Hypertension increases risks of adverse cardiovascular outcomes in adults. Because of lack of long-term outcome data to link a blood pressure (BP) threshold in childhood that predicts elevated risk for future cardiovascular events, hypertension is defined differently in pediatric patients. Despite the difference in definition, which is statistically based (≥95th percentile according to sex, age, and height percentile), hypertension is present in a substantial number of asymptomatic children and adolescents. Although outcome data on benefit versus risk of treatment in children with established hypertension are limited, available clinical trial data indicate that lowering BP in hypertensive children with antihypertensive medications is generally effective and safe. Hypertension that is secondary to an underlying cause is thought to be more common in childhood, which raises evaluation issues, especially as primary hypertension is now commonly found in childhood. A recent report by Flynn et al1 provides observational clarity on secondary versus primary hypertension in childhood. The authors analyzed contemporary demographic and clinical characteristics at baseline of 351 hypertensive children and adolescents enrolled from multiple sites in a clinical trial. When compared with children in midchildhood (aged, 6 to <12 years) and adolescents (aged, 12 to <17 years), the younger children (aged, <6 years) were significantly more likely to have secondary hypertension, were less likely to be obese, and had significantly higher diastolic BP. Thus secondary hypertension is more likely to be detected in nonobese younger children with higher BP, whereas primary hypertension is more commonly found in late childhood and adolescence and is associated with overweight/obesity and modest BP elevations.

Recent pediatric reports provide other tools that can be applied in clinical evaluation of hypertensive children. Ambulatory BP monitoring has become a useful diagnostic procedure in evaluation of hypertensive children and adults. A Scientific Statement From the American Heart Association2 provides guidance on the use of ambulatory BP monitoring measurement in children and adolescents. Target organ damage (TOD) is detectable in some hypertensive children. There are now published normative reference data on LVMI3 and more recently on cIMT4 in children and adolescents. These tools represent considerable advancement for clinical research and clinical management of children with hypertension and also children with prehypertension.

Increasing BP Level and Prevalence of High BP in Childhood

An examination of epidemiological studies on BP in children and adolescents conducted during the past decade demonstrates a significant increase in BP level and an increase in prevalence of hypertension.5 An analysis of data from the National Health and Nutrition Examination Survey (NHANES) by Munter et al6 in 2004 reported that the increase in childhood BP level was largely, but not entirely, attributable to the increase in the prevalence of obesity in children and adolescence. Large school-based BP screening studies,7 and analysis of BP data in electronic medical records from large primary pediatric care clinics,8 report a prevalence of childhood hypertension (based on repeated BP measurement) at 3.5% and a prevalence of prehypertension also at 3.5%. However, a much lower prevalence was reported in an analysis of electronic medical data of BP in a large cohort of children receiving primary care within the Kaiser Permanente health system.9 Consistent among all reports is the observation that rates of high BP were higher among overweight and obese children. Childhood BP trends were recently re-examined by Rosner et al.10 The authors analyzed a population-based sample of 3248 children in NHANES III (1988–1994) and 8388 children in continuous NHANES (1999–2008), aged 8 to 17 years and determined the prevalence of high BP (prehypertension and hypertension combined). Within this 10-year period, the prevalence of high BP (based on single measurement) increased from 15.8% to 19.2% among boys and the prevalence of high BP increased from 8.2% to 12.6% among girls. Although the analyses were limited to 1 BP measurement session, these data document a striking increase in the prevalence of high-risk BP among otherwise healthy children. The increasing prevalence of childhood obesity was again determined to be the major, but not the only, determinant of the population increase in high BP prevalence among children. Other countries are also experiencing marked increases in childhood obesity. Investigators in China...
reported concordant upward trends in body mass index (BMI) and BP level in Chinese children aged from 7 to 17 years. Data obtained from 2 separate cross-sectional surveys in 2005 and 2010 on a total of 391,982 children were compared. The data demonstrate a population increase in BP among both boys and girls. In the same 5-year interval, there was also a significant increase in BMI. After adjustment for BMI, the mean increase in systolic BP was reduced by 40.5%, indicating that increasing obesity was a leading determinant of the child population increase in BP. However, the BMI adjustment indicated that some other factor could also be contributing to the childhood increase in BP level.

The childhood obesity epidemic and concurrent increasing rates of high BP strongly suggest an increase in risk for premature cardiovascular disease in adulthood. A pooled analysis of 4 prospective cohort studies that include data on >6000 individuals from childhood into young adulthood found the relative risk for hypertension as adults among those who were obese in childhood was increased (relative risk 2.7; 95% confidence interval, 2.2–3.3) with similar increases in risk for other metabolic cardiovascular risk factors. However, individuals who were overweight or obese during childhood but became nonobese as adults had outcome risks that were similar to individuals who were in a normal weight range in childhood and as adults. Other reports describe similar outcomes for cIMT in young adulthood relative to high BP and visceral fatness in childhood. In another cohort, Suglia et al analyzed prospective data from the National Longitudinal Study of Adolescent Health. This cohort included data on individuals from adolescence to adulthood, including Black, Hispanic, and white participants. The results demonstrate a higher risk for hypertension among those who were chronically overweight from adolescence to adulthood and those who became obese as adults. The results also demonstrate that the risk for hypertension in adulthood is lower among those who were overweight in adolescence and subsequently lost weight. An exception was observed among black men, who have a higher risk for hypertension regardless of weight gain or weight loss. These reports from longitudinal cohort data support the potential long-term health benefits of interventions to prevent and reverse childhood obesity. However, the observation that the risk for hypertension is not lower among black men who lose weight as adults indicates additional health disparity among black men.

**Dietary Salt and BP in Childhood**

Epidemiological and clinical evidence consistently support a strong association of dietary salt intake with BP level and hypertension among adults. Data in support of this relationship have been less clear in childhood. A meta-analysis on 13 randomized clinical trials in healthy adolescents on effects of reduction in dietary salt intake detected a small but statistically significant effect in lowering BP. The same investigators recently conducted a cross-sectional study to quantify dietary salt intake among children in the South London. The study stratified healthy children into 3 age groups: 5 to 6 years, 8 to 9 years, and adolescents age 13 to 17 years. Salt intake was computed from a combination of 24-hour urinary sodium excretion and a 24-hour photographic food diary. Valid 24-hour urine collections were obtained in 340 children. Mean salt intake, which increased with age, was 3.75 g/d in 5- to 6-year-olds, 4.72 g/d in 8- to 9-year-olds, and 7.44 g/d in adolescents. Overall the salt intake was greater than the maximum daily salt intake recommendations in 66% of 5- to 6-year-olds, 73% of 8- to 9-year-olds, and 73% of adolescents. Analysis of diet quality determined that the predominant source of dietary salt was from processed foods. Similar results were reported on sodium intake in US children, based on analysis of recent NHANES data. Average daily sodium intake for children aged 6 to 10 years was 2903 mg, and for children 11 to 13 years was 3194 mg, and for adolescents (14–18 years) was 3672 mg. The predominant source of dietary sodium was also processed and fast foods.

The epidemiological studies cited above demonstrate that childhood overweight and obesity explain much, but not all, of the increasing BP levels in children. There seems to be something else that is contributing to the BP increase in children, and there is now evidence that salt intake also adds to BP increase in children. Two recent reports add further insights on the effect of high salt intake in children. Yang et al examined recent NHANES 2003 to 2008 data to determine whether there was an association between dietary sodium intake and BP level in children aged 8 to 18 years. The study sample included 6235 children of whom 37% had BMI ≥85th percentile indicating overweight or obese. On the basis of analysis of multiple 24-hour dietary recall measures, estimated average sodium intake was 3.89 g/d. Overall, each 1000 mg/d of sodium intake was associated with +1.0 mm Hg increase in systolic BP. However, among overweight/obese children, systolic BP increased by 1.5 mm Hg for each 1000 mg/d sodium intake. The investigators then stratified the children by quartiles of sodium intake. For the entire sample, the adjusted odds ratios comparing the risk for prehypertension and hypertension combined in the highest sodium intake quartile to the lowest sodium intake quartile was 2.0 (95% confidence interval, 0.95–4.1; P=0.062). Among overweight/obese children, the adjusted odds ratio for prehypertension/hypertension in the high sodium intake quartile increased to 3.5 (95% confidence interval, 1.2–9.2; P=0.013). These findings were further advanced in the study by Rosner et al. As described above, NHANES data from 1988 to 2008 were analyzed for child BP trends and risk factors. A significant increase in BP among children over this time period was demonstrated. An analysis on associated risk factors determined that BMI, waist circumference, and dietary sodium intake were each independently associated with the prevalence of prehypertension/hypertension among children aged 8 to 17 years. Together, these data indicate that the effect of a high sodium intake on BP is amplified among children who are also overweight or obese.

An association of serum uric acid levels with hypertension, which has been commonly observed in adults, is now being reported in childhood. In a sample of children referred for the evaluation of hypertension, Feig and Johnson reported significantly higher mean serum uric acid levels in children with primary hypertension when compared with children with secondary hypertension or white coat hypertension. Subsequent clinical studies in hypertensive children have replicated these observations. The effect of uric acid is not limited
to hypertension because data from the Bogalusa Heart Study demonstrate a significant correlation childhood uric acid levels with both childhood BP and later BP in adulthood. Further support of an independent effect of uric acid on BP in the young was reported from a randomized placebo-controlled study to determine whether lowering uric acid lowers BP in adolescents with stage 1 hypertension. In this study, treatment with allopurinol 200 mg twice daily for 4 weeks resulted in a significant reduction in BP. The mechanism through which uric acid affects an increase in BP, especially in the young, is not clear. As reviewed by Feig, a plausible mechanistic pathway is metabolic consequences of high fructose consumption. This concept is supported by both experimental and clinical studies that demonstrate a relationship of high fructose consumption with elevated uric acid levels and also other components of metabolic syndrome. Therefore, a high intake of processed foods sweetened with fructose, especially among obese children, may also contribute to increasing BP levels in the young.

These reports contribute clarity on the early phase of primary hypertension beginning in childhood. BP levels in the young are increasing largely because of childhood obesity with concurrent secular diet changes, including salt and possibly fructose exposure. Considering the rapid changes in BMI and diet patterns in childhood, it would seem unlikely that genetics would play a significant role in the increasing BP levels observed among children. However, a recent report from a study by Xi et al adds additional insights on obesity-associated hypertension in childhood. The investigators genotyped 610 hypertensive children and 2458 normotensive children from the Beijing Child and Adolescent Metabolic Syndrome Study in a case–control study on genetic variants thought to be associated with hypertension. On the basis of previous genome-wide association studies for hypertension in adults, 6 single nucleotide polymorphisms (SNPs) were selected for the study. There were no significant associations of SNPs with BP in normal weight children regardless of BP status. Among obese children, 3 SNPs were significantly associated with higher systolic BP. There were also significant associations of 4 SNPs with hypertension in obese children. Thus, the investigators identified a significant association of hypertension susceptibility loci with BP level and with hypertension in Chinese children, but this was found only among obese children. It is also striking that 3 of the 4 SNPs associated with hypertension in obese children were reported to be linked with renal sodium regulation. This genetic study connects SNPs on renal sodium regulation with 2 environmental exposures: obesity and salt intake.

**Birth Weight and Intrauterine Effects on Childhood BP**

The fetal programming theory, wherein certain adverse intrauterine exposures during fetal development can set the stage for chronic diseases in later life, is a topic of research interest. Epidemiological studies link low birth weight with adverse outcomes in later adulthood; and experimental research has developed plausible mechanistic pathways. However, reports from clinical studies in children have been inconsistent. Recent reports describe potential maternal stressors that may have an effect on subsequent BP and other metabolic risk factors in childhood. Fraser et al conducted a study to determine whether maternal hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension, are associated with BP and metabolic risk factors in adolescent offspring. Their study, on mother–offspring pairs from the Avon Longitudinal study of Parents and Children, measured BP and metabolic parameters in offspring at the age of 17 years. When compared with offspring of normotensive pregnancies, there were no differences in insulin, glucose, or lipid values in offspring of both preeclampsia and gestational hypertension pregnancies. However, BP was significantly higher in offspring of both hypertensive disorders of pregnancy. The BP in offspring of hypertensive pregnancies remained significantly higher after the adjustment for potential confounders, suggesting that the association may be driven by genetic or familial risk factors. Another secondary analysis of data from the same Avon Longitudinal Study cohort examined the relative contribution of different growth periods to BP level at the age of 10 years. An inverse association of birth weight with systolic BP was found. In subsequent child growth periods, all growth parameters, including weight, height, and weight-for-height (an adiposity measure) were all positively associated with systolic BP. The authors concluded that the development of excess adiposity during early child growth periods was a modifiable determinant of later BP. In another study, the effect of maternal and paternal obesity on child cardiovascular risk factors was examined in 6-year-old children in the Generation R cohort. The investigators reported that higher maternal and paternal prepregnancy BMI were associated with higher childhood BMI, abdominal fat mass, systolic BP, and insulin levels with lower high-density lipoprotein-cholesterol levels. The associations were stronger for maternal BMI than for paternal BMI. Although birth weight did not seem to be different between mothers with and without prepregnancy obesity, the authors suggest that these results may indicate that maternal prepregnancy BMI may influence later cardiometabolic health status of offspring through direct intrauterine mechanisms. These reports, based on secondary analyses of data from relatively large prospective cohorts, describe relationships between maternal status, birth parameters, and child cardiovascular risk status. Wolfenstetter et al used an alternative approach in a study designed to determine whether children born with low birth weight have altered cardiovascular rhythmicity (an indirect estimate of sympathetic nervous system activity). The investigators examined healthy children (mean age, 8 years) born with low birth weight and control children matched for age and sex with 24-hour ambulatory BP monitoring. The 24-hour, daytime, and night BP levels were higher in low birth weight children than in controls. BP rhythmicity, computed by Fourier analysis, was different between the groups with blunted circadian and ultradian BP rhythmicity detected in the children with low birth weight. These unique observations suggest possible intrauterine programming with subtle alterations in cardiovascular regulation in children having low birth weight.

Findings in the above reports were based on analysis of data in existing cohorts or studies in children selected for a history of low or normal birth weight. Prospective studies on offspring
of normal pregnancies beginning in the newborn period are limited. Lurbe et al\textsuperscript{31} conducted a small but rigorous prospective study on a sample of healthy full-term newborn infants stratified by birth weight as small (SGA), appropriate, or large for gestational age. BP measured at 2 days was positively associated with birth weight. Subsequent BP and growth parameters were measured at 6 months, 2 years, and 5 years; and at the 5-year examination, a blood sample was obtained for metabolic parameters including glucose, insulin, and lipids. Each birth weight group gained a similar amount of weight between each examination interval. SGA infants remained the smallest and large for gestational age infants remained the largest at subsequent examinations. After 6 months, current weight and weight gain were positively associated with birth weight, and birth weight was not associated with BP level. The metabolic measures delineate interesting findings at the age of 5 years when the birth weight groups were further stratified according to current weight status. Fasting insulin levels were higher in all infants who became heavy at the age of 5 years, and highest among the SGA group. However, the homeostatic model assessment index, an estimate of insulin resistance, is higher in the entire SGA group regardless of relative weight status at the age of 5 years. In addition to relative insulin resistance, the SGA group also had lower high-density lipoprotein-cholesterol and higher uric acid levels than the other birth weight groups. These findings suggest that intrauterine factors related to lower birth weight may have induced metabolic programming for relative insulin resistance that is sustained, at least in early childhood, regardless of later weight status. The metabolic measures also indicate subtle emerging features of metabolic syndrome. It is possible that high BP may emerge later as a consequence of the insulin resistance or metabolic syndrome.

Several potential mechanisms have been examined, in experimental studies, to explain perinatal programming, or the effect of the intrauterine environment on later health or chronic disease. In response to suboptimal intrauterine nutrition or other stresses, there could be changes in size of various organs, neuroendocrine changes, or other changes that involve epigenetic modifications. Epigenetic alterations indicate modifications in DNA without changes in DNA sequence through DNA methylation, post-translational histone modifications, modification of nuclear receptors, and microRNAs.\textsuperscript{32,33} Clinical studies that examine epigenetic modification and clinical outcomes in childhood are limited. An example of a recent study that applied epigenetic strategies to cardiovascular pathophysiology in the young was reported by Breton et al.\textsuperscript{34} These investigators measured DNA methylation of nitric oxide synthase and identified an association of percentage DNA methylation of nitric oxide synthase 1 with carotid intima-media thickness in children. Additional studies, beginning in childhood, that apply similar molecular strategies are needed to delineate the pathway from intrauterine experiences and epigenetic modification to evolution of chronic disease markers.

**BP and TOD in Childhood**

A recent publication that resulted in strong responses from pediatric hypertension specialists was the US Preventive Services Task Force (USPSTF) recommendation statement on Screening for Hypertension in Children and Adolescents.\textsuperscript{35} Based on an evidence review, the USPSTF stated that “current evidence is insufficient to assess the balance of benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood and adulthood.” As summarized in a response by Urbina et al,\textsuperscript{36} the USPSTF created 8 key questions and performed an evidence-based review to answer the questions. From a literature review of 6435 potentially relevant articles, only 35 articles met USPSTF criteria of acceptable evidence, all of which were small relatively short randomized controlled clinical trials. All reports based on observational studies were excluded, including prospective cohort studies that demonstrate a significant relationship of high BP in childhood with hypertension in young adulthood and also evidence of TOD in young adulthood. Cross-sectional studies that describe TOD in hypertensive children were also not considered. The issues not considered by the USPSTF, especially hypertension-related TOD in childhood, represent substantial advancements in pediatric hypertension.

Several reports during the past decade demonstrate that TOD is detectable in hypertensive children and is associated with other cardiovascular and metabolic risk factors. Left ventricular hypertrophy on echocardiographic measurement of LVM has been described in adolescents with mild untreated high BP.\textsuperscript{37,38} On the basis of evidence of an association of LVM with BP level in children, the National Heart Lung and Blood Institute–sponsored Fourth Report on high BP in children and adolescents\textsuperscript{39} recommended including an evaluation for TOD in children with confirmed hypertension. Since publication of that 2004 report, additional data have emerged from cross-sectional studies, confirming that TOD is detectable in the young\textsuperscript{40,41} and is not limited to increases in LVM. When compared with normotensive children, a measurable increase in cIMT, a surrogate marker for preclinical atherosclerosis in adults, has been reported in children with high BP, as well as in children with diabetes mellitus and familial hypercholesterolemia.\textsuperscript{42,43} Increased arterial stiffness, or loss of elasticity, a change generally associated with aging, has been detected in pediatric patients with high BP and other conditions linked with cardiovascular disease, including obesity, diabetes mellitus, and dyslipidemia.\textsuperscript{44,45} Retinal arteriolar narrowing, an established consequence of hypertension in adults, has recently been described in children with higher BP.\textsuperscript{46} Hypertensive adults have heightened risk of developing cognitive impairment. In recent studies, Lande et al\textsuperscript{47–49} detected a comparable link between high BP and cognitive function in children. In both the NHANES III data, and in subsequent small clinical studies, children with high BP perform at a lower level in measures of executive function compared with age-matched normotensive children. Findings of TOD in childhood years may not be limited to patients with established hypertension because recent reports describe evidence of TOD among prehypertensive adolescents. In a cohort that included type 2 diabetic adolescents, Urbina et al\textsuperscript{50} reported greater LVMI among prehypertensive participants than among normotensives. The investigators also found higher pulse wave velocity, indicative of vascular stiffness, in prehypertensives than in
normotensives. In another study on a cohort of black adolescents, the effects of prehypertension and obesity were examined. The investigators reported significantly higher LVMI among prehypertensive adolescents than among normotensives. LVMI was highest, with more left ventricular hypertrophy, among those with both prehypertension and obesity. In this study, the effects of prehypertension and obesity on LVMI were found to be additive. Overall, recent reports on hypertension related TOD in the young demonstrate evidence of underlying vascular pathology among children with primary hypertension. Recent reports that detected left ventricular hypertrophy and vascular stiffness among prehypertensive adolescents strongly suggest that the BP level for heightened risk for TOD may be lower than the 95th percentile, which is the current definition of hypertension in childhood.

Summary
Epidemiological reports describe a child population increase in BP level and an increase in prevalence of hypertension, that is largely, but not entirely, driven by a concurrent increase in childhood obesity. Given current estimates, 10% of adolescents have hypertension or prehypertension. In addition to obesity, dietary salt intake and waist circumference, a marker of visceral obesity, are found to be independently associated with the rise in BP among children and adolescents. Dietary salt intake in urban children is well above recommended levels largely because of consumption of processed and fast foods. Childhood exposures, such as stress, salt, and fructose, as well as lifestyles, including food sources, sleep patterns, and reductions in physical activity may have a role in obesity–high BP associations. In addition, clinical and translational evidence is mounting that intrauterine exposures alter can effect changes in fetal development that have an enduring effect on cardiovascular and metabolic function later in life. These effects can be detected even in children who are products of a term otherwise normal pregnancy.

Hypertension in childhood has been defined statistically (BP≥95th percentile) because of lack of outcome data that links a BP level with heightened risk for future cardiovascular events. Therefore, primary hypertension had been considered a risk factor for later hypertension in adulthood. Intermediate markers of TOD, including cardiac hypertrophy, vascular stiffness, and increases in cIMT, are detectable in adolescents with primary hypertension. Evidence that vascular injury is present in the early phase of hypertension and even in prehypertension warrants consideration on the current definition of pediatric hypertension. With further studies on TOD and other risk factors in addition to high BP, it may be possible to shift from a statistical definition to a definition of childhood hypertension that is evidence based.

Preventing or reducing childhood obesity would have substantial benefit in countering the documented increase in BP levels and prevalence of high BP in childhood. Weight control in overweight and obese children, along with dietary changes and increases in physical activity, has benefit on BP levels in childhood. Prevention of childhood obesity and BP risk will require multiple levels of intervention, including public health, health policy, and attention to food supply to foster the necessary lifestyle changes to prevent and reduce childhood obesity.

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Recent Clinical and Translational Advances in Pediatric Hypertension

Bonita Falkner

High blood pressure increases the risk of heart disease and stroke. Circulation is only one of many factors that contribute to these conditions. In the developing world, where heart disease is not a major concern, the primary focus is on the prevention of heart disease. The goal of this study is to evaluate the impact of blood pressure on the risk of heart disease. We have studied the relationship between blood pressure and heart disease in the United States, United Kingdom, and France. The results of our study have shown that blood pressure is a strong predictor of heart disease. We have also found that blood pressure is a strong predictor of stroke. The results of our study have been published in the American Journal of Hypertension. DOI: 10.1161/HYPERTENSIONAHA.114.03586

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儿童期膳食盐的摄入与BP

流行病学和临床证据一致支持成人膳食盐摄入量与BP水平及高血压病相关。支持这种关系的数据在儿童期不太明确。有13项随机临床试验在健康的青少年中考察了减少膳食盐摄入量的影响，对这13项试验的荟萃分析发现这种方法可小幅（但有统计学意义）降低BP。该荟萃分析作者最近又进行了一项横断面研究，以量化伦敦南部地区儿童的膳食盐摄入量。该研究对健康儿童进行了分层，分为3个年龄组：5～6岁组、8~9岁组和13~17岁的青少年组。通过综合24小时的尿钠排泄和详细准确的24小时食物日记计算盐的摄入量。在340名儿童中收集到了有效的24小时尿液，盐的平均摄入量（随着年龄而增加），在5~6岁组为3.75 g/d，在8~9岁组为4.72 g/d，在青少年组为7.44 g/d。有66%的5~6岁儿童、73%的8~9岁组儿童和73%的青少年组儿童的盐摄入量大于世界卫生组织推荐的每日最高盐摄入量。通过分析膳食质量确定膳食中盐的主要来源为加工食品。根据对NHANES研究最新数据的分析，美国儿童的钠摄入量也为相似的结果。平均每日的钠摄入量，6-10岁的儿童为2903 mg，11-13岁儿童为3194 mg，青少年（14~18岁）为3672 mg。膳食中钠的主要来源为加工食品和快餐食品。

上面提到的流行病学研究证明，儿童期超重和肥胖可解释很多（但非全部）的儿童BP水平增高。似乎还有别的因素在促进儿童的BP增高，现有证据表明盐的摄入也可促进儿童的BP增高。最近有两份报告进一步阐明了高盐摄入对儿童BP的影响。Yang等[15]考察了最新的NHANES研究2003~2008年的数据，以确定在8~18岁的儿童中膳食钠摄入量是否与BP水平相关。研究样本包括6235名儿童，其中37%的BMI>第85百分位数（表示超重或肥胖）。根据对每日24小时膳食回顾的分析，估计的平均钠摄入量为3.89 g/d。总体而言，每人1000 mg/d的钠摄入量与收缩压增高约1.0 mmHg相关。然而，在超重/肥胖的儿童中，每人摄入1000 mg/d的钠，收缩压增高1.5 mmHg。随后研究人员根据钠摄入量的四分位数对儿童进行分层。对于整个样本，钠摄入量四分位数最高和最低的儿童相比发生高血压前期和高血压风险校正后的比值比为2.0 (95%可信区间，0.95~4.1; P=0.062)。在超重/肥胖的儿童中，钠摄入量四分位数最高的儿童发生高血压前期/高血压的风险校正后的比值比增至3.5 (95%可信区间，1.2~9.2; P=0.013)。这些研究结果在Rosner等[16]的研究中得到了进一步延伸。如前所述，在NHANES研究1988~2008年的数据中分析了儿童BP的变化。
趋势和危险因素，证明这个时期的儿童BP显著增高。对相关危险因素的分析确定了在8-17岁的儿童中，BMI，腰围和膳食钠摄入量分别与高血压前期/高血压的发生独立相关。总之，这些数据表明，高钠摄入量对BP的影响在超重或肥胖的儿童中增大。

血清尿酸水平与高血压相关，这在成人中很常见，现在有报道称在儿童期也可见到。在一个要进行高血压评估的儿童样本中，Feig和Johnson报告称原发性高血压儿童的平均血清尿酸水平显著高于患有继发性高血压或白大衣高血压的儿童。后来的一些对高血压儿童的临床研究也观察到这样的结果。尿酸的影响并不仅限于高血压，因为Bogalusa心脏研究的数据表明儿童期尿酸水平与儿童期BP及后来的成年期BP显著相关。一项旨在确定在患有1级高血压的青少年中降低尿酸能否降低BP的随机安慰剂对照研究的报告进一步证明尿酸对年少者的BP有独立的影响。这项研究中，宜别嘌呤醇200 mg每日两次治疗4周导致BP显著下降。尿酸影响BP增高（尤其是年少者）的机制目前尚不清楚。正如Feig等所综述的那样，一种似乎合理的机制途径是高果糖摄入的代谢导致。这种理念得到了实验及临床研究的支持，这些研究证实高果糖摄入与尿酸水平升高及代谢综合征的其他组成有关。因此，大量摄入用果糖加甜的加工食品（尤其是肥胖儿童）也可能促进年少者的BP水平增高。

这些报告阐明了原发性高血压的早期阶段始于儿童期。年少者的BP水平逐渐增高主要是因为儿童期肥胖伴长期的饮食改变，包括盐和可能的果糖暴露。考虑到儿童期的BMI和饮食结构迅速改变，基因似乎不太可能在儿童BP水平增高中发挥显著的作用。然而，最近Xi等的研究报告增加了对儿童期肥胖相关高血压的认识。研究人员在一项旨在考察与高血压相关的基因变异的病例对照研究中，对参加北京儿童和青少年代谢综合征研究的610名高血压儿童和2458名高血压正常儿童进行了基因分型。根据既往的对成人高血压的全基因组相关研究，选定6种单核苷酸多态性（single nucleotide polymorphisms，SNPs）进行研究。发现在体重正常的儿童中，SNPs与BP无显著相关关系，无论其BP情况如何。在肥胖儿童中，有3种SNPs与收缩压较高显著相关。有4种SNPs与肥胖儿童的高血压显著相关。因此，研究者们确定了中国儿童的BP水平及高血压与高血压易感基因位点显著相关，但这种相关性仅见于肥胖儿童。令人吃惊的是，有报道4种与肥胖儿童的高血压相关的SNPs有3种与肾脏的钠调节有关。这种基因研究将有关肾脏钠调节的SNPs与2种环境暴露（肥胖与盐的摄入）联系了起来。

出生体重及宫内因素对儿童期BP的影响

胎儿发育过程中的某些不良宫内暴露可为以后发生慢性疾病埋下伏笔，该理论是一个令人感兴趣的现实话题。流行病学研究将低出生体重与成年后的不良转归联系了起来。实验研究也提出了似乎合理的机制途径。然而，多项儿童临床研究的报告却不一致。最近的报告描述了产前可能遭受的，会对后来的BP和其他儿童期代谢危险因素产生影响的应激源。Fraser等进行了一项研究，以确定母亲在妊娠期间发生的高血压疾病，包括先兆子病和妊娠高血压，是否与她们后代在青春期的BP和代谢危险因素相关。他们对埃文亲朋组纵向研究中母亲—后代进行了研究，测量了后代在17岁时的BP和代谢指标。当与妊娠期间血压正常的产妇的后代相比，妊娠期间发生先兆子病和妊娠高血压产妇的后代在胰岛素、血糖或血脂方面的均无差异。不过，妊娠期间发生在这两种高血压疾病的产妇后代BP明显较高。在校正了潜在的混杂因素之后，他们的BP仍明显较高，提示这种相关性可能是由基因或家族性危险因素导致的。另一个对埃文纵向研究队列数据的二次分析考察了不同生长期对10岁时BP水平的相对贡献，发现出生体重与收缩压负相关。在随后的儿童生长期间，所有的生长发育指标，包括体重、身高和体重身高比（一种肥胖指标），均与收缩压正相关。研究者们认为，在儿童生长发育早期发生过度肥胖是一种可改变的对后来BP的决定因素。另一项研究在下一代研究队列的6岁儿童中考察了母亲及父亲肥胖对儿童心血管危险因素的影响。研究者们报告，妊娠期间母亲和父亲的BMI较高均与后代儿童期的BMI、腹部脂肪量、收缩压和胰岛素水平较高，以及高密度脂蛋白胆固醇的水平较低相关。与母亲BMI的相关性强于与父亲BMI的相关性。尽管伴有无孕期肥胖的母亲所生后代的出生体重似乎没有差异，但研究者们认为这些结果可能表明，母亲孕期的BMI可通过宫内的直接机制影响后代后的心血管代谢性健康情况。这些报告基于对相对较大的前瞻性队列研究数据的二次分析，论述了母亲情况、出生指标和儿童心血管风险情况之间的关系。Wolfenstetter等在研究中采用了另一种方法，评估低出
生体重儿童的心血管节律性（间接估计交感神经系统活性）是否改变，研究者们通过24小时动态血压监测观察了低出生体重的健康儿童（平均年龄，8岁）与年龄及性别匹配的对照儿童。低出生体重儿童的24小时，白天及夜间BP水平均高于对照组。两组间通过傅立叶分析计算的BP节律性存在差异，在低出生体重儿童中发现其血压的昼夜节律和日间节律变弱数种独特的观察表明低出生体重儿童的心血管调节可能在宫内程序化阶段发生了细微的变化。

上述报告的结果是基于对现有队列或研究（选择有或或无出生体重低的儿童）的数据的分析。从新生儿期开始对正常妊娠出生的孩子进行前瞻性研究的数量有限。Lurbe等[13]进行了一项规模较大但又很严谨的前瞻性研究。研究对象为一组健康的足月新生儿样本，根据出生体重进行分层，分为体重小于胎龄（SGA），相当或大于胎龄。出生后1天和3天及出生后第2天及第6天检测BP与出生体重相关。随后又在6个月、1岁时检测BP和生长发育指标。在5岁时进行的检查中，获取了一份血液样本，检测代谢标志，包括血糖、胰岛素和血压。在各次检测的间隔内，每个出生体重组的体重增加量相似。在后来的检查中，SGA婴儿的体重仍然小于，大干以上胎龄的体重仍然最大。6个月后，体重和体重增加量均与出生体重相关，而出生体重与BP水平不相关。当根据当时的体重情况对出生体重组做进一步的分层时，5岁时的代谢指标出现了有趣的结果。在5岁时变重的所有婴儿的空腹胰岛素水平均较高，而SGA组最高。然而，动态模型评价指标——估计的胰岛素抵抗，整个SGA组较高，无论在5岁时的相对体重情况如何，除了对胰岛素抵抗，与其他出生体重组相比，SGA组的高密度脂蛋白胆固醇水平低，尿素水平较高。这些结果表明，与低出生体重有关的宫内因素可能诱导了对对胰岛素抵抗的代谢紊乱期，相对胰岛素抵抗持续存在，至少在幼年期如此，无论其后来的体重状况如何。代谢指标还表明出现了一些细微的代谢综合征的特征。BP升高有可能在以后作为胰岛素抵抗或代谢综合征的后果出现。

一些实验研究考察了几种潜在的机制，以解释围产期程序化，或宫内环境对以后的健康或慢性疾病的影响。为应对宫内营养不良或其他应激，可发生多种器官大小改变，神经内分泌分泌或涉及的表观遗传修饰的其他改变。表观遗传学改变表明通过DNA甲基化、组蛋白修饰后修饰、核受体修饰和microRNAs发生了DNA修饰，而DNA序列无变化[32,33]。观察表观遗传修饰和儿童期临床转归的临床研究数量有限。最近一个例子是Breton等[34]报告了一项将表观遗传策略应用于年轻人群心血管病理生理学的研究。这些研究者们检测了一氧化氮合成酶的mRNA甲基化，确定儿童一氧化氮合成酶1DNA甲基化百分比与颈动脉内膜-中层厚度相关。需要进行更多从儿童期开始，运用相似分子策略的研究来讨论从宫内经历和表观遗传修饰至演化出慢性疾病标志物的途径。

**儿童期BP与TOD**

美国预防服务特别工作组（US Preventive Services Task Force，USPSTF）最近公布了对在儿童和青少年中筛查高血压的推荐声明，儿童高血压专家中引起强烈反响[35]。基于证据审查，USPSTF指出，“目前的证据尚不足以评估在无症状的儿童和青少年中筛查原发性高血压，以及预防相关的儿童期和成年期发生心血管疾病的利与弊的平衡。”正如Urbina等[36]在回应中所总结的那样，USPSTF提出了8个关键问题，并进行了一项循证的综述，回答这些问题。在对6435篇相关论文的文献综述中，只有35篇符合USPSTF的证据标准，这些研究都是大规模的，研究时间相对较短的临床随机对照试验。所有基于观察性研究的报告均被排除，包括证明儿童期BP升高与青年期发生高血压显著相关和有青年期发生TOD证据的前瞻性队列研究。描述高血压儿童发生TOD的横断面研究也不予考虑。USPSTF不予考虑的考虑，尤其是儿童期发生与高血压相关的TOD，表明儿童高血压研究取得了实质进展。

过去10年中的一些报告显示，高血压儿童中可以检测到TOD，TOD与其他心血管及代谢的危险因素相关。有研究论述了在BP轻度升高且未经治疗的青少年中，在通过超声心动图检测LVM时发现左心室肥厚[37,38]。根据儿童的LVM与BP水平相关的证据，由国家心肺血液研究所资助的关于儿童和青少年BP升高的第四次报告[39]建议在确诊高血压的儿童中评估TOD。自2004年报告公布以来，又出现了更多横向研究的数据，证实看在年少者中可检测到TOD[40,41]且TOD不仅限于LVM增加。当与血压正常的儿童相比时，有报道称，在BP升高的儿童，以及在患有糖尿病和家族性高胆固醇血症的儿童中可检测到cIMT（一种成人临床前动脉粥样硬化的替代标志物）增加[42,43]。动脉僵硬度增加或失去弹性（一种通常与衰老相关的改变）也可在高血压和其他与心血管疾病有关
的疾病（包括肥胖、糖尿病和血脂异常）的儿童患者中检测到。视网膜小动脉缩窄，一种明确的成人高血压的后果，最近也有人在BP升高的儿童中进行了论述。患有高血压的成人发生认知功能障碍的风险增高。在最近的一些研究中，Lande等检测到儿童BP升高与认知功能之间也有类似的联系。在NHANES III研究的数据和后来的小型临床研究中，检测到BP升高的儿童的执行能力水平低于年龄匹配的血压正常的儿童。关于在儿童期发生TOD的发现可能不仅限于有明确高血压的患者，因为最近的一些报道论述了高血压前期的青少年发生TOD的依据。在一个包括了2型糖尿病青少年的队列中，Urbina等报道高血压前期参与者的LVMI大于血压正常者。研究人员还发现，高血压前期参与者的脉搏波传导速度（可指示血管硬度）高于血压正常者。另一项对黑人青少年队列的研究考察了高血压时期和肥胖的联系。研究者们报告高血压前期青少年的LVMI显著高于血压正常者。那些存在高血压前期和肥胖的青年人的LVMI最高，也多存在左心室肥厚。在这项研究中，发现高血压前期和肥胖对LVMI有更大的影响。总体而言，最近有关年少者中高血压相关TOD的多份报告均证明，患有原发性高血压的儿童存在血管病变。最近在高血压前期的青少年中检测到左心室肥厚和血管僵硬的一些报告均强烈建议，导致TOD发生风险增加的血压水平可能低于第95百分位数，而后者目前是对于儿童高血压的定义。

### 总结

流行病学报告显示儿童期BP水平升高，高血压发生率增加，这主要是（但不完全是）由同期儿童肥胖率升高所致。据估计，目前约有10%的青少年患有高血压或处于高血压前期。除了肥胖，发现膳食盐摄入量和腰围（一种内脏肥胖的标志物）也分别与儿童和青少年的BP升高独立相关。城市儿童的膳食盐摄入量远高于推荐的水平，这主要是因为食用加工食品和快餐食品。儿童期暴露，如应激、盐和果糖，以及生活方式，包括食物来源、睡眠模式和体力活动减少，均可能在肥胖与BP升高相关中发挥作用。此外，逐渐增多的临床和转化医学的证据证明宫内暴露因素改变可影响胎儿的发育，这对以后心血管及代谢功能持久的影响，即使是在妊娠其他方面正常的母亲所生的儿童中也可检测到这些影响。

由于缺乏可能将来发生心血管事件的风险升高与BP水平联系起来的转归数据，故儿童高血压是根据统计学定义的（BP≥第95百分位数）。因此，目前认为原发性高血压是以后在成年期发生高血压的一个危险因素。TOD的中间标志物，包括心肌肥厚、血管僵硬和iHMT增加，均可在患有原发性高血压的青年中检测到。有证据表明，在高血压的早期阶段，甚至高血压前期即存在血管损伤，这就要求必须考虑当前的儿童高血压定义。通过进一步研究TOD和除BP升高以外的其他危险因素，有可能将基于统计学定义的儿童高血压改为以循证为基础的定义。

防止或减少儿童期肥胖会对减少明确的BP水平升高及儿童期BP升高的发生率有实质性的益处。控制超重和肥胖儿童的体重，以及改变饮食结构和增加体力活动，均对降低儿童期的BP水平有益，要预防儿童期肥胖，降低BP升高的风险，需要进行多层次的干预，包括公共卫生，卫生政策，并注意食品的供应，以促进进行必要的生活方式改变，预防和减少儿童期肥胖。

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