Chinese-Americans, both NHA and Hispanics experienced significant changes in obesity levels between the first and second generations. Second- and third-generation Hispanic youth were more likely to be obese than first-generation adolescents, while NHA girls were considerably less likely to be obese, although the obesity level for second-generation NHA youth more than doubled from first-generation adolescents.69 Hypertension rates were found to be lower in Central and South American first-generation, less acculturated Hispanic immigrants than in NHW and NHB, regardless of WC or body weight, and BP was lower in first-generation compared to second-generation MA.30

Racial heritage is clearly a factor in obesity-related disease outcomes; however, diseases classified by race should not be confounded with diseases classified by ethnicity. Ethnicity incorporates cultural aspects, such as diet, religion, and language, as well as genetics. Ethnic heritage is modified by socioeconomic conditions and lifestyle adaptations driven by the geographic region of the world where a person lives. Similar ethnic groups in different geographic locations may therefore have very different disease rates and risk factors.71 There may also be a physiological factor in how psychosocial stressors affect people of different races; those who have a vascular response (α-adrenergic) may eventually develop hypertension, while those who have a cardiac response (β-adrenergic) may be more affected by atherosclerosis.72

The leading cause of death in Hispanics is CVD (28% in males, 34% in females),73 but NHB and NHW have higher rates of death from cardiovascular events and higher rates of death from all causes than Hispanics. The tendency toward obesity and T2DM is similar in Hispanics and NHB, while obesity rates and IR are significantly different between NHW and Hispanics. NHB have higher risks for hypertension and certain obesity-related cancers and higher rates of prostate cancer, while Hispanics have higher risk of fatty liver disease and lower rates of some chronic illnesses, despite the fact that many experience lower SES.30

Lower childhood SES has been correlated with smaller decreases in nighttime BP, called nocturnal nondipping, both in adolescence and in adulthood and may contribute to risk of developing CVD or hypertension later in life.72,74 Studies have shown that in adolescents, BP nondipping is negatively associated with childhood SES but is not associated with BMI,72,74 and BP nondipping is more prevalent in NHB and low SES adults.72 Nocturnal nondipping has been associated with organ damage and is thought to be more frequent among those with posttraumatic stress disorder,74 and those with greater chronic stress or negative emotions,72,74 and often occurs before sustained hypertension develops.24 Some of the racial differences in nocturnal nondipping may be due to the greater psychosocial stressors that are concurrent with low SES, which disproportionately affects immigrant and minority populations.

Psychosocial and Mental Health Influences

Research has shown a relationship between childhood overweight/obesity and psychosocial stressors such as migration background, SES, parental discord or divorce, domestic violence, child abuse, and chronic physical or mental health conditions of family members.45,75 These factors have been found to be more predominant in low-income, immigrant, and minority youth, and to have a significant negative influence on the outcome of weight loss programs.45,75 In addition to psychosocial stressors, mental health issues significantly influence whether disadvantaged youth are overweight or obese, and whether they are successful at weight loss efforts. Depression in disadvantaged youth is highly correlated with increased likelihood of overweight or obesity.75 Compared to their normal weight peers, overweight and obese children experience greater depression, suicidal thoughts, feelings of worthlessness or hopelessness, anxiety, body dissatisfaction, and poor academic performance.76 Obese children are perceived as lazy, unhealthy, unhygienic, socially inept, and academically unsuccessful, and these stereotypes result in low self-esteem, sadness, loneliness, social isolation, and high-risk behaviors, all of which contribute to
significantly reduced quality of life. It is not clear which of these factors contribute to, and which are consequences of, obesity.

A 10-year study of adolescent girls, which evaluated the most important factors for predicting future changes in BMI and onset of overweight or obesity, found that income and race/ethnicity were two of the most important independent predictors for weight gain, onset of overweight, and BMI percentile change, with NHB and low SES adolescents being most affected. BMI percentile change was predicted by body dissatisfaction and drive for thinness, which includes excessive dietary restraint. These psychological traits have been associated with a greater increase in BMI, possibly due to extreme dieting or skipping meals followed by overeating or binge eating/bulimia.

In contrast, onset of overweight and obesity was predicted by the psychological traits of perfectionism, emotional eating, ineffectiveness, and interoceptive awareness, which is the ability to distinguish between hunger and satiety, to be aware of bodily sensations, and to identify and be aware of feelings. Feelings of worthlessness, inadequacy, insecurity, and lack of control over life are components of ineffectiveness. These psychological factors, taken together, comprise self-regulatory skills; if these are poorly developed, compensatory overeating may occur, especially if negative emotions are involved.

School-based programs using cognitive behavioral therapy have been found to be an effective means of addressing some of these mental health issues. In one study, participants not only lost weight but also reduced their degree of anxiety and/or depression and increased their commitment to make healthy lifestyle choices. Another behavioral weight control program for obese adolescents, which combined dietary modification, prescribed group physical activity, and intensive behavior modification therapy for the adolescents along with parental support therapy, resulted in significant weight loss and improvements in self-concept and self-confidence; a 2-year follow-up study with the original participants found that the improvement in self-efficacy from the initial intervention was sustained over a 24-month period.

In addition to the inherent and perhaps unfamiliar challenges of losing weight, adolescents are simultaneously navigating the new and complex factors of increasing peer pressure, more autonomy from parental influences, and physiological changes due to pubertal hormones. Pubertal stage is an important and often overlooked factor that is unique to adolescence, and it must be considered when evaluating adiposity and hypertension in adolescents.

**Gender and Pubertal Influences**

A well-designed study reported that BMI as a measure of adiposity is not independent from pubertal stage, race, gender, or waist/hip ratio, and that the same BMI percentile does not in any way indicate differences in percentage of body fat by distribution (peripheral vs central adiposity), between girls and boys (girls have more), or between races (NHW have more than NHB). This study found that pubertal stage is significantly more closely correlated than age with BMI; that adolescents who have reached puberty have a lower body fat percentage than prepubertal adolescents of the same BMI; and that those with central adiposity may have a lower BMI despite having a greater percentage of body fat than those with overall subcutaneous fat.

Research has also shown that the pubertal growth spurt occurs earlier for girls than for boys; that it is significantly associated with increases in SBP and DBP in both genders; that BP increases more rapidly during the growth spurt than before or after it; and that boys have a significantly greater increase in BP than girls. These studies used height as a proxy for timing the pubertal growth spurt and reported that the peak of increase in BP coincided with the peak in acceleration of height. The pubertal growth spurt lasted about 4.5 to 5 years, with onset approximately 3 years before the peak in height acceleration and BP was reached. During this growth spurt, SBP and DBP increased significantly, but SBP increased significantly more in boys than in girls, while DBP increased more in girls than in boys.

During pubertal growth, mean SBP was noticeably higher in boys than girls (107.2 vs 99.2 mm Hg), and of note, the mean age at which pubertal growth peaked in NHB youth was 6 to 11 months sooner than for NHW youth, suggesting that at all chronological ages, NHB adolescents may have higher BP than NHW adolescents. During the pubertal growth spurt in NHB youth, there was also a greater increase in SBP if one parent had hypertension than if both parents had normal BP. The gender difference in BP continues after puberty as well; in a study of 17 year olds, mean SBP was higher in boys than girls (117.9 vs 108.6 mm Hg), the prevalence of prehypertension was 36% for boys and 8.9% for girls, while the prevalence of hypertension was 2.2% for boys and 0.3% for girls.

In a large, prospective, multiyear study that assessed the presence or absence of masked hypertension at baseline, when compared with normotensive participants, children with masked hypertension had significantly higher ABP and conventional BP, and boys (but not girls) more frequently had a parental history of hypertension. There were significant differences during follow-up
between boys and girls with masked hypertension: both were more likely to develop sustained hypertension, but the rates were astonishingly different: 17.4% versus 0.8% of girls, and 50.0% versus 1.9% of boys, respectively, when compared to normotensive subjects. In addition, 23.1% of girls and 6.2% of boys maintained masked hypertension, while 56.5% of girls and 37.5% of boys reverted from masked hypertension to normal BP during the follow-up period. Male gender and baseline masked hypertension were found to be independent risk factors for developing sustained hypertension. Girls with undiagnosed masked hypertension may be at greater risk for developing sustained hypertension during pregnancy or while using OC.

Because estrogen is associated with increased epithelial sodium channel proteins, it may limit the effect of the pubertal growth spurt on BP in girls, while in males, testosterone may exacerbate the effect of the growth spurt: BP has been reduced in a hypertensive mouse model (SHR/y) by use of either androgen receptor blockers or castration. In addition to the pubertal model (SHR/y) by use of either androgen receptor blockers or castration,81 in addition to the pubertal growth spurt, there are other complex physiological and hormonal changes during puberty that should not be ignored or underestimated. Leptin is positively correlated with estrogen and negatively correlated with testosterone, and these factors account for the gender differences noted with changes in body composition and body fat percentages that occur during puberty.84 Early menarche occurs twice as frequently in girls with a BMI greater than the 85th percentile, and IR is common during early puberty,35 with insulin sensitivity being negatively correlated to body fatness, but unrelated to testosterone or estradiol.85

As with BP, there are also gender and racial differences in the prevalence of overweight/obesity and MetS. Based on the National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 data,86 which did not evaluate NHA youth, the estimated overall prevalence of MetS in adolescents was 8.6%, with NHW at 8.9%, but the prevalence in NHB was much lower at 4.0%, while Hispanics had the highest rate at 11.2%. The prevalence of MetS in Hispanic boys (12.9%) and NHW boys (11.8%) was significantly higher than in Hispanic girls (9.4%) and NHW girls (5.8%), while the prevalence in NHB boys (3.9%) was slightly lower than for NHB girls (4.2%).86

In their 2011-2012 report, the Centers for Disease Control and Prevention (CDC) found that the overall prevalence of overweight and obesity in adolescents was 34.5% with 14.0% classified as overweight and 20.5% classified as obese, but there were some significant differences by race and gender. The overall prevalence in NHA was the lowest at 24.6%, with 13.5% being overweight and 11.1% being obese, but when considered by gender, the prevalence in NHA girls was 15.0% (7.7% overweight, 7.3% obese) while the prevalence in NHA boys was 33.9% (19.1% overweight, 14.8% obese). NHW overall rates were 31.2% with 11.6% overweight and 19.6% obese, while the prevalence in NHW girls was 31.0% (10.1% overweight, 20.9% obese) and the prevalence in NHW boys was 31.5% (13.2% overweight, 18.3% obese).87

Hispanic overall rates were 38.1% with 15.5% overweight and 22.6% obese, while the prevalence in Hispanic girls was 36.5% (15.2% overweight, 21.3% obese) and the prevalence in Hispanic boys was 39.6% (15.7% overweight, 23.9% obese). NHB had the highest overall rates at 39.8% with 17.7% overweight and 21.1% obese, but the prevalence in NHB girls was 42.5% (19.8% overweight, 22.7% obese) while the prevalence in NHB boys was 37.3% (15.9% overweight, 21.4% obese).87 Consistent with other researchers,27,28,57,59 the CDC report cautioned that different sex, age, and race/ethnicity groups may have different amounts of body fat or different distributions of body fat at the same BMI, and therefore may have different risks for obesity-related diseases.

**Genetic and Metabolic Influences**

The most common indicator of metabolic changes related to obesity is IR, which can eventually result in development of T2DM and/or MetS, but blood sugar levels are often normal despite IR because higher amounts of insulin are secreted in response to impaired glucose metabolism.59,77 When IR is used as a screening criterion, significantly more children are diagnosed with MetS, and for this reason, homeostasis model assessment of insulin resistance (HOMA-IR) is recommended as a better test for MetS in adolescents, instead of fasting glucose levels.59 Markers of IR include insulin sensitivity, elevated proinsulin and fasting insulin levels, impaired fasting glucose, and impaired glucose tolerance.62 Vitamin D enhances insulin sensitivity,88 and a meta-analysis of 8 longitudinal studies reported that the incidence of diabetes was 43% higher in those with serum vitamin D concentrations below 35 nmol/L when compared to those with concentrations greater than 62.5 nmol/L.89

The bioavailable circulating form of vitamin D is serum 25-hydroxyvitamin D [25(OH)D], which is hydroxylated in the liver. It is converted to the active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], by additional hydroxylation in the kidney, macrophages, and other cells in the body and plays a major role in calcium homeostasis and negative regulation of the
There is an inverse relationship between vitamin D and RAAS activity, parathyroid hormone levels, coronary artery calcification, left ventricular hypertrophy (LVH), endothelial dysfunction, hypertension, lipid dysregulation, platelet aggregation, stroke, and other CVD. There is an inverse relationship between serum 25(OH)D concentration and obesity, possibly due to increased storage of vitamin D in adipose tissue.

Risk factors for low serum 25(OH)D concentration include obesity, dark skin, old age, indoor living, lack of exposure to sunlight, living at extreme north or south latitudes, genetic variations in metabolic pathways, and vitamin D receptor polymorphisms. Vitamin D receptors are located on pancreatic β-cells, adipocytes, and inflammatory cells; there is a negative correlation of serum 25(OH)D concentration with β-cell dysfunction and IR, and a positive correlation with fatty acid metabolism and insulin sensitivity. In addition, there is an inverse association between serum 25(OH)D concentration and obesity, possibly due to increased storage of vitamin D in adipose tissue.

A 2008 study found that NHW have less IR than Hispanics and NHB, who have similar rates of IR, and that both Hispanics and NHB respond to IR by increasing secretion of insulin from pancreatic β-cells, but NHB also reduce insulin clearance through the liver, resulting in hyperinsulinemia. NHB are more likely than Hispanics to experience insulin-related cancers and much higher obesity-related hyperinsulinemia and insulin-like growth factor 1 (IGF-1) concentrations, while Hispanics are more likely than NHB to experience non-alcoholic fatty liver disease and T2DM resulting from β-cell failure. This study also found that NHB and Hispanics respond differently to increasing obesity, with IGF-1 concentrations increasing in NHB and decreasing in Hispanics. IGF-1 influences adipocyte proliferation and, with increasing adiposity, may result in an increased number of adipocyte cells in NHB, but an increased size of adipocyte cells in Hispanics. Larger adipocytes are more susceptible to cell death, resulting in lipid deposits in insulin-sensitive tissues such as the liver and are associated with increased IR and development of T2DM.

Other studies have found that NHA have a greater susceptibility to MetS and T2DM than NHW, independent of adiposity, and that in obese Hispanic adolescents, when compared to those without fatty liver, those with elevated liver fat had less insulin sensitivity, elevated HOMA-IR, more acute insulin response to glucose, and significantly higher concentrations of certain inflammatory markers. Another study suggested that central adiposity among Hispanic youth may have less effect on BP than genetic polymorphisms, decreased vascular resistance, and higher renal sodium excretion rates.

Clearly, genetic and racial heritage is associated with predispositions to IR, MetS, obesity, and hypertension, and it may be the key to more effective treatment strategies. Twin studies have shown that body weight and adiposity have a genetic basis, and molecular genetics and neurochemistry have revealed the genetic mechanisms behind neurotransmitters and hormones (such as melanocort, adiponectin, leptin, ghrelin, growth hormone, and neuropeptide Y) that influence appetite, satiety, hunger, lipogenesis, lipolysis, and fat distribution, but much work remains to fully understand these factors.

Research on genetic polymorphisms has found that they can be fairly straightforward or have complex effects. Variations in serum triglyceride and fibrinogen have been associated with polymorphisms in the lipoprotein lipase gene and the fibrinogen gene, respectively. A more complex but fairly common insertion/deletion (I/D) polymorphism that has been widely studied in adults is the angiotensin I-converting enzyme (ACE) gene, which is an important regulatory agent in RAAS. One study found that low, intermediate, and high concentrations of circulating ACE were associated with II, ID, and DD genotypes, respectively, and explained 47% of the variance in circulating ACE, but perhaps the most important finding was that the alleles had an additive effect, suggesting that they were codominant. This polymorphism has been associated with arterial hypertension, obesity, coronary artery disease, and diabetic nephropathy in adults.

A genetic polymorphism may explain the higher rate of masked hypertension in boys with a parental history of hypertension. A recent study of the ACE I/D polymorphism in obese youth reported a significant and independent D-allele effect in boys but not in girls between the ACE I/D polymorphism, arterial hypertension, and obesity-related traits, and these associations were not affected by other factors such as insulin.
secretion, insulin sensitivity, or glucose tolerance. The presence of the D-allele in boys was found to be positively associated with higher BP, body weight, body fat mass, BMI, and WC, and had independent and additive effects with IR and body fat mass.94

The X-linked angiotensin converting enzyme-2 gene, which is highly expressed in renal and cardiac tissue, is thought to negatively regulate RAAS by increasing the concentrations of Angiotensin-(1-7), a vasodilator that modulates BP.96 A single nucleotide polymorphism in this gene was the focus of a longitudinal study in adolescents that reported statistically significant differences by gender and ethnicity, with males and those of European ancestry being most affected, but with different effects on SBP and DBP depending on the single nucleotide polymorphism and gender.97 These gender-specific differences in adolescents are significant because research has shown that testosterone stimulates RAAS activity, while estrogens have the opposite effect.94

On RAAS activation, vasoconstriction occurs, blood flow to the kidneys is reduced, sodium and water are retained, and BP rises. RAAS activity is stimulated by the sympathetic nervous system (SNS), which is thought to be stimulated by high concentrations of insulin and leptin, which are strongly associated with obesity.77 However, a study in Pima Indians,98 who have a low prevalence of hypertension despite high rates of obesity and hyperinsulinemia, suggests that there are ethnic differences in SNS stimulation and effects of obesity that need to be further explored. Hyperinsulinemia may be one mechanism that results in greater SNS activity leading to increased BP, but ethnic differences in β-adrenergic sensitivity, the effect of insulin on sodium excretion by the kidneys, and obesity-related changes that affect structure and function in the cardiovascular and renal systems may be other mechanisms that have effects on BP without SNS stimulation.98

Several studies have shown that BP is higher during winter months, and this may be due to seasonal variations in serum 25(OH)D concentration, which is a negative regulator of RAAS.99,101 Another mechanism may be hyperuricemia, which is strongly correlated with hypertension and appears to have both short-term and long-term effects on it: hyperuricemia initially activates RAAS and reduces endothelial nitric oxide synthesis, resulting in (uric acid-dependent and reversible) vasoconstriction and elevated BP, and then plays a central role in renal afferent arteriolosclerosis, resulting in decreased renal blood flow and glomerular filtration rate, increased secretion of renin, and a (uric acid-independent and irreversible) shift in urinary excretion of sodium and sodium-sensitive hypertension.102

Hypertension and MetS have been correlated with serum uric acid concentrations in adolescents and are predictive of cardiovascular events in adults, even when concentrations are within the normal range.103 Studies of hyperuricemia in children have reported that a serum uric acid concentration of at least 5.5 mg/dL had a specificity of 86%, a sensitivity of 87%, and an 82% positive predictive value for primary hypertension4 and that those with concentrations of at least 5.5 mg/dL were twice as likely to have elevated BP than those with concentrations below 5.5 mg/dL.104 Another study in adolescents reported hyperuricemia (greater than 8.0 mg/dL) in 9.5% of normotensives, 43% of prehypertensives, and 73% of those who had moderate or severe hypertension.105 The obese have a 3-fold higher risk of elevated serum uric acid, but hyperuricemia can also result from genetic polymorphisms in anion transporter genes, small bowel disease, kidney disease, or excessive consumption of seafood, fatty meats, alcohol, and high-fructose corn syrup, as well as medications and diuretics that affect uric acid clearance by the kidneys.102

In a multi-ethnic study, mean serum uric acid concentrations were significantly elevated in children with primary (6.7 ± 1.3 mg/dL) and secondary (4.3 ± 1.4 mg/dL) hypertension when compared to children with white coat hypertension (3.6 ± 0.7 mg/dL).4 Hemoglobin was significantly higher in children with primary hypertension (14.6 ± 1.3 g/dL) when compared to children with secondary (12.8 ± 1.6 g/dL) or white coat (12.5 ± 1.2 g/dL) hypertension, and when serum uric acid concentrations exceeded 6 mg/dL, average hemoglobin levels were 15.4 ± 1.4 g/dL.102 These results suggest that hemoglobin and uric acid, if used in conjunction with OBP and ABP, may be useful markers for improving diagnosis of primary hypertension.

In addition to its role in BP homeostasis, RAAS also plays a role in weight regulation that is not fully understood, but it is known that RAAS acts in adipocytes, that RAAS activity is positively correlated with body weight and body fat mass, and that reduced RAAS activity is associated with weight loss.94 Adipocytes are the primary producers of reactive oxidative species (ROS), which are associated with increased inflammatory markers such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor, and adipokines.106 In addition to ROS, adipocytes secrete proteins such as leptin, adiponectin, resistin, and retinol binding protein-4, which play important roles in metabolism; some may also be markers for MetS.59

Obesity results in higher production of ROS and increases oxidative stress, which has been associated with increased risk of IR, T2DM, endothelial dysfunction, atherosclerosis and other CVD, as well as reduced antioxidant protection, increased lipid peroxidation, fatty liver, hypertension, hyperglycemia, and chronic
low-level inflammation. Obesity affects the distribution of zinc in the body, resulting in low circulating zinc, which may disrupt membrane signaling involved in hormone regulation and contribute to IR.

Obesity is also associated with reduced adiponectin; adiponectin protects against T2DM by increasing insulin sensitivity and glucose metabolism, and is an anti-inflammatory agent that protects endothelial function and prevents atherogenesis. The association between obesity and leptin is noteworthy: one study found significantly higher leptin in overweight and obese children than in normal weight children (19.70 ng/mL vs 5.85 ng/mL, respectively), and leptin concentrations were strongly correlated with increased heart rate as well as SBP and DBP percentiles. Another study reported that hyperleptinemia has been demonstrated to cause sustained increases in BP.

Just as there is a significant effect of adiposity on BP, which may be mediated by leptin, obesity may also affect renin and aldosterone concentrations, but there are some differences associated with racial heritage. A prospective study of NHB and NHW children and adolescents analyzed the effect of obesity on plasma aldosterone concentration (PAC), plasma renin activity (PRA), and aldosterone-renin ratio (ARR), known as the renin-aldosterone axis. This study found that ARR was slightly lower and PRA and PAC were statistically significantly lower in NHB than in NHW when smoothed for age and BMI. In addition, at all ages, PAC increased with BMI in NHW and PRA decreased with BMI in NHB, while both PAC and PRA were lower on average in NHB than in NHW. However, SBP was higher in NHB with lower PRA, higher PAC, and higher ARR; lower PRA has been associated with greater extracellular fluid volume, which may explain the higher SBP found in the NHB participants.

The effect of obesity on the renin-aldosterone axis may explain the results of a study of NHB adults, which reported that both SBP and DBP were significantly correlated with serum cholesterol and anthropometric measures such as BMI, WC, waist/hip ratio, and percent body fat in normotensive subjects, but in untreated hypertensive subjects, no significant correlations were found with either serum cholesterol or anthropometric measures. Conversely, WC was found to be predictive of SBP in untreated hypertensives, but not in those with normal BP. If obese NHB have greater fluid volume due to greater sodium reabsorption in the kidneys, this could increase BP sensitivity to adiposity. Salt sensitivity is known to be associated with low PRA and has also been associated with lower hemoglobin and even slower breathing rates.

The normal mechanism for BP control is a feedback loop called pressure natriuresis, wherein increased renal perfusion pressure results in increased sodium and fluid excretion, followed by lowered BP. The set-point for BP regulation through this mechanism is sodium balance, where sodium intake and sodium output are equal. Research has shown that hypertension may be the result of a permanent shift in renal pressure natriuresis that initiates and then sustains chronic hypertension, driven by maintenance of sodium balance, and that excess weight gain may contribute to the impairment of pressure natriuresis through increased compression of the kidneys by the excess adipose tissue. Sodium balance is not the only mechanism that regulates BP, however; serum calcium also influences hypertension, possibly through its role in vascular smooth muscle contractility, and possibly through signaling pathways for secretion and action of hormones that regulate and control BP and homeostasis.

Salt-sensitive hypertensive patients with low renin concentrations have lower serum ionized calcium concentrations and higher 1,25(OH)2D concentrations; these patients appear to have a “calcium deficiency” calcium-metabolic profile. The opposite is found in salt-insensitive hypertensives: they have high renin concentrations, higher serum ionized calcium concentrations, and lower 1,25(OH)2D concentrations, with an apparent “calcium excess” calcium-metabolic profile. These 2 distinct calcium-metabolic profiles, low renin/low serum ionized calcium and high renin/high serum ionized calcium, have different RAAS effects, may result from different calcium-regulating hormone concentrations, and have increased and blunted responses, respectively, to dietary sodium and calcium intake.

Serum calcium has been positively correlated with BP in adults, independent of race/ethnicity, age, gender, BMI, or serum 25(OH)D concentration. Calcium is required for proper β-cell function and insulin secretion and plays an important role in insulin receptor sensitivity and glucose uptake by cells. A study in adolescents reported that those with serum calcium in the highest quartile (at least 2.53 mmol/L) had twice the prevalence of hypertension as those in the lowest quartile (no more than 2.37 mmol/L). Another study found that those with serum calcium in the highest tertile had greater fasting glucose and greater insulin resistance than those in the lowest tertile.

There is also an inverse relationship between circulating 1,25(OH)2D and serum calcium concentrations and a significant and inverse relationship between dietary calcium intake and body fat. Higher concentrations of 1,25(OH)2D have been found to significantly stimulate calcium uptake in adipocytes; calcium influx inhibits lipolysis and stimulates lipogenesis and fatty acid synthase expression and activity.
Conversely, increased dietary calcium suppresses serum 1,25(OH)$_2$D concentrations, resulting in less lipogenesis and greater weight loss, even without calorie restriction. NHB have the lowest dietary calcium intake and the highest prevalence of obesity; a study evaluating calcium as an antihypertensive in obese NHB noted that increased dietary calcium intake resulted in reduction in body fat.

Dietary Influences

In humans, dietary calcium from dairy sources is 50% to 100% more effective for weight and fat loss when compared to calcium carbonate supplements or calcium-fortified cereal. Studies in mice showed that those fed a low-calcium diet had reduced lipolysis, increased lipogenesis, and significant increases in body weight and fat mass, but when placed on a high-calcium diet, had a 3- to 5-fold increase in lipolysis, 51% reduction of lipogenesis, and 26% to 39% reduction in body weight and fat mass, with greater effects derived from dairy sources.

There are few vitamin D supplementation studies in obese adolescents. One study reported that, at 2,000 international units (IU) per day of vitamin D$_3$ intake over 3 months, only 59% of obese youth achieved an increase in serum 25(OH)D concentrations when compared to nonobese youth, with serum 25(OH)D concentrations reaching adequate levels in 89% of nonobese youth but in only 50% of obese youth. Another study found that 4000 IU per day of vitamin D$_3$ supplementation over 6 months resulted in significant improvements in insulin resistance and insulin sensitivity, similar to metformin results, and independent of body weight. This study reported that leptin was reduced by 15.6% and adiponectin was increased by 3.6% in the group receiving vitamin D$_3$ supplementation; leptin regulates insulin secretion and increases glucose uptake, and adiponectin increases insulin sensitivity, but these results were only seen after 6 months of supplementation. These results suggest that long-term vitamin D$_3$ supplementation may be of significant benefit for obese youth, but both studies concluded that obese youth require greater amounts of vitamin D$_3$ supplementation than nonobese youth, due to sequestration of vitamin D in adipocytes.

Vitamin D supplementation has been shown to improve hypertension, although the reductions were small, but dietary calcium was found to be negatively correlated with hypertension, and dairy sources of calcium were twice as effective and more consistently effective on BP than nondairy supplements. Those who are low renin/salt-sensitive have a greater response to calcium intake than those who are high renin/salt-insensitive, and higher dietary salt intake may actually lower BP more for salt-sensitive hypertensives taking calcium channel blockers. Salt-sensitivity has been associated with low birth weight, physical activity, genetic factors, renal disease, obesity, and NHB racial heritage, but the effect of salt on BP varies between individuals, with about half of hypertensives, but only 25% to 33% of normotensives, being salt-sensitive.

A review of NHANES 2003 to 2008 data reported that salt intake in children aged 8 to 18 averaged 8.5 grams per day (3.4 grams of sodium per day), and even though sodium intake was significantly lower in overweight or obese adolescents, it had a much greater effect than in normal weight youth. An increase of just 1 gram of sodium intake per day profoundly increased the risk of prehypertension and hypertension in overweight/obese youth compared to normal weight youth (74% vs 6%, respectively). A review of NHANES 1988 to 2008 data reported a 36% increase in risk of elevated BP for children with sodium intake exceeding 3450 mg compared to intake of less than 2300 mg, after adjustment for age, gender, race, BMI, and WC, and that BMI, WC, and sodium intake were independently associated with prevalence of higher BP. In the United States, more than 65% of sodium consumption is due to sodium enrichment of prepared foods such as cheese, breads, and cereals, whereas in developing countries, sodium intake is primarily from addition to food during cooking or at table, for example, from soy sauce.

Soft drinks are an additional source of dietary sodium, as well as caffeine and sugar; sugar-sweetened (regular) sodas are a major source of dietary added sugars, primarily from high-fructose corn syrup, and are strongly correlated with the development of excess weight in children and adolescents. However, the United States?

Department of Agriculture estimates that only one third of sugar consumption comes from soft drinks, with the remainder from fruit drinks, candies, bakery products, and dairy desserts. A cross-sectional analysis of NHANES 2003 to 2006 food questionnaire data reported that the average adult fructose consumption was 74 g/day (the amount contained in 2.5 regular soft drinks), with 50% of the study cohort consuming at or above 74 g/day. This study found that intake at or above 74 g/day was associated with increased risk of elevated SBP, with a 36% greater risk for those with SBP between 140 and 159 mm Hg, and more than double the risk for those with SBP of at least 160 mm Hg, independent of kilocalorie intake, sodium intake, or weight.

In a large ethnically diverse study of children and adolescents, regular soda consumption more than doubled between the ages of 13 and 18, from 30% to 62% in...
girls and 73% in boys.120 In one study, chronically increased consumption of high-fructose corn syrup resulted in chronically high serum uric acid and consistently elevated BP,102 but another study found a strong correlation between fructose intake and higher SBP, independent of serum uric acid concentrations.121 The effect on SBP may be due to decreased excretion of urinary sodium and/or increased sodium intake,103 and fructose research in animals indicates that there may be several mechanisms involved in elevation of BP, including increased absorption of sodium in the intestine, stimulation of the SNS and/or uric acid production, or inhibition of endothelial nitric oxide production.121

Even small amounts of fructose when regularly consumed can have a significant impact; daily intake of just 12 ounces of regular soda or other sugar-sweetened beverages (SSB) increases the risk of obesity by 60% and is associated with regular consumption of other unhealthy foods.120 and those with a higher SSB intake also have an increased likelihood of smoking and drinking alcohol.103 An analysis of NHANES data from 1999 to 2004 found that 82.5% of adolescents consumed SSB daily, with over 45% consuming more than 24 ounces, and over 27% consuming more than 36 ounces per day.103 Consumption of SSB was positively correlated with total kilocalorie, sodium, and caffeine consumption; negatively correlated with consumption of milk and diet beverages; and higher in adolescents who were older and male.103

**Other Controllable Influences**

While the effects of dietary factors like sugar, sodium, and caffeine intake may seem fairly obvious, there are other less obvious influences on health during adolescence. A large study of 17 year olds reported a significant positive association between SSB, male gender, alcohol consumption, and OC use in girls, independent of BMI or dietary patterns.83 In this study, a significant positive correlation was found between higher SBP and alcohol consumption in boys but not girls, with a stronger association found in heavy or binge drinkers; girls using OC had both higher SBP and DBP than girls not using OC; and increasing BMI had a significantly greater effect on SSB in boys than in girls.83

Another less-than-obvious but important influence is sleep quality and duration. Sleep duration refers to the difference between bedtime and wake-up time,122 and sleep quality refers to sleep efficiency or the percentage of time in bed spent asleep.123 Sleep duration studies in adolescents have reported that elevated BP was significantly associated with alcohol consumption in younger adolescents,122 and that shorter sleepers were more likely to experience nocturnal nondipping, higher 24-hour ABP, and a higher BP classification.125 A longitudinal study of sleep duration and BMI found a strong association between shorter sleep and higher BMI in boys but not in girls, with the greatest effect of short sleep found in younger adolescents.124

Short sleep duration is thought to lower leptin concentrations and increase appetite; when combined with testosterone’s stimulatory effect on body mass, it is perhaps not surprising that there is a greater effect on BMI in boys, whereas the increased leptin concentrations in adolescent girls protects from the leptin-reducing effects of sleep deprivation, and there is less impact on BMI.84,124 In a study focused on adolescent sleep duration and macronutrient intake, weeknight sleep duration ranged from 4.3 to 11.0 hours, with the average being 7.55 hours.125 This study found that only about one third of adolescents achieved the recommended amount of sleep, which is 9 hours per night, and that shorter sleep duration was associated with increased snacking and greater appetite for high-fat, high-carbohydrate foods, resulting in an increase in caloric intake of nearly 500 kilocalories per day.125

Another adolescent study found that weeknight sleep duration averaged 7.71 hours, that both short sleep duration and low sleep efficiency were twice as common in prehypertensives when compared with normotensives, and that those with sleep efficiency of 85% or less were 3.5 times more likely to have prehypertension or hypertension, independent of gender or adiposity and after adjustment for sleep duration.126 In both adults and adolescents, shorter sleep duration has been associated with impaired glucose tolerance, metabolic and endocrine dysfunction, and increased risk of obesity.126 In adult studies, SDB and sleep apnea affected BP via SNS activation, while short sleep duration resulted in elevated BP, increased SNS activity, and reduced insulin sensitivity, and was associated with renal impairment and increased risk of CVD.127

A recent large study in adolescents found that they also face increased cardiovascular risk from inadequate sleep; however, poor sleep quality seemed to have a greater effect than short sleep duration.128 Short sleep duration was associated with greater consumption of caffeinated drinks and sodas, increased screen time, and less physical activity, while poor sleep quality was associated with these factors plus increased consumption of fried foods, sweets, and other high-energy foods and snacks. This study concluded that poor sleep quality was associated with increased cardiovascular risk (defined as BMI exceeding the 85th percentile, higher cholesterol, and/or elevated BP), but that short sleep duration was not.
A more obvious influence on adolescent health is exercise. Gender differences in adolescent exercise rates were found in a review of studies based on the nationally representative Youth Risk Behavior Surveillance (YRBS) surveys from 1991 through 2007, which reported that only 43.7% of boys and 25.6% of girls achieved recommended amounts of physical activity (PA). The national average of youth who achieved the recommended amount of PA was 34.7%, but there were racial/ethnic differences as well, with 37.0% of NHW, 31.1% of NHB, 30.2% of Hispanics, and 32.4% of Others achieving this amount of PA.129

Recommended PA is defined in the YRBS surveys as any activity that increases the heart rate and makes the participant breathe hard for at least 60 minutes per day on at least 5 of the previous 7 days; sufficient vigorous PA is defined as activity that increases the heart rate and makes the participant breathe hard for at least 20 minutes on at least 3 of the previous 7 days; and sufficient moderate PA is defined as activity that does not increase the heart rate or make the participant breathe hard for at least 30 minutes per day on at least 5 of the previous 7 days.129 The minimum daily exercise recommended for children by the Institute of Medicine is at least 60 minutes to maintain healthy weight and 90 minutes for weight loss, while an analysis of PA intervention studies done in children recommended moderate intensity aerobic PA (defined as 70% to 80% of maximal fitness) for at least 40 minutes on at least 5 days each week to lower BP and improve vascular function in obese children.130

The analysis of YRBS data found that sufficient vigorous or moderate PA was basically unchanged (from 65.8% to 64.1%, and from 26.7% to 26.5%, respectively), daily physical education (PE) attendance and PE exercise duration increased significantly (from 25.4% to 30.3%, and from 69.7% to 84.0%, respectively), while television viewing of at least 3 hours per day decreased significantly (from 42.8% to 35.4%).129 Although PA decreased and sedentary behaviors increased with age in adolescents, inactivity was greatest in older girls and minorities.129 Importantly, this study concluded that although recommended PA amounts were not achieved, activity levels among United States youth did not change sufficiently to support the common belief that the recent increase in obesity in United States adolescents is due to increased sedentary behaviors and reduced PA.129

Exercise programs for overweight or obese adolescents have reported that even modest reductions in weight resulted in statistically significant improvements in BP, dyslipidemia, and IR.29,130 Similarly, in adults, regular PA and cardiorespiratory fitness (fitness) have been associated with reduced risk of obesity, hypertension, and other chronic diseases,130,131 and even a weight loss of 5% to 10% from baseline has been found to be effective in lowering BP, independent of sodium intake.131 Several studies in adults investigated the possible mechanisms involved in the reduction of BP concurrent with weight loss, such as lower blood volume and/or cardiac output, suppression of the SNS, reduced RAAS activation, and less IR, and found that lower norepinephrine and PRA and improved insulin sensitivity were predictors for lower BP after weight loss.131

A review of the published research on PA and high BP in children reported lower SNS activation in normotensive obese individuals when compared to obese individuals with high BP, greater IR in normal weight hypertensives as well as obese hypertensives when compared with normotensive BMI-matched peers, and reduced serum norepinephrine concentrations following weight loss.130 Transgenic research has revealed that hyperinsulinemia and regulation of MAP can be uncoupled, indicating they may share similar pathways that are affected by weight gain, and perhaps explaining why they so often appear together and respond in a similar manner to weight gain or loss.130 Surprisingly, studies of high BP in overweight children found that the mechanisms were greater resting cardiac output and increased stroke volume, rather than higher systemic vascular resistance, and the reduction in SBP was correlated with slower heart rate in response to increased PA.130

Improved fitness should be one of the desired outcomes of any PA intervention focused on weight loss, but improved fitness and the associated health benefits are possible whether significant weight loss occurs or not. A recent large study found that improvements in fitness (as measured by estimated oxygen consumption) significantly reduced MAP in overweight and obese children, and there was a greater reduction in MAP in obese/fit than in overweight/fit youth.132 This is a significant finding, because although MAP was elevated in only 15% of the study participants overall, 36% of obese/ unfit participants had elevated MAP, and while only 23% of the total study participants were found to be unfit, just 16% of normal weight participants were unfit, whereas the prevalence was much higher in the overweight and obese participants, with 35% and 63%, respectively, being classified as unfit. When compared to normal weight/fit peers, the risk of elevated MAP was higher for boys than girls, but greater fitness significantly improved this risk for both genders: in males, the risk decreased from 4.28 in obese/unfit to 1.93 in obese/fit, and in females, the risk was reduced from 3.39 in obese/unfit to 1.64 in obese/fit.132

A recent study found that youth with a higher SES, nonminorities, and those with a lower weight status were more physically active than youth who were
low-income, ethnic minorities, or those with a higher weight status; however, higher weight status had an inverse influence on PA levels, regardless of other factors such as motivation or emotional support. This study reported that an increase in motivation correlated with an increase in PA in those who were normal weight, and therefore could be an effective obesity prevention strategy, but in those who were already overweight or obese, increased motivation actually resulted in decreased PA.

Two extensive literature reviews of PA interventions in adolescents found that a variety of exercise types, duration, intensity, and frequency were used, some in combination with diet and/or lifestyle changes, and the results were understandably inconsistent at best and left many unanswered questions. Results of intervention studies suggest that increased PA is associated with lowered BP and improved fitness, but unfortunately, physiological improvements achieved during the studies returned to baseline within a few months after the studies concluded. This is consistent with a meta-analysis of 64 obesity prevention programs for adolescents, which found that while 13 (21%) were successful from pretest to posttest, similar to prevention programs for which found that while 13 (21%) were successful from pretest to posttest, similar to prevention programs for

Outcomes

Changing maladaptive health behaviors is inherently difficult, and increasing PA in overweight and obese adolescents has proven to be challenging, so it is unrealistic to expect that these adolescents can successfully manage weight loss without significant support. This is underscored by the fact that between 1999 and 2008 the prevalence of youth with extreme obesity increased, while the prevalence of overweight and obese youth remained virtually unchanged. The epidemic of excess adiposity and the prevalence of undiagnosed and untreated hypertension among children and adolescents are creating a public health crisis with lifelong consequences for the children and staggering healthcare and socioeconomic costs.

Improving Diagnosis and Treatment}

The High Cost of Hypertension and Obesity

There is growing public awareness of the health consequences of excess weight, such as the probability of developing hypertension, CVD, T2DM, MetS, or chronic kidney disease (CKD) in the future, but this knowledge has not led to substantial weight loss in children or adolescents. Although about half of hypertensive adolescents are also obese, childhood hypertension occurs even without excess adiposity, and is frequently undiagnosed and untreated. Perhaps because the small and seemingly inconsequential changes in blood lipids, BP, glucose metabolism, and blood sugar concentrations, and less obvious physiological changes such as arterial stiffness, inflammation, atherosclerosis, and endothelial dysfunction, occur so gradually, these early warning signs are easy to ignore or miss altogether in overweight and moderately obese children, and are rarely checked for in MONW children. By the time these changes are significant enough to cause concern, measureable and permanent organ damage has often occurred, including increased heart mass, LVH, increased thickness of the carotid artery wall, narrowing of the arteries in the kidneys and retina, and impaired vascular functionality due to calcification, atherosclerosis, and arterial stiffening. LVH is the most common type of organ damage associated with hypertension, with 50% of hypertensive children having enlargement that exceeds the 90th percentile, and 14% having enlargement that exceeds the 99th percentile. The severity of obesity and hypertension is directly correlated with the degree of increased heart mass and LVH, which predict future development of congestive heart failure. Nonalcoholic fatty liver disease is also common, occurring in up to 77% of children aged 2 to 19, with greater prevalence by age and obesity status.

Impaired vascular functionality may include impaired cerebrovascular reactivity, with associated neurocognitive implications. Studies of hypertensive adults have found decreased neurocognitive performance and evidence of possible heritability of cognitive defects in normotensive adult children of hypertensive parents, and recent studies of hypertensive children have found neurocognitive and behavioral impairments when compared to normotensive controls, with hypertensive children having a 4-fold greater likelihood of being diagnosed with a learning disability or attention deficit-hyperactivity disorder. It is not yet clear whether hypertension and associated cerebrovascular remodeling result in cognitive impairment, or whether structural changes in the brain underlie both increased BP and decreased cognitive performance. Cognitive impairment and structural changes in the brain were also seen in obese adolescents with MetS but without T2DM: of the 5 markers used to classify a child with MetS, only IR was significantly correlated with smaller hippocampal size and larger volume of cerebrospinal fluid, independent of age, gender, and degree of
obesity. Although still within normal parameters, those with MetS scored significantly lower on spelling, arithmetic, attention, and mental flexibility assessments and had lower estimated IQ, and as the number of MetS markers present increased, greater impairment in cognitive performance was seen; similar but more pronounced cognitive impairments and reduced hippocampal volume have been seen in obese adolescents and adults with T2DM. These findings provide preliminary evidence that obesity and/or hypertension are sufficient to impair neurocognitive function, that metabolic dysregulation affects brain structure, and that these effects are present much earlier in the progression of these diseases than had been thought. Given the high degree of tracking from adolescence into adulthood for obesity, hypertension, CVD, T2DM, and MetS, and the health consequences and socioeconomic impact of these conditions, these neurocognitive findings should be of great concern. It is not known whether improvement in MetS parameters, hypertensive status, or degree of obesity will reverse these changes, and it is difficult to measure the impact of these impairments on future academic and professional progress, earning potential, and quality of life.

Youth with extreme obesity face additional medical consequences as well, including gallstones, which may require surgical removal; polycystic ovary syndrome, which increases risk of infertility and MetS; cirrhosis of the liver, requiring liver transplant; slipped capital femoral epiphysis, requiring surgery to repair the fracture; pseudotumor cerebri, which can lead to permanent loss of vision if intracranial pressure is not relieved; severe degenerative joint disease, which can severely restrict movement; premature heart disease; and premature death. Not surprisingly, body mass alone can impair mobility and prevent the extremely obese from independently performing activities of daily living or engaging in exercise.

The foregoing physical and medical consequences of adolescent hypertension and obesity are serious. Equally serious but perhaps less well-recognized are the psychosocial consequences, which include anxiety, depression, eating disorders, psychiatric disorders, high-risk behaviors, impaired psychosocial functioning, and reduced quality of life. Those with extreme obesity also experience these consequences, but the severity and prevalence are greater; for example, clinically significant depression was reported in 30% and clinical binge-eating was reported in 67% of extremely obese adolescents who sought treatment. In addition, severely obese adolescents face social isolation and high levels of unemployment due to functional impairment and stigmatization, and very few seek medical treatment for their obesity.

**Interventions**

The single most effective way to prevent or reduce hypertension in adolescents is to measure height, weight, BP, and WC, and calculate BMI %, for every child, every year, in every school grade, so that early signs can be followed up and corrective measures can be taken before organ damage occurs. As the literature has shown, conventional practices are not all-inclusive; many health care screenings do not include BP measurements for children, and BMI is rarely calculated or used unless the child is already obese. These simple screening measurements could be incorporated into existing school or community programs, and should include children who have little or no access to regular health care, such as low-income, immigrant, and minority youth, who are most at risk for and most affected by hypertension and obesity. Early intervention and preventive measures would reduce the number of children and adolescents who reach adulthood before they are diagnosed with hypertension.

Prevention is also the best strategy for reducing the incidence of overweight and obesity, and exercise for personal fitness should be emphasized in physical education programs. Obese children should be evaluated for hypertension before beginning any exercise regimen. Interventions focused on preventing or minimizing further weight gain are needed, which combine the expertise of professionals in the fields of exercise physiology, physical therapy, behavioral health, and nutrition as appropriate. Nutritional counseling to achieve weight loss is an important part of managing hypertension and obesity and should include family.

Dietary interventions need to emphasize reduced intake of SSB, fruit-flavored drinks, and other foods containing high-fructose corn syrup, promote increased consumption of low-fat milk or 100% fruit juice, and provide calcium-rich alternatives for lactose-intolerant children. The sale of energy-dense, nutrient-poor drinks and snacks through school-based stores, vending machines, and snack bars should be reduced or eliminated. Intervention strategies should focus on replacing unhealthy selections with better-quality options in the home, school, and child care environments, modeling of healthy behaviors by parents and educators, and reducing children’s exposure to marketing that promotes unhealthy choices.

Normal adolescent thought development includes fluctuations between concrete and abstract thinking, overconfidence (underestimation of difficulty in
changing behaviors, or oversimplification of barriers to progress), and hypersensitivity to being “different,” which can be exacerbated by teasing and bullying. These unique developmental factors must be taken into consideration when designing interventions. Multidimensional behavioral modification approaches that include lifestyle, diet, and exercise components have been shown to result in significantly greater sustained weight reduction in adolescents when compared to conventional programs that focus just on changes to diet or PA.45,79

Encouraging lifestyle and behavior modifications that incorporate more physical activity, develop healthy eating behaviors, and promote coping strategies for effectively dealing with stressors are especially important during adolescence because lifelong diet and exercise habits are established before adulthood is reached.76,141 The most successful programs also incorporate parental support and encourage parental modeling of desired healthy behaviors, thereby providing greater support for adolescents.26,79 Cognitive behavioral approaches are particularly important for adolescents who have anxiety or depression, to reinforce self-efficacy and coping skills and healthy lifestyle behavior choices.76

Although further research is needed to establish causal relationships, clinical screening and therapeutic strategies for adolescent girls should include psychological factors such as ineffectiveness, lack of interoceptive awareness, emotional eating, drive for thinness, and body dissatisfaction, which are all significantly correlated with increased risk of weight gain.78 Interventions that rely on PA to prevent or reduce overweight and obesity need to address the very low amounts of PA that are the norm for adolescent girls, particularly among NHB girls and those from low SES households.78 In addition, efforts to prevent or reduce childhood overweight and obesity in populations with psychosocial stressors need to include programs to help children learn how to cope effectively with these issues.35

Standard therapeutic approaches also need to be adapted to address additional issues that these populations face, such as differences in cultural backgrounds, language barriers, or perceptions of health and illness.45 For example, different cultures have different beliefs about what constitutes a healthy or attractive weight,32 and in some high-risk families, even extreme obesity is not perceived as a cause for concern.45 Higher psychosocial risk factors (migration background, low SES, parental unemployment) or more extreme baseline obesity are correlated with significantly less access to and participation in therapeutic programs, and therefore significantly less weight loss.45

Overweight and obese youth may particularly benefit from behavioral weight control interventions that are specifically designed to increase self-efficacy, minimize embarrassment about physical appearance or ability, and can be modified as needed to accommodate body mass or deconditioning issues. Instead of competitive sports, which provide little opportunity for obese participants to excel, activities such as walking, dancing, or resistance training may prove to be more attractive alternatives that can reduce weight, increase strength, and improve health outcomes.141 Appropriately monitored youth with severe hypertension who want to engage in strength training exercises should start with more repetitions of lower weights until their BP is under control.24

The lack of long-term success in intervention programs may have been explained by a meta-analysis of the published literature pertaining to the effects of PA in overweight and obese adolescents,134 which found that the most common activities chosen for these interventions were aerobic activities similar to those used with adults, such as running, circuit training, cycle ergometer exercise, or team games. These activities may have been chosen for ease of control and measurement of outcomes, but were monotonous, boring, and uninviting for obese and overweight participants, and had not been adapted for the unique physical challenges facing these adolescents or to make them more interesting or enjoyable. Perhaps not surprisingly, none of the studies reported whether the participants enjoyed the PA activities, none reported on the adolescents’ satisfaction or compliance with the PA program, and most did not report the dropout rates from their PA interventions.134

In adolescents, exercise plus calorie restriction and behavior change had a greater effect on lowering BP than just calorie restriction and behavior change; changes in MAP as a result of weight loss were correlated with reduced visceral fat volume but not with changes in BMI or overall body weight, and were independent of sodium reduction.131 Weight loss with orlistat was correlated with lower SBP and DBP, with greater effects seen in those who lost more than 10% of baseline weight.131 Modest weight loss of just 5% to 10% of baseline weight, even when ideal weight is not reached, can improve or normalize BP and insulin sensitivity and consequently prevent, reduce, or eliminate the need for medications, reduce the risk of T2DM and cardiovascular disturbances, and improve quality of life and psychological well-being.131

Increased moderate or vigorous PA, weight loss, and reduced sodium intake have been shown to be the best nonpharmacological approaches to preventing or reducing elevated BP, especially in children with excess adiposity.3,12,43,131 If these measures are not sufficient,
antihypertensives, such as ACE inhibitors, have been effective in reducing BP, reversing LVH, and reducing proteinuria and progression of CKD in hypertensive children. A 5-year study of children and adolescents with CKD reported that aggressively controlling MAP below the 50th percentile for BP decreased proteinuria and prevented progressive deterioration of kidney function. Antihypertensive medications used in conjunction with nonpharmacological therapies in children with an elevated cardiovascular risk profile, especially if T2DM is present, may be an option. Calcium antagonists, β-adrenergic blockers, and angiotensin receptor blockers have not been studied as extensively in children, but appear to also be effective antihypertensive medications.

There are very few medications approved for weight loss use in children and adolescents, and metformin is the only oral medication approved for use in children with T2DM. A meta-analysis of 5 studies of metformin in youth reported a BMI reduction of 1.42 kg/m², but no studies have been done to determine if it will delay onset of T2DM, and studies have not been reported in adolescents with severe obesity. Studies in obese youth of exenatide, which enhances glycemic control in T2DM, and orlistat, which blocks intestinal absorption of fats, have both reported mild to moderate gastrointestinal side effects, modest reductions in weight or BMI, and very little improvement in cardiometabolic risk factors. Only orlistat is approved for use in adolescents, but tolerability issues have limited its use.

There may be another alternative for some children. Incretin-based therapies are already used for regulating blood sugar and management of T2DM and recent research has shown great promise for reducing hypertension, although reduction of BP was not the primary goal of these studies. The incretin system is composed of 3 hormones: glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and dipeptidylpeptidase 4, which promote insulin release, regulate satiety, and promote weight loss. Glucagon-like peptide-1 receptor agonists such as exenatide and liraglutide, and dipeptidylpeptidase 4 inhibitors such as sitagliptin, are not antihypertensive drugs but were found to be effective in lowering BP independent of weight loss, and may play a role in reducing inflammation and oxidative stress, preventing RAAS overactivity, and protecting the kidneys and cardiovascular system. Incretin-based therapies are an area of intense research activity with great potential for improving health outcomes for diabetic, hypertensive, and obese adolescents.

For extremely obese adolescents, there are very few good alternatives. Traditional weight loss approaches based on pharmacological interventions or the paradigm of increased PA and reduced calories have a high failure rate, and bariatric surgery is still in the experimental stage, although it has a high success rate. A German study is investigating the effectiveness of an intervention program that focuses on improving psychosocial functioning, reducing social isolation, improving self-esteem, increasing employment, providing obesity-related education, and raising awareness of long-term consequences of obesity. This study will be a starting point for presurgery assessment of extremely obese adolescents who may then have the option of bariatric surgery.

While highly controversial, bariatric surgery for severely obese adolescents has proven to be much more successful than behavior-based weight management programs, with safety and weight-loss outcomes comparable to adults and improvement or resolution of many of the associated conditions, such as hypertension, dyslipidemia, OSA, T2DM, MetS, pseudotumor cerebri, and psychosocial disorders. Much of the research has focused on roux en y gastric bypass (RYGB) and adjustable gastric banding, but recent small studies with laparoscopic vertical gastric banding have reported comparable weight loss outcomes, fewer complications, and fewer nutritional risks than RYGB, although more research is needed to verify that vertical gastric banding is a safer alternative.

With RYGB and adjustable gastric banding, BMI reductions of up to 37% have been reported in the first year postsurgery, compared to about 3% BMI reduction achieved by control groups following a behavior-based weight management program, and the long-term weight regain seen with the control groups was not seen with the postsurgery patients. However, bariatric surgery is not an option for many severely obese youth, either because they are too young, lack emotional maturity or family support, do not want it, or cannot afford it. Because it has not been approved for use in adolescents, insurance reimbursement should not be expected.

Barriers

Lack of insurance coverage for prevention of overweight and obesity, weight management, and obesity care, and limited reimbursement for prevention, treatment, and third-party services, are significant barriers for families and disincentives for physicians and other health care providers. A survey of pediatricians found that effective weight management efforts were hampered by lack of insurance coverage for weight management programs (69%) or dietary services (more than 50%), lack of referral services for their overweight patients (more than 50%), not having a dietitian or
nutritionist on staff (80%), inability to bill separately from well visits for overweight counseling and treatment (85%), and insufficient insurance reimbursement for these services (56%).

This survey of pediatricians also found that 67% did not have enough time for counseling about weight during well visits, that most believed counseling had poor results, that only 23% believed there were good treatments for overweight children, and that there was disagreement about whether treatments were effective. The biggest influence on behavior was that pediatricians felt helpless or skeptical that they could influence their patients’ weight status; this lack of self-efficacy may explain in part the low level of compliance with BMI treatment (85%), and insufficient insurance reimbursement for these services (56%).

Survey results showed that 92% of physicians were interested in preventing childhood overweight and obesity and half believed it was preventable, but only 59% believed that families wanted to discuss weight at well visits; despite this, 89% regularly discussed fruit and vegetable consumption, 86% encouraged increased PA, and 76% suggested reduced screen time.

On a community scale, efforts to combat obesity and hypertension too often are hampered by competition for limited funding; lack of cooperation and collaboration between existing government agencies, community and grass-roots organizations, schools, businesses, and health care systems; and failure to develop culturally appropriate interventions that are designed for specific communities or at-risk populations. Eliminating food deserts, increasing access to healthy foods, encouraging community gardens, and providing lactation support are ways to prevent and reduce obesity and support healthy weight among at-risk populations, but they require coordinated effort, long-term commitment, and skilled leadership.

Low SES and minority adolescents face many barriers to increasing PA, such as lack of gyms, athletic fields, or recreational facilities in their schools and local communities; lack of PA programs, coaches, or PE teachers; fewer role models; and lack of support from their parents and family. Local community and government agencies, schools, and public health professionals must work together to provide accessible and affordable facilities and programs, convenient public transportation, and safer streets and parks, so that students have a supportive environment that encourages increased PA and development of active lifestyles.

Government programs for improved childhood nutrition and prevention of overweight and obesity have received public exposure but the prevalence and risks of pediatric hypertension are not as well known by the general public. Development of comprehensive programs for prevention and treatment of pediatric hypertension are hampered by limited or lacking insurance reimbursement of costs associated with investigation of long-term treatment options. Lack of funding for studies of pediatric hypertension is a serious impediment to developing evidence-based recommendations for diagnosis and treatment; contributes to undiagnosed hypertension, undetected target-organ damage, and poor BP management; and has serious long-term consequences for children’s health.

A Call to Action

This literature review indicates that controllable factors such as poor diet, reduced activity, increased stress, and sleep deprivation initiate or contribute to a certain degree of hormonal and metabolic changes. Eventually, these small incremental factors can play a significant role in dysregulation of homeostasis and are considered to be important influences on the development of obesity and/or hypertension. The adage that “a calorie is a calorie” is touted to support the idea that the solution to obesity is simply to eat less and exercise more, but if it were that easy to manage weight, everyone would be able to do it and there would not be an obesity epidemic.

The fact that so many try but fail to lose weight or to keep it off has not been interpreted as a need for a new approach, but instead has led to the common perception that those who are overweight or obese are not motivated to change. It is true that some overweight or obese adolescents have an eating disorder, and those children should be identified and given appropriate treatment. However, since many of the interventions that have been tried have proven to be less than effective in the long term, perhaps it is time to consider that the problem is with something other than the motivation of the participants.

This review has provided an abundance of evidence that gender, pubertal stage, genetics, and racial and cultural heritage are factors that play a significant role in the development and severity of adolescent hypertension, overweight, and obesity. These factors are beyond the control of any individual, and therefore must be recognized and their influence must be incorporated into the development of effective treatment approaches, so that a one-size-fits-all model does not guarantee failure for the majority who try it.

The long-term effects of adolescent hypertension and obesity are quite profound and sobering, and this review has shown that the causes are multifaceted, complex, overlapping, and sometimes confounding. Defining obesity as a disease is a good beginning, and with that definition must come the understanding that, in many
cases, obesity is not the patient’s fault, just as hypertension is not. The lack of adequate insurance reimbursement for prevention and treatment of overweight and obesity prolongs the epidemic. Funding for further research is needed to fully understand the causes of obesity and hypertension, and to find interventions that are effective for those who struggle with these conditions. 
The self-perpetuating nature of these complex diseases requires that every effort be made to find solutions for the current generation of children and adolescents who will become the parents of tomorrow.

Author Contributions

DRE contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy. 
LAH contributed to conception and design, contributed to interpretation, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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