REVIEW

Development of hypertension in overweight adolescents: a review

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Abstract: The upward trend in adolescent hypertension is widely attributed to the adolescent obesity epidemic. Secular trends in adolescent prehypertension and hypertension have risen in congruence with increasing trends in the prevalence of overweight and obesity. The correlation between body mass index and blood pressure in adolescence is moderate to strong in most studies and strongest in those classified as overweight or obese. The mechanisms relating to the development of hypertension in overweight adolescents are unclear; however, a number of nonmodifiable and modifiable factors have been implicated. Importantly, certain clinical and biochemical markers in overweight adolescents are indicative of high risk for hypertension, including family history of hypertension and hyperinsulinemia. These characteristics may prove useful in stratifying overweight adolescents as high or low risk of comorbid hypertension. The treatment of overweight and obesity related hypertension in this population focuses on two key modalities: lifestyle change and pharmacotherapy. These approaches focus almost exclusively on weight reduction; however, a number of emerging strategies target hypertension more specifically. Among adolescents with overt hypertension there are also several factors that indicate higher risk of concurrent subclinical disease, persistent adult hypertension, and adult cardiovascular disease. This group may benefit substantially from more aggressive pharmacological treatments. Limitations in the literature relate to the paucity of studies reporting specific effects for the adolescent age group of overweight and obese individuals. Nonetheless, intervention for adiposity-related hypertension in adolescence may partially mitigate some of the cardiovascular risk in adulthood.

Keywords: blood pressure, obesity, prevention, risk factors, childhood

Introduction

Adolescent overweight and obesity is an issue of epidemic proportions worldwide.[1] It is estimated that 32% of adolescents are either overweight or obese.[2] Increased body mass index (BMI) in adolescence, defined as the period from 10 to 19 years, is strongly associated with morbidity and mortality in adulthood.[3,4] However, an increasing number of studies suggest that several of these complications are already present during adolescence. Adolescent overweight has been linked to comorbidities such as dyslipidemia, nonalcoholic steatohepatitis, diabetes mellitus type 2, obstructive sleep apnea, and hypertension.[5]

Hypertension is the most common comorbidity identified in overweight adolescents and the leading risk for mortality in adulthood, attributable to approximately 12.8% of deaths worldwide.[6] A number of studies have investigated the association between BMI and blood pressure (BP) in pediatric and adolescent populations, with the majority

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finding moderate to strong associations, with the majority of correlation coefficients >0.3.[7] The most recently published investigation was a cross-sectional study of 714,922 subjects aged 16–19 years which demonstrated that each one unit increase in BMI was associated with a higher risk of systolic BP (SBP) greater than 130 mmHg.[8] In view of these data, it is not surprising that secular trends show an increase in adolescent hypertension that parallels the rise in overweight and obesity. These trends challenge the previously held assertion that hypertension in adolescence was only a result of secondary causes such as renal disease. In fact, essential (primary) hypertension now accounts for the vast majority of hypertension identified in adolescence.[9]

As a consequence, overweight-related hypertension in adolescence has become increasingly investigated. Hypertension in the context of overweight and obesity indicates a higher potential for cardiovascular disease (CVD) than is associated with either risk factor alone. Results from the Bogalusa Heart Study demonstrated that multiple risk factors in childhood have multiplicative rather than additive effects on the severity of coronary artery lesions.[10] Overweight adolescents with hypertension have a higher likelihood of both elevated weight and BP persisting into adulthood.[11,12] In addition, some complications of obesity are independently related to elevated BP, such as obstructive sleep apnea.[13] Because of their high-risk status, intervention in overweight adolescents with associated comorbidities, such as hypertension, should be considered. Fortunately, studies have demonstrated that those who reverse their obesity status prior to adulthood are less likely to be hypertensive in adulthood.[14] Likewise those who resolve their elevated BP in youth have less risk of elevated BP and subclinical atherosclerosis in adulthood, with this reversal primarily linked to smaller gains in BMI in the time between adolescence and adulthood.[15] This recognizes that adolescence is an opportune time for intervention and prevention of overweight- and obesity-related hypertension. Despite the importance of this issue, there is little consensus worldwide as to how best to identify hypertension in overweight adolescents and the treatments that will result in the lowering of BP in this group.

Overview of causes and incidence of hypertension in adolescence

The most widely applied criteria for determining adolescent BP classification has been devised by the National High Blood Pressure Education Program (NHBPEP).[16] This classification outlines that adolescents with a BP between the 90th and 95th age-, sex-, and height-determined percentiles

are prehypertensive whilst those with a BP between the 95th and 100th age-, sex-, and height-determined percentiles are hypertensive. This classification is applied to adolescents aged 17 years or younger, with BP status of adolescents aged 18–19 years determined using adult thresholds.[17] Elevated SBP and/or diastolic BP (DBP) measured on at least three occasions is necessary to diagnose elevated BP (hypertension or prehypertension). Nevertheless, this criterion is rarely met in cross-sectional and longitudinal studies.

Hypertension can further be classified as essential, with no directly identifiable cause, or secondary due to detectable medical conditions. Essential hypertension is recognized significantly more in adolescence than in childhood, comprising approximately 85%–95% of diagnoses.[9] Essential hypertension is largely asymptomatic and there are usually few findings on the physical examination, although high-risk signs, such as arteriovenous nipping of the retinal vessels, may be present in a minority.[16] Whilst there is no single identifiable cause for essential hypertension in adolescence, there are a number of important risk factors. Although excess weight and adiposity are key, there are a number of other factors that affect the likelihood of developing hypertension in this age group. Adolescent hypertension has been linked to diets high in fat and sodium, sedentary behavior, insufficient physical activity, family history of hypertension or early CVD, and birth weight.[16] The effects of ethnicity and sex have been less consistently demonstrated. It is possible these factors modify the strength of the relationship between BP and adiposity.

A recent publication from the National Health and Nutrition Examination Survey (NHANES) suggests the prevalence of prehypertension and hypertension in 8- to 17-year-olds is approximately one in ten.[18] However, the exact worldwide prevalence of hypertension in adolescents is unclear and data regarding the extent of hypertension among this age group are not apparent given that many studies do not present age-stratified findings. In addition, it would be important to have BP classification based on normal-weight children. Otherwise, due to the strong association between BP and overweight/obesity, the inclusion of a high proportion of overweight/obese children would raise the threshold for normal BP. In a recent systematic review with meta-analysis, the prevalence issue was addressed by pooling BP data from 122,053 adolescents in 55 studies. They reported that the prevalence of elevated BP was 11.2% with higher rates found among males and those from low- and middle-income countries.[19] Prehypertension appears to account for the largest proportion of the burden of elevated BP. In 2007,

Din-Dzietham et al[20] reported that in children and adolescents aged 8–17 years, 10% were prehypertensive and 3.7% were hypertensive. An estimate in 2012 placed the prevalence of hypertension at 2.5% and prehypertension at 11.5%, suggesting that the relative proportion of prehypertensive adolescents may be on the rise.[21] Moreover, other recent studies have largely demonstrated that the overall prevalence of childhood and adolescent hypertension and prehypertension is increasing. Data from the NHANES has revealed that from 1988–1994 to 1999–2008 the odds of elevated BP increased by 27%.[22] This upward trend is largely supported,[23–26] though not completely.[27,28] There is still large heterogeneity across studies reporting the prevalence of elevated BP in adolescence and this may be attributable to differences in study methodology.[21] Overall, elevated BP in adolescence appears to be increasing and this rise can be explained at least in part by the increase in overweight and obesity.

Review of evidence linking hypertension and overweight in adolescents

There is a large amount of evidence linking hypertension and overweight in the adolescent population. Adolescents are overweight or obese according to the internationally accepted percentile charts based on an international multi-center survey.[29] Overweight is defined as a BMI between the 85th and 95th age- and sex-specific percentiles, and obesity is defined as a BMI greater than the 95th age- and sex-specific percentile. Unlike BP, these percentile charts extend from 2 to 20 years and thus adult classifications are not necessary in later adolescence.

Several studies in adolescence have now investigated secular BP trends in relation to secular BMI trends. Overweight and obesity have been increasing rapidly over the last three decades and this parallels the rise in BP. Data from the US NHANES have revealed that 33.6% of adolescents aged 12–19 years were overweight or obese.[2] Nevertheless, the trajectory of BP has not been as linear as the increases in BMI. Din-Dzietham et al[20] revealed that between 1963 and 1988, there was a downward trend in adolescent BP which is consistent with adult data over the same period.[30] Through this period, there was a relative plateau in population BMI levels. A steep increase in overweight and obesity was observed initially in the 1980s and there was a subsequent upswing in hypertension and prehypertension in adolescents.[20,23] A subsequent publication reported that the proportion of overweight and obese adolescents (16–19 years) in an Israeli cohort increased from 13.2% to 21% between 1998 and 2011.[8] This is incongruous with recent data illustrating that in 8- to 17-year-olds, hypertension decreased marginally (from 3.0% to 1.6%) while rate of prehypertension increased slightly (from 10.6% to 11.0%) during a similar time frame.[18] Nonetheless, the trajectory of BP appears to lag 10 years behind that of BMI and this may explain some of the variation in BP and BMI between these trends. These secular trends suggest that there is a relationship between excess weight and hypertension in adolescents. Further evidence in cross-sectional studies has been reviewed to evaluate this relationship. This relationship is particularly difficult to study in adolescence due to the paucity of studies exclusively in this age group.

Table 1 summarizes 13 studies that have examined the association between BMI and BP in adolescence using correlation coefficients. Studies were included in this table if they fulfilled the following requirements: 1) participants were aged between 10 and 19 years; 2) they reported correlation coefficients for association between BMI and BP; and 3) the publication was in English. A number of studies were identified which included results for adolescents and children combined and thus were excluded. Further, five studies presented their results stratified by sex and region and therefore there were a total of 21 data points for SBP and 20 data points for DBP. The age of participants ranged from 10 to 19 years and the mean age of subjects was 14.2 years. Sample sizes ranged from n=24 to n=3,363 participants. All studies included male and female participants, excepting one study of adolescent females from Brazil.[31] Overall, this analysis revealed correlation coefficients between BMI and SBP ranging from $r=0.18$ to $r=0.48$ with a mean of 0.34. Correlation coefficients between BMI and DBP ranged from $r=0.05$ to $r=0.36$ with a mean of 0.21. This shows the tendency for SBP to have a higher association with BMI than DBP. This is consistent with reports that overweight adolescents are more likely to have isolated SBP or a rise in both BP components rather than an isolated elevation in DBP.[32] Importantly, some studies have demonstrated that this association is only significant beyond a certain threshold of BMI[33] and, therefore, associations may be stronger in the overweight and obese subpopulations during adolescence.[34]

The difference in the relationship between BMI and BP in adolescents was assessed on the basis of the relative proportion of overweight subjects and obese subjects in the cohort (Figure 1). Figure 1 illustrates that studies with higher proportions of obese or overweight adolescent participants tended to have higher correlation coefficients, although there was a great deal of inconsistency that may have resulted from the small number of studies (N=13) evaluated.

**Table 1** Summary of studies investigating the association between blood pressure and body mass index in adolescents

Publication	Location	N	Age range (years)	Sex (% male)	Obese (%)	Overweight (%)	SBP CC	DBP CC
Song et al[135]	Korea	1,757	10–19	100.0%	NA	15.7%	0.31*	0.11*
		1,606		0.0%	NA	20.8%	0.20*	0.05
Abdul Razzak et al[136]	Kuwait	209	11–19	61.2%	100.0%	NA	0.18*	0.16*
Duncan et al[137]	Portugal	445	10–17	43.4%	3.7%	22.1%	0.32*	0.23*
Kim et al[138]	Korea	336	12–16	100.0%	NA	NA	0.47*	0.29*
		229		0.0%	NA	NA	0.48*	0.36*
Mehdad et al[139]	Morocco	44	11–17	100.0%	13.6%	47.7%	0.42*	0.28
		123		0.0%	12.2%	22.8%	0.45*	0.34
Pecin et al[140]	Croatia	756	15–18	49.6%	3.5%	NA	0.18*	0.20*
Rutkowski et al[141]	Poland	889	14–15	51.9%	8.0%	8.0%	0.36*	0.22*
Ying-Xiu et al[142]	China	464	12	100.0%	14.4%	15.9%	0.38*	0.28*
		456		0.0%	8.1%	7.9%	0.36*	0.23*
Pereira et al[31]	Brazil	113	14–19	0.0%	NA	31.0%	0.34*	0.27*
Duncan et al[143]	UK	661	11–14	58.1%	7.4%	21.8%	0.37*	0.21*
Larsson et al[144]	Sweden	144	10	44.0%	2.0%	18.0%	0.24*	0.17*
Salvi et al[145]	Algeria	388	15–19	100.0%	1.0%	4.6%	0.33*	0.21*
		734		0.0%	1.7%	8.4%	0.23*	0.14*
	Italy	407		100.0%	3.4%	13.7%	0.42*	0.23*
		528		0.0%	0.8%	9.3%	0.29*	0.12*
Guimarães et al[146]	Brazil	536	11–18	41.0%	23.5%	36.9%	0.44*	NA
Caprio et al[147]	USA	24	10–16	0.0%	58.3%	NA	0.33	−0.19

Note: *P<0.05.
Abbreviations: CC, correlation coefficient; DBP, diastolic blood pressure; NA, not available; SBP, systolic blood pressure.

Comparing the relative proportions of hypertension in overweight and non-overweight adolescents also provides useful information for risk prediction. Koebnick et al[35] reported that the prevalence of hypertension in overweight adolescents (2.1%) was twice that of normal-weight adolescents (0.8%) aged 12–19 years. Further, prevalence of hypertension increased in a stepwise fashion according to magnitude of weight for all subgroups of age and sex. These findings are consistent with other studies showing that the odds of hypertension in overweight adolescents are significantly higher
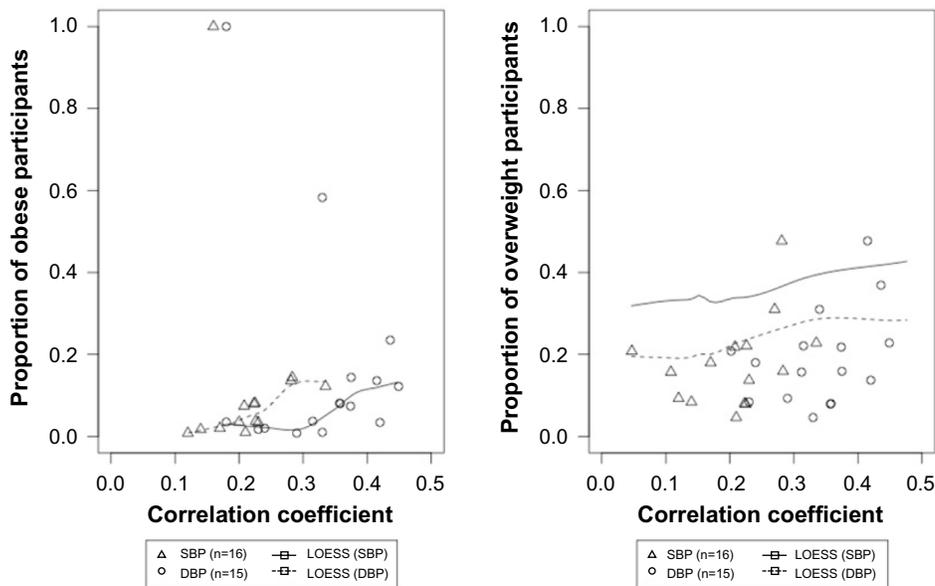
Figure 1 Scatterplot demonstrating the relationship between proportion of obese participants and proportion of overweight participants and the magnitude of SBP and DBP correlation coefficients.
Notes: LOESS creates smoothed curves for both SBP and DBP. There were 16 SBP data points and 15 DBP data points. Some data points are stratified according to sex or region.
Abbreviations: DBP, diastolic blood pressure; LOESS, locally-weighted scatterplot smoothing; SBP, systolic blood pressure.

compared to normal-weight individuals and lower compared to obese individuals.[36–40,138] It is clear that these prevalence rates reflect a dose–response relationship; however, the general classifications of overweight and obesity disregard the continuous positive association between BP and BMI levels. It is estimated that for each decile increase in BMI, SBP increases by 10 mmHg and DBP increases by 3 mmHg.[8] These are substantial differences that, if maintained into adulthood, would have a substantial impact on CVD risk.

Excess weight is evidently responsible for a large number of hypertension cases in adolescence. In a study of 7,746 adolescents aged 12–16 years by Chiolero et al,[41] the attributable fraction (AF) for combined overweight and obesity was highest among males aged 12–13 years (AF =39%) and females aged 15–16 years (AF =39%). Comparatively, in children aged 5–6 years, increased BMI only accounted for 5% and 9% of hypertension in girls and boys, respectively. Population AFs in adulthood are also lower and have been reported as 28% and 11% in two separate studies.[42,43] Therefore, the proportion of hypertension explained by excess weight is greater during adolescence.

Mechanisms of hypertension in overweight adolescents

It is apparent that those adolescents who are overweight and obese have a higher likelihood of developing hypertension; however, the exact size of this effect is variable. This indicates that there may be additional factors influencing the likelihood of developing hypertension in overweight adolescents. The characteristics that distinguish overweight adolescents with hypertension from overweight adolescents who are normotensive are unclear. The cross-sectional data available in the overweight adolescent population is limited and thus factors in cohorts of overweight adolescents and children have also been investigated in this review. These nonmodifiable and modifiable factors have been examined and are summarized in Figure 2 and Table S1.

Figure 2 illustrates that there are factors that both attenuate and stimulate the development of hypertension in overweight adolescents. Despite clear evidence that male sex is a risk factor for the development of elevated BP in adolescence, the role of male sex in overweight adolescents is less certain and studies have provided conflicting results.[44–46] Nevertheless, population data suggest that the overall likelihood of developing hypertension in adolescent males is higher. A large population cohort study demonstrated that sex did not modify the relationship between BMI and high BP.[35] Stronger evidence exists for age affecting the development of hypertension in this group. A number of studies have reported that older adolescents have a greater BP response to alterations in BMI.[35,36] This effect may be due to higher levels of hormones, such as estrogen, present
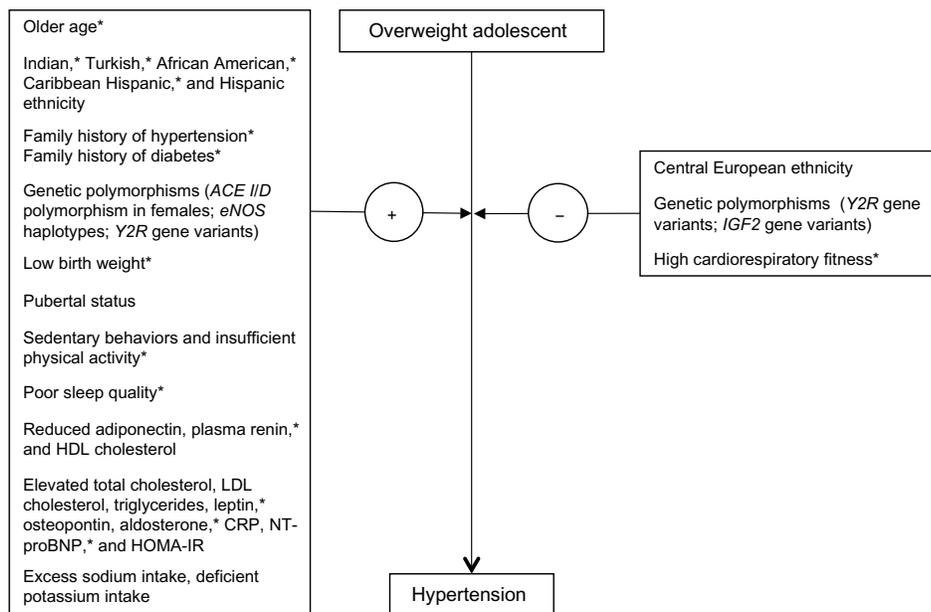
Figure 2 Factors associated with the development of hypertension in overweight adolescents.
Note: *Denotes studies that present effective estimates in adolescents only.
Abbreviations: ACE I/D, angiotensin converting enzyme insertion/deletion; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-estimated insulin resistance; IGF2, insulin-like growth factor; LDL, low-density lipoprotein; NT-proBNP, n-terminal pro-brain natriuretic peptide; Y2R, Y2 receptor.

during puberty. Siklar et al[47] reported pubertal or postpubertal overweight adolescents are significantly more likely to develop elevations in BP compared to their prepubertal counterparts. However, this can only be a marginal stimulus for BP increases given that a large proportion of prepubertal individuals experience hypertensive change and subclinical changes initiating in childhood.

Ethnicity is another important factor in determining progression to hypertension in overweight adolescents who are Indian, African-American, Caribbean Hispanic, or Turkish.[44,48–50] Harding et al[48] noted that obese Indian adolescents were 8.43-times more likely to develop high SBP compared to obese white adolescents in the UK. The risk for hypertension was not significantly higher in nonobese Indian adolescents suggesting that the effect of ethnicity in this population is weight-dependent. A further study in the US has demonstrated that elevated BP was ten-times more common in obese minority youth (African American or Caribbean Hispanic).[50] This may explain some of the differences observed in the genetic markers of those at highest risk for weight-related hypertension. A number of publications have looked at the influence of unique genetic polymorphisms, yet none have investigated this exclusively in adolescents. In such studies, *endothelial nitric oxide synthase* (*eNOS*), *insulin-like growth factor* (*IGF2*), and *angiotensin converting enzyme insertion/deletion* (*ACE I/D*) gene variants have been implicated in higher likelihood of hypertension whilst certain YR2 polymorphisms may be protective.[51,52] These genetic variants related primarily to the physiological mechanisms regulating BP such as enzymes (*ACE I/D*, *eNOS*), hormones (*IGF2*), and receptors (*Y2R*). In a cohort of obese children and adolescents, Santoro et al demonstrated that those with the T585 allele of the *Y2 receptor* were less likely to develop hypertension than those with the CC and CT gene variants (odds ratio =0.5).[53] Family history of hypertension or diabetes has also been shown to affect hypertensive status in obese adolescents,[45,47] although one report is conflicting.[54] Further, low birth weight is also a strong predictor of hypertension in overweight adolescents.[55,56]

There are a number of potentially modifiable risk factors that are more likely to be present in those overweight adolescents with hypertension. Studies in overweight adolescents have revealed that high cardiorespiratory fitness may be protective for hypertension,[57] yet very high levels of physical activity does not appear to have any effect.[58] Marcelino et al[57] showed that the protective effect of cardiorespiratory fitness arose only in those with high body fat but not necessarily high BMI. Conversely, low cardiorespiratory fitness increases the likelihood of hypertension in this group and those with both higher BMI and low maximal oxygen uptake were at highest risk of metabolic syndrome, which includes hypertension. Further, sedentary behaviors such as video game playing and television watching have been linked to an increased risk of developing hypertension in overweight adolescents.[59,60] Interestingly, Goldfield et al[59] observed that video game playing was the only behavior independently linked to elevated BP in overweight adolescents. Excess sodium intake and low potassium intake have been associated with elevated BMI and BP in adolescent cohorts.[61–63] Yang et al[63] reported that for every 100 mg increase in daily dietary sodium of 8- to 18-year-olds, SBP increased by a standard deviation of 0.097 in all subjects and 0.141 in overweight or obese subjects. Of course, data from prospective cohort studies and randomized controlled trials can also be examined to determine if modifying these characteristics may be useful interventions, and this will be discussed further.

Overall, there are a number of characteristics that differentiate those overweight adolescents who are more likely to develop hypertension, but the biological mechanisms underlying these changes are uncertain. Several biochemical factors have been identified as elevated or reduced in those overweight adolescents who have hypertension as opposed to overweight adolescents who are normotensive (Figure 2 and Table S2). These subclinical markers may be implicated in the pathogenesis of hypertension or rather they may be a consequence of the disease itself. A number of hormones derived from adipose tissue have been linked to increased BP in overweight adolescents, including leptin, adiponectin, and osteopontin. A study in overweight adolescents revealed that SBP and DBP were inversely related to adiponectin levels independent of BMI.[64] The regulatory role of hypoadiponectinemia has been confirmed in subsequent studies.[65] Leptin has also been implicated as a mediator of the BP and weight relationship in adolescents. Tu et al[66] reported concurrent rises in SBP, leptin, and heart rate, demonstrating that the effects of leptin on SBP may be occurring via sympathetic nervous system modulation and subsequent increased heart rate. Csabi et al[67] also linked hyperinsulinemia to the development of hypertension in obese adolescents due to the activation of the sympathetic nervous system. In addition, there is also a trend toward higher levels of total cholesterol and low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol in hypertensive and overweight adolescents that may represent a clustering of risk factors.[47,68] Adult studies have extensively investigated the weight modulation of the renin–angiotensin system and

both renin and aldosterone have shown to be elevated in hypertensive obese adolescents.[69,70] Further, higher levels of CRP and NT-proBNP as well as microalbuminuria have been implicated.[71,72]

These factors provide an important insight into the possible mechanisms for the development of hypertension in overweight adolescents. The literature in adulthood is still unclear but implicates a number of factors.[73] Although the evidence in adolescence is limited, the available data suggest similar processes to those in adulthood. The aforementioned risk factors and subclinical markers may ultimately prove useful in the stratification of those overweight adolescents with a higher likelihood of developing hypertension.

Evaluation of current methods used in identifying low- and high-risk hypertension in overweight adolescents

No universal guidelines or recommendations exist to define high-risk versus low-risk hypertension in overweight adolescents. However European, North American, and international guidelines clearly note the importance of evaluating for both complications and comorbidities associated with excess weight. These guidelines largely suggest screening all overweight and obese adolescents for hypertension.[74–78,81,82] For example; US expert committee recommendations regarding adolescent overweight and obesity recommend an evaluation of BP in all those with a BMI above the 85th percentile.[83] Hansen et al[84] indicated that prior identification of obesity status was associated with increased likelihood (odds ratio =2.61) of a correct hypertension diagnosis in those aged between 8 and 19 years. This suggests that pediatricians and family practitioners are aware that hypertension in an important complication in the overweight group of adolescents. Despite the appreciable evidence behind such guidelines, assessing overweight adolescents in clinical practice is problematic given that 33.6% of 12- to 19-year-olds are overweight.[2] The individual and biochemical characteristics noted in the previous section may prove useful in distinguishing those overweight adolescents who would benefit most from early intervention.

Evaluation of BP in overweight adolescents should start with confirming the diagnosis of hypertension; however, there are a number of methodological issues that complicate the measurement of BP in this population. This is problematic due to the inherent variability of BP during childhood and adolescence and also the documented issues of BP misclassification in overweight subjects.[85,86] Choosing an inappropriate cuff size is the most common source of methodological error in BP measurement of overweight or obese individuals and care should be taken to choose an appropriate cuff.[87] In particular, small cuffs in overweight adolescents result in overestimation of BP and over-diagnoses of hypertension.[88] Elevated BP must be detected on at least three separate occasions for a formal diagnosis. The results of a study of 1,020 adolescents showed that 20% had at least one measurement of elevated BP over the course of three visits although only 11.5% could be classified as having persistent prehypertension.[21] In large cohort studies it is often not possible to fulfill this criteria and multiple measurements performed on a single occasion is standard practice.[16,17] Although secondary hypertension is uncommon in adolescence, it is still necessary to exclude adverse and potentially treatable causes of hypertension, such as renal artery stenosis and pheochromocytoma.[89] The likelihood of a secondary diagnosis is less in those already identified as being overweight or obese. Identification is further complicated by the use of a complex BP percentile system that uses critical values for each age, sex, and height percentile for those aged less than 18 years, which may impair the ability of physicians to immediately and accurately identify hypertension.[84] Simplified alternatives to the NHBPEP definition have demonstrated similar predictive utility and may be useful given the increasing trend in adolescent weight-related hypertension.[90–92]

Although preventative management is ideal, a large proportion of those identified as overweight or obese have already developed hypertension and management is necessary. Such individuals can be further assessed as having high-risk or low-risk hypertension. In this context it is useful to consider two different types of risk, concurrent and future risk. Concurrent risk relates to the likelihood of hypertensive target-organ damage in overweight adolescents whereas future risk describes the risk of persistent hypertension in adulthood or adult CVD. Those identified as having target-organ damage (eg, retinal changes or deterioration in renal function) can be considered as being high-risk for future complications based on this discovery alone. Those hypertensive and overweight adolescents at high risk may be an important subgroup to target more intensive interventions. The NHBPEP guidelines note that antihypertensive management should be targeted at lower thresholds (≤90th percentile) for those with concurrent comorbidities including overweight and obesity.[16] There are some clear qualities relating to individual BP, adiposity, and demographics that increase the risk of current and future complications.

There are a number of factors relating to BP which may be important in distinguishing risk of hypertensive disease in overweight adolescents. Magnitude of hypertension during adolescence appears to affect the risk of all-cause mortality. A longitudinal study of adolescent Swedish male conscripts showed that risk of all-cause mortality in adulthood increased proportionally with BP.[93] Further, Hietalampi et al[94] assessed 418 adolescents and noted that for every 1 mmHg increase in SBP there was a 0.5 g increase in left ventricular mass. Consequently, the NHB-PEP Working group recommends staging of hypertension in adolescents based on BP severity as this is often useful in determining treatment options and future risk.[95] Regardless of BP magnitude, evidence of subclinical pathology should always be considered a marker of high-risk disease in overweight adolescents.[96,97] Lubrano et al[96] demonstrated that microalbuminuria was evident in those diagnosed as only prehypertensive. Individual components of BP may also confer risk and DBP has been established to be most predictive of future CVD risk in the adolescent population. Sundstrom et al[93] showed that isolated DBP in male adolescents was more predictive of all-cause mortality in adulthood than isolated SBP. Despite this, it appears that the majority of overweight adolescents will have an isolated rise in SBP or a rise in both SBP and DBP; however, some studies are conflicting.[98] Other research in adulthood describe that mean arterial pressure and pulse pressure are better predictors of future CVD and that this association is intensified if the adults are overweight or obese.[99] This has not yet been demonstrated in normal-weight or overweight adolescents and further study is necessary to determine if these domains of BP would be useful in risk prediction. Ambulatory BP monitoring (ABPM) may be an alternate method to office BP measurement in distinguishing between high-risk and low-risk hypertension and serves to minimize BP variability and the incidence of white-coat hypertension. Several studies have concluded that the BP load, BP variability, and nighttime BP components of ABPM are superior predictors of left ventricular hypertrophy in overweight adolescents.[86,95,100]

Indicators of adiposity, other than BMI, have some utility in predicting additional risk in overweight hypertensive adolescents. Waist circumference, skin-fold thickness, and waist–height ratio have been investigated as isolated and combined measures of adiposity alongside BMI and revealed BMI to be a superior predictor of hypertensive disease overall.[35,42] Although waist circumference, as a measure of both subcutaneous and visceral adiposity, may provide some additional benefit in detecting target-organ damage in overweight adolescents.[101]

A number of nonmodifiable characteristics are linked to high-risk hypertension independent of the extent of BMI or BP elevation. Age at diagnosis of hypertension represents higher-risk of persistence into adulthood. A systematic review revealed that those aged 15 years or older had the strongest tracking of BP from youth to adulthood with correlation coefficients of 0.43 for SBP and 0.31 for DBP.[12] Ethnicity in overweight adolescents affects the likelihood of initially developing hypertension and certain ethnicities also confer a higher level of overall cardiovascular risk. Brady et al[102] showed that non-white hypertensive overweight adolescents had higher likelihood of left ventricular hypertrophy compared to white individuals. Those with a triad of overweight, hypertension, and family history of hypertension in adolescence had poorer left ventricular function compared to paired or single combinations of these risk factors.[103] Evaluation of the hypertensive and overweight adolescent may reveal other modifiable comorbidities, such as insulin resistance. Clustering of risk factors is common in this scenario and indicates a higher likelihood of target-organ damage.[104,105]

Evidently, factors such as elevated magnitude of BMI and BP, older age, family history of hypertension, and non-white ethnicity may indicate high-risk hypertension. This is useful in determining subgroups that may benefit more from specific management strategies, although the evidence is still tenuous and not widely integrated into clinical practice. Those with low-magnitude BP in the prehypertensive index should still be monitored as this is still estimated to progress to hypertension in a substantial proportion of individuals. Falkner et al[106] reported that in the NHANES cohort, prehypertension progressed to hypertension at a rate of approximately 7% per year. Likewise those classed as overweight as opposed to obese represent a higher overall number of individuals likely to develop adverse outcomes in adulthood.

Recommendations for management and prevention

Treatment of hypertension in overweight adults has shown definite benefit for long-term morbidity and mortality related to CVD, with resolution of elevated BP prior to adulthood resulting in further risk reduction. The exact threshold at which overweight and hypertensive individuals would benefit most from intervention is unclear. It is possible that adolescence is the optimal period for preventing permanent cardiovascular damage, as it is early enough to reverse

pathological changes but avoids issues of over-diagnoses experienced with screening in earlier childhood. As such, there is increasing interest in hypertension prevention and treatment strategies for overweight adolescents.

The cornerstone of hypertension management in overweight adolescents is weight reduction, in view of the strong association between adiposity and BP. Despite many studies investigating the management of excess weight in adolescence, few explore the results of such treatment on BP. The most recent US expert committee recommendations regarding the treatment of overweight adolescents cite only two papers relating to the management of hypertension.[78–80] Nevertheless, a number of studies report BP as a secondary outcome. Dietary restriction of kilojoules and increased physical activity in isolation or combination has been compared in several randomized controlled trials. Results from the Special Turku Coronary Risk Factor Intervention Study revealed that a low-saturated-fat diet resulted in BP decreases in adolescents, although it was unclear if this effect is different between normal and overweight participants.[107,108] Aerobic exercise appears to be highly effective at decreasing BP.[109–113] A review of physical activity interventions in obese adolescents demonstrated that approximately 40 minutes of aerobic type activities three to five times a week is necessary to reduce BP in this group.[114] The size of BP reduction appears to be dependent on the intensity of aerobic exercise. A study of an aerobic exercise intervention in 43 obese adolescents showed that a high-intensity program results in greater BP decreases than a low-intensity program, although this difference in effect was only observed after 6 months.[109,110] One preliminary study revealed that weight-training in combination with aerobic exercise resulted in lower SBP levels and assisted in maintaining lowered DBP in overweight adolescent subjects, although no studies have confirmed this effect.[115] Overall, the literature shows combination regimes of diet and physical activity to be the most effective in reducing weight and BP in overweight adolescents although caloric restriction alone is still successful.[116–118] Rocchini et al[118] reported that SBP level and pathological vascular markers were lowered further when regular physical activity was added into a schedule of caloric restriction and counseling. The addition of psychological care is crucial and the interim report of the World Health Organization Commission on Ending Childhood Obesity emphasized the importance of a multidimensional approach to adolescent overweight.[119] Dâmaso et al[120] showed that a multidisciplinary approach involving nutrition, exercise, and behavioral therapy resulted in a 21% and 12% decrease in the prevalence of elevated SBP and DBP, respectively. Brownell et al[79] also

showed that maternal involvement in counseling sessions resulted in larger long-term reductions in BP.

Expert committee guidelines for the management of overweight in adolescents suggest that pharmacological therapy be reserved for individuals resistant to lifestyle and behavioral modification.[78] Currently, the US Food and Drug Administration has only approved orlistat for the indication of pediatric obesity.[121] A randomized controlled trial of 539 obese adolescents revealed that DBP significantly decreased in those treated with orlistat.[122] Orlistat was not associated with a significant reduction in SBP in the same study. These findings were not consistent with one previous study, which demonstrated no change in BP.[123] Metformin is another pharmacological agent that has proved useful in decreasing both BMI and BP in overweight adults. A systematic review has indicated that no strong evidence exists to suggest that metformin has a treatment effect on elevated BP levels in overweight adolescents.[124] Bariatric surgery is not recommended for those adolescents in the overweight class. Nevertheless, it is important to note that studies have demonstrated the Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, and sleeve gastrectomy to be associated with appreciable reductions in BP postsurgery in adolescents.[125–127]

A smaller proportion of strategies focus exclusively on targeting BP reductions. Studies looking at dietary interventions have largely focused on caloric restriction leading to weight reduction in adolescents; however, some macronutrients and micronutrients may have effects on BP independent of weight reduction. A trial of successive 2-week periods of high-sodium and low-sodium diet in obese and nonobese participants revealed that greater reductions in SBP and DBP were experienced by the obese group.[128] Further, those who participated in a 20-week weight-loss trial and lost at least 1 kg of weight experienced decreases in BP sodium sensitivity suggesting that adiposity modulates the relationship between BP and sodium. In contrast, milk proteins may be protective for BP increases in overweight adolescents. Arnberg et al[129] demonstrated reductions of 1.8 mmHg (2.7%) in DBP of overweight adolescents following a 12-week intervention with casein protein. These results are consistent with adult studies demonstrating a 3% reduction in DBP following administration of casein.[130] The effect on DBP is of particular interest given that DBP is known to be the strongest predictor of adult CVD in young adults.[131] Guidelines for management of hypertension in children and adolescents further suggest that higher potassium, magnesium, and low-fat dairy may be useful; however, it is uncertain if these nutrients are of

specific benefit in those with increased adiposity. Couch et al[132] conducted a 3-month clinic-based trial of adolescents and demonstrated that adopting a "dietary approaches to stop hypertension" diet assisted in reducing baseline SBP and DBP. The dietary approaches to stop hypertension diet had relatively higher levels of fruit intake, potassium, magnesium, and low-fat dairy and lower levels of overall fat consumption compared to the hospital-based nutrition care (control) group.

Halbach et al[133] outlined key indications for pharmacological treatment of hypertension in obese adolescents, including diabetes mellitus (type 1 and type 2), secondary hypertension, target-organ damage, and failure of nonpharmacologic therapy alone. This reflects treatment recommendations in the NHBPEP although no distinct set of advice is provided for those with concurrent overweight and hypertension in adolescence.[16] ACE inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers, and diuretics are agents that can be prescribed in adolescent hypertension. Those who are overweight or obese maybe benefit additionally from those with renal protective properties (ACE inhibitors or angiotensin-receptor blockers).[7] As previously noted, uric acid has been implicated in the development of hypertension in overweight adolescents. Consequently, Soletsky and Feig[134] studied the effect of uric acid reduction using pharmacological agents (xanthine oxidase inhibitor, allopurinol, uricosuric drugs, or probenecid) in obese adolescents aged 11–17 years for 7 weeks. Those provided with urate-lowering therapy experienced significant reductions in SBP (10.2 mmHg) and DBP (9.0 mmHg) whilst those in the placebo group experienced only minor increases in BP.

Overall, management of hypertension in overweight adolescents should primarily involve lifestyle modification; however, a lower threshold for pharmaceutical intervention might be considered. Prevention of hypertension in overweight adolescents focuses on the behavioral therapies outlined above although no targeted long-term follow-up trials were identified. Lastly, trials with prolonged follow-up periods should be considered given that the reversal of vascular dysfunction is apparent only over a longer period of time.

Conclusion

The incidence of hypertension in adolescence appears to be increasing alongside the epidemic of adolescent obesity. As a result, obesity has been widely implicated in the pathogenesis of adolescent hypertension although, as in adulthood, the mechanisms still remain unclear. Overweight adolescents with a family history of hypertension, low birth weight, non-white ethnicity, sedentary behavior or insufficient physical activity, and poor sleep quality have a higher likelihood of developing hypertension. Evidence also suggests high cardiorespiratory fitness and certain genetic polymorphisms may be protective in this setting. Further studies investigating biochemical markers in hypertensive overweight adolescents have found variations in the levels of hormones and enzymes involved in the renin–angiotensin system, lipid metabolism, and inflammation. Adolescents who develop hypertension may be considered high-risk for concurrent target hypertensive organ damage and future CVD risk based on several factors, including BP magnitude, BMI magnitude, age, family history, and ethnicity. Overall, the majority of studies reviewed pertained to obese adolescents and literature specific to the overweight subgroup is limited. Continued research is necessary to determine the value of treatment and screening in hypertensive overweight adolescents. Lifestyle modification and pharmacotherapies have been demonstrated to be successful in preventing hypertension and reducing already elevated BP in this group.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Factors associated with the development of hypertension in overweight adolescents

Factors	Publication	Year	Effect in overweight adolescents
Nonmodifiable factors			
Age	La Manna et al[1,*]	1982	Age >13 years associated with hypertension.
	Siklar et al[2]	2011	Older age associated with hypertension.
Sex	Koenigsberg et al[3,*]	2006	Hypertension more likely in males >11 years.
	La Manna et al[1,*]	1982	Hypertension more likely in females.
	Hannon et al[4]	2015	Not significant.
Ethnicity	Harding et al[5,*]	2008	Indian participants had higher risk of hypertension.
	Martin et al[6]	2015	Turkish participants had a higher risk of hypertension whereas Central European participants had a lower risk.
	Puri et al[7,*]	2008	African American and Caribbean Hispanic had a higher risk compared to white participants.
	Hannon et al[4]	2015	African American and Hispanic participants had a higher risk of hypertension compared to white participants.
Genetics	Siklar et al[2]	2011	*ACE I/D* polymorphism not significant.
	Santoro et al[8]	2008	The presence of certain *Y2R* gene variants (T allele and T585 allele) was protective for hypertension. Other *Y2R* gene variants (CC and CT) were associated with higher risk of hypertension.
	Souza-Costa et al[9]	2011	The *eNOS* haplotype C b Glu is associated with hypertension.
	Faienza et al[10]	2010	*IGF2* gene variants (6815 A/T and T6815) are associated with higher risk of hypertension, *IGF2* variant A6815 allele is associated with lower risk.
	Lemes et al[11]	2013	*ACE I/D* polymorphism is associated with hypertension in males only.
	Guerra et al[12]	2003	ApoE polymorphism not significant.
Family history of hypertension	Nishina et al[13]	2003	Family history of hypertension not significant.
	La Manna et al[1]	1982	Family history of hypertension associated with hypertension.
	Siklar et al[2]	2011	Family history of hypertension associated with hypertension.
Family history of diabetes	La Manna et al[1]	1982	Family history of diabetes associated with hypertension.
Low birth weight	Lurbe et al[14,*]	2009	Lower birth weight associated with higher systolic BP values.
	Strufaldi et al[15]	2009	Risk of hypertension significantly higher in those with both low birth weight and current obesity.
Pubertal status	Siklar et al[2]	2011	Participants who were pubertal or postpubertal were more likely to have hypertension.
Modifiable factors			
Physical activity	Hayes et al[16]	2013	Physical activity did not attenuate blood pressure risk.
Cardiorespiratory fitness	Nielsen et al[17]	2003	BMI was a stronger predictor of hypertension in female individuals with low fitness levels. Higher fitness levels were associated with lower risk.
	Eisenmann et al[18]	2007	Those with both elevated BMI and low fitness had the highest levels of metabolic syndrome.
	Shaibi et al[19]	2005	VO$_2$ max is not associated with any individual risk factors in overweight youth.
	Marcelino et al[20]	2012	High cardiorespiratory fitness is protective for hypertension in those with high body fat but not high BMI.
Sedentary behaviors	Pardee et al[21]	2007	Hypertension in obese children is associated with time spent watching television.
	Goldfield et al[22,*]	2011	In obese adolescents, time spent playing video games was independently associated with hypertension.
Sleep	Hannon et al[4]	2015	Lack of REM sleep is associated with hypertension.

Note: *Denotes studies that present effective estimates in adolescents only.
Abbreviations: *ACE I/D*, *angiotensin converting enzyme insertion/deletion*; BP, blood pressure; BMI, body mass index; *eNOS*, *endothelial nitric oxide synthase*; *IGF2*, *insulin-like growth factor*; REM, rapid eye movement; VO$_2$ max, maximal oxygen uptake; *Y2R*, *Y2 receptor*; ApoE, apolipoprotein E.

Table S2 Subclinical markers associated with hypertension in overweight adolescents

Biochemical marker	Publications
Hypercholesterolemia	Glowinska et al[23]
High LDL	Glowinska et al[23]
Hypertriglyceridemia	Siklar et al[2]
High triglyceride/HDL cholesterol ratio	Siklar et al[2]
Low HDL	Siklar et al[2]
Hyperinsulinemia	Nishina et al;[13] Libman et al;[24] Csabi et al[25]
Low adiponectin	De Las Heras et al;[26,*] Lezhenko et al;[27,*] Shatat et al[28,*]
High leptin	Tu et al;[29] Nishina et al;[13] Hirose et al[30,*]
High NT-proBNP (males only)	Pervanidou et al[31,*]
High osteopontin	Lezhenko et al[27]
High aldosterone	Rocchini et al;[32,*] Shatat et al[33,*]
Low plasma renin	Shatat et al[33,*]
High CRP	Noronha et al[34]
Microalbuminuria	Nguyen et al[35,*]
High IR-HOMA	Siklar et al[2]

Note: *Denotes studies that present effective estimates in adolescents only.
Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, n-terminal pro-brain natriuretic peptide; IR-HOMA, insulin resistance homeostasis model assessment.

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