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The Childhood Role in Development of Primary Hypertension

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Key words: Blood Pressure, Hypertension, Children, Adolescents, Obesity, Sodium

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Abstract:

Primary hypertension is not just an adult disorder. Current US population data on children and adolescents demonstrate a prevalence of elevated blood pressure (BP) and hypertension combined of over 10%. Recent reports from prospective cohort studies describe an association of high BP in childhood with hypertension in young adulthood. Excess adiposity is strongly associated with higher BP in childhood and increases risk for hypertension in adulthood. In

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addition to overweight/obesity, other exposures that raise the risk for high BP include low birthweight, dietary sodium, and stress. Using intermediate markers of cardiovascular injury, studies on hypertensive children report findings of cardiac hypertrophy, vascular stiffness, and early atherosclerotic changes. Impaired cognitive function has also been demonstrated in hypertensive children. Recent advances in clinical and translational research support the concept that the evolution of primary hypertension begins in childhood.

Introduction:

Reports from clinical and translational studies on blood pressure (BP) and hypertension in childhood over the past decade provide new insights on the evolution of primary hypertension beginning in the young. Hypertension in children and adolescents has traditionally been defined statistically as $\geq 95^{\text{th}}$ percentile of the sex, age, and height adjusted normal BP distribution. With this definition as a framework, clinical studies that use repeated measurements to confirm a diagnosis of hypertension indicate that the prevalence of hypertension in childhood is approximately 3.5% and the prevalence of prehypertension is approximately 3.5% with higher rates in adolescence.^{1,2} Many studies report findings that fill gaps in knowledge on childhood hypertension, including life-course trends in BP levels and associated risk factors in youth, exposures that heighten risk for elevated BP in children and adolescents, and evidence of target organ damage associated with childhood hypertension. This review will discuss key areas of advancement in knowledge on childhood hypertension. The advancements in clinical and translational research provide a platform for further considerations regarding effective strategies on management and prevention of childhood hypertension with subsequent reduction of premature cardiovascular disease.

Blood Pressure Trends in Childhood:

The childhood obesity epidemic has made a substantial impact on the prevalence of elevated blood pressure and hypertension in children and adolescents. Several reports on cross-sectional studies confirmed a higher prevalence of hypertension among obese children and adolescents.^{1,3} Studies that compared childhood BP levels from data in serial periods of the National Health and Nutrition Surveys (NHANES) also report a progressive increase in childhood blood pressure levels. While there are variations according to race, the trend of increasing BP level is largely parallel with the trend of increasing adiposity.⁴⁻⁶ The effect of excess adiposity on BP can even be detected in early childhood among children age 2 to 4 years of age.³ In an analysis of data on the relationship of BP with BMI in a cohort of children Tu et al.⁷ demonstrated a stable relationship of BP with BMI up to the 85th percentile of BMI. As

BMI exceeds the 85th percentile there is a marked increase in risk for elevated BP in children and adolescents. Thus, the risk for elevated BP in children is not limited to obesity (BMI \geq 95th percentile) but increases with overweight status (BMI = 85th to 94th percentile).

In adults, the association of hypertension with increased risk for adverse cardiovascular and cerebral-vascular outcomes have been clearly established. There are no outcome data on the BP level in childhood that increases risk for adverse events later in adulthood. Therefore, hypertension in children and adolescents has been defined statistically as \geq 95th percentile.⁸ The database from which the normative childhood BP distributions are determined and delineate the BP levels at the 95th percentile in boys and girls according to age and height percentile, does include overweight and obese children. Rosner et al.⁹ conducted a re-analysis of this database, but included only children and adolescents with normal BMI (<85th percentile). The results demonstrated that the sex, age, and height adjusted BP levels at the 95th percentile were lower than BP levels in the existing tables of the Fourth Report on evaluation and management of hypertension in childhood published in 2004.⁸ These results also became a key consideration in the subsequent update of the clinical guidelines on pediatric hypertension.

The childhood obesity epidemic with parallel increase in prevalence of elevated BP predict heightened risk for premature cardiovascular disease in adulthood. New insights regarding this concern have been gained from prospective studies on cohorts that enrolled participants in childhood and conducted periodic re-examinations into young adulthood. The International Childhood Cardiovascular Cohort Consortium is comprised of four prospective cohort studies that together include data on >6,000 individuals, collected prospectively from childhood to young adulthood. An analysis of data on BMI status from childhood to adulthood was conducted to determine the risk of excess adiposity for hypertension and other metabolic parameters in adulthood. Compared to individuals with normal BMI status in both childhood and as adults, individuals with consistently high BMI in both childhood and adulthood had an increased risk of hypertension with relative risk (RR) 2.7 [2.2-3.3]. With additional metabolic risk factors in childhood the risk increased. However, individuals with high BMI in childhood but normal BMI in adulthood had a RR similar to those with consistently normal BMI in both childhood and adulthood.¹⁰ A similar analysis of combined data was conducted by this consortium to determine the effects of child and adult elevated BP on subclinical atherosclerosis in adulthood, ascertained by carotid intimal thickness (cIMT) in 4210 participants. Elevated BP in childhood was defined as systolic or diastolic BP \geq 90th percentile and in adulthood as >120/80 mm Hg or self-reported anti-hypertension medication use. Individuals with persistently child and adult elevated BP and individuals with normal childhood BP, but elevated adult BP had increased risk of high cIMT; RR 1.82 [1.47-2.38] and 1.57 [1.22-2.02] respectively compared to individuals with normal child and adult BP. Individuals with elevated BP as children, but not as adults, did not have increased risk; 1.24 [0.92-1.67].¹¹ Two other recent reports, on prospective cohort studies, describe similar results on the heightened risk for vascular stiffness among individuals with persistent elevated BP from childhood to adulthood.

Also, among individuals with elevated BP in childhood but normal BP in adulthood, the risk for vascular stiffness is similar to those with consistently normal BP from childhood to adulthood.^{12,13}

The findings from life-course studies spanning childhood to young adulthood demonstrate the heightened risk of obesity and elevated BP in childhood on young adult hypertension and provide evidence of atherosclerotic injury in early adulthood. A similar life-course study by Ferreira et al spanning age 13 to 36 years detected greater carotid artery stiffness in adulthood among those with higher BP and greater central adiposity from adolescence to adulthood. It is notable that the effects of BP and central adiposity on carotid stiffness were statistically independent of each other. The striking finding, of these prospective cohort studies from childhood to young adulthood, is that when childhood obesity and elevated BP are reversed by adulthood the risk for abnormal measures of vascular injury are similar to individuals with normal BMI status. It is also notable that the effects of high BP and obesity appear to be statistically independent of each other.¹²

Two recent publications provide additional clarity on the progression of BP levels in childhood to elevated BP and hypertension in adulthood. Theodore et al.¹⁴ conducted an analysis of prospective data from the Dunedin Multidisciplinary Health and Development Study to identify subgroups with different risks of developing hypertension in young adulthood. BP and related risk factors were measured at age 7 years with periodic repeated measurements up to age 38 years in a cohort that included 975 individuals. Using group-based trajectory modeling, four distinct trajectory groups were identified based on BP classification at age 38 years; normal (21.8%), high-normal (43.3%), prehypertension (31.6%), and hypertensive (4.2%). The trajectory curves for systolic BP provide a distinct progression in BP level from age 7 years to age 38 years in each BP category, with clear separation of the BP groups by early adolescence. Most notable is that systolic BP levels in the normal and high normal BP groups remain under 120 mm Hg until the final measurement at age 38 years. Antecedent risk factors, detected by age 7 years, increased the risk for later hypertension and included family history of hypertension, male sex, being first born, and low birth weight. Modifiable risk factors including higher BMI and cigarette smoking resulted in increasing BP across trajectories in the higher BP groups. In a similar study, Hao et al.¹⁵ analyzed existing data in the Longitudinal Georgia Stress and Heart Study, a cohort of 683 participants examined prospectively from childhood to young adulthood. Data on left ventricular mass index (LVMI) and cIMT were available for analysis on 546 participants. These investigators identified three systolic BP trajectory groups designated as high-increasing, moderate-increasing, and low-increasing groups. By age 18 years, the high-increasing BP group had significantly greater LVMI and cIMT compared to the low-increasing group. Again, it is notable by the trajectory curves that systolic BP exceeded 120 mm Hg by age 14 years in the high-increasing group. Together these studies advance knowledge on the origins of hypertension beginning in the young. The findings also provide insights on potential cardiovascular health benefits of interventions on modifiable risk factors, including preventing or correcting childhood obesity and other related health behaviors.

Ambulatory Blood Pressure Monitoring (ABPM):

BP measurement in population studies, such as NHANES, and the cohort studies described above are obtained according to a standard and rigorous measurement protocol to ensure measurement quality. BP measurements obtained in children during a clinic setting are known to be less reliable due to variations in the conditions of measurement, inaccurate auscultation technique, and use of various automated BP instruments. Recent applications of 24-hour ABPM in children have been an advancement in confirming the clinical diagnosis of hypertension in children and adolescents. Reference normative ABPM data in childhood are now available and criteria for ambulatory hypertension have been described.¹⁶ ABPM was originally used to confirm hypertension or identify white coat hypertension, a condition in which clinic BP measurements are elevated but BP measurements outside a clinic setting are normal. ABPM has also become a powerful tool in clinical research in children as well as adolescents. Masked hypertension, a condition wherein clinic BP measurements are considered normal but BP levels outside the clinic are elevated, has been recognized in adults and is considered to be a significant risk condition for adverse cardiovascular outcomes. The first to identify masked hypertension in childhood were Lurbe et al.¹⁷ who performed 24-hour ABPM on 592 children and adolescents age 6 to 18 years of age. In this cohort of healthy children normal office BP and ambulatory hypertension, consistent with masked hypertension, was detected in 45 (7.6%) children. In a subsequent study these investigators found a progression from masked hypertension to sustained hypertension over a three-year period of 7% per year, that was largely among boys.¹⁸ Subsequent reports describe masked hypertension in children with other clinical conditions including chronic kidney disease, diabetes type 1 and type 2, solid organ transplant, and sickle cell disease.¹⁹

ABPM has also been recently utilized to develop novel insights on mechanistic pathways of primary hypertension in childhood. Based on observations of BP variability in children, Litwin et al.²⁰ investigated cardiovascular rhythms by Fourier analysis of 24-hour ABPM data in a sample of 129 hypertensive and 140 normotensive control children. They detected an increased prevalence of 12 hour rhythms in the hypertensives compared to controls (67% vs 51%, $P < 0.0001$), and the amplitudes of the 24, 8, and 6 hour rhythms were reduced in hypertensive vs control children ($P < 0.05$), findings consistent with altered BP rhythmicity in primary hypertension onset in youth and indicative of alterations in sympathetic nervous system activity. In a subsequent study by these investigators obtained data on 24-hour ABPM, left ventricular mass (LVM), CIMT, and visceral and subcutaneous adipose tissue mass (quantified by MRI) in 50 hypertensive boys before and following 12 months of antihypertensive treatment to lower BP. Following treatment, 68% of the hypertensive boys were normotensive. LVM and CIMT were decreased in 60% and 62% of the boys. There were no differences in changes in BP or heart rate rhythms between patients who did or did not achieve normal BP or regression of LVM and CIMT. However, there were rhythmicity findings related to visceral fat. A decrease in visceral fat correlated with the decrease in 24-hour mean arterial pressure and heart rate acrophases

($p < 0.05$). These results indicate that abnormal cardiovascular rhythmicity in hypertensive youth persists despite reduction in BP, suggesting that abnormal rhythmicity could be a primary abnormality or that the abnormal rhythmicity could be mediated by visceral fat.²¹

Overall, ABPM can be a clinical research tool to unravel the linkage between elevated BP, obesity, and sympathetic nervous system activity. ABPM has also become a diagnostic procedure to confirm hypertension and BP status. Guidelines for clinical application and use of ABPM and diagnostic criteria for hypertension, elevated BP, white coat hypertension, and masked hypertension have been recently updated.²² Based on the prevailing evidence, ABPM is now recommended to confirm the diagnosis of hypertension in children and adolescents in the 2017 clinical practice guidelines on hypertension in children and adolescents.²³

Risk Factors for High BP in Childhood:

Low birth weight is a recognized risk factor for development of hypertension later in life. The low birth weight hypothesis is based on the theory of fetal programming wherein adverse intrauterine exposures set the stage for chronic disease in adulthood. Epidemiological studies have identified a relationship of low birth weight with adverse outcomes in later adulthood; and experimental research has developed plausible mechanistic pathways to chronic hypertension. However, evidence of a direct link of low birthweight to elevated BP in childhood remains limited. Recent epidemiologic studies have reported an association of low birth weight with higher BP in offspring of maternal hypertensive disorders,²⁴ with accelerated growth periods in early childhood and subsequent elevated BP,²⁵ and in offspring of maternal and paternal obesity.²⁶ Another study examined a sample of healthy young children, mean age 8 years, who by history had low birth weight, to determine if low birth is associated with alterations in cardiovascular rhythmicity computed from 24-hour ABPM data. Compared to age and sex matched children with normal birth weight, the average daytime and night time BP levels were higher in the children with low birth weight. BP rhythmicity was different between the groups indicating heightened sympathetic nervous system activity in the children with low birth weight.²⁷

Prospective studies to address the risks of low birth weight on offspring of normal pregnancies that begin in the newborn period are limited. In a small, but rigorous, prospective study by Lurbe et al.²⁸ a sample of healthy full-term newborn offspring of normal pregnancies were stratified by birth weight as small (SGA), appropriate, or large for gestational age. BP at 2 days was positively associated with birth weight. Subsequent BP and growth parameters were measured at 6 months, 2 years, and 5 years. After 6 months, current weight and weight gain were positively associated with birth weight; and birth weight was not associated with BP level. At the 5-year examination, a blood sample was obtained for metabolic parameters, including glucose, insulin, and lipids; and the birth weight groups were further stratified according to

current weight (heavy, middle, small). Fasting insulin levels were higher in all infants who became heavy at age 5 years and was highest among those who were SGA. Moreover, insulin resistance estimated by the homeostatic model assessment index, was higher in the entire SGA group. In addition to relative insulin resistance, the SGA group also had lower high-density lipoprotein-cholesterol and higher uric acid levels compared to the other birth weight groups. These findings suggest that some intrauterine exposure 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. It is plausible that high BP could emerge later as a consequence of insulin resistance.

Other exposures in the extra-uterine environment can have an impact on BP levels. The strong association of high dietary sodium intake on BP levels in adults is well known. Data to support the association of sodium intake with BP levels in childhood have been less clear. An earlier report on a meta-analysis of 13 randomized clinical trials in healthy adolescents on the effects of a reduction in dietary salt intake detected a small but statistically significant effect in lowering BP.²⁹ Recent estimates of dietary salt intake among children and adolescents in the UK³⁰ and in the US³¹ are high and exceed recommended levels. Based on NHANES data, the average sodium intake of children age 6 to 10 years is 2,903 mg/d. Average sodium intake is 3,194 mg/d for ages 11 to 14 years, and for adolescents at 14 to 18 years the average sodium intake is 3,672 mg/d. There is now childhood population data that demonstrate a significant association of sodium intake on BP level and prevalence of elevated BP especially among overweight and obese children and adolescents. An analysis of NHANES 2003 to 2008 data was conducted by Yang et al.³² to determine if there is an association of dietary salt intake with BP. In a data sample that included 6235 children age 3 to 18 years, 37% had a BMI >85th percentile indicating overweight or obese status. Based on analysis of multiple 24-hour dietary recall measures, the estimated average intake of sodium was 3,890 mg/d. For the entire sample of children, each 1000 mg/d of sodium intake was associated with approximately 1.0 mm Hg increase in systolic BP. Among only overweight/obese children, each 1000 mg/d of sodium intake was associated with an increase in systolic BP of 1.5 mm Hg. All children were stratified according to quartiles of sodium intake and the prevalence of prehypertension and hypertension (high BP) combined in each quartile was determined. For the entire sample the adjusted odds ratio for high BP in the high sodium intake group compared to the low sodium intake was 2.0 (95% confidence interval; 0.95-4.1, p=0.062). For the overweight/obese participants the adjusted odds ratio for high BP in the high sodium intake group compared to low sodium intake increased to 3.5 (95% confidence interval; 1.2-9.2, p=0.013). These findings were advanced in a subsequent study by Rosner et al.⁶ An analysis of NHANES data from 1988 to 2008 was conducted to investigate trends in childhood BP levels. A progressive and significant increase in childhood BP levels were demonstrated over this time period. An analysis of risk factors associated with development of high BP determined that BMI, waist circumference, and dietary sodium intake were each independently associated with the combined prevalence of prehypertension and hypertension. The results of these two studies on NHANES data provide evidence of BP sensitivity to sodium intake among children with excess adiposity, beginning with overweight status.

Stress, especially mental stress, is known to increase BP levels in children as well as adults. In several studies, Harshfield and colleagues have investigated the role of mental stress on the concept of pressure-induced natriuresis in youth. These investigators established a rigorous protocol that includes three days of a controlled diet with moderate sodium intake (4000 mg Na) that is followed by a 5-hour procedure of 2-hour pretest rest (baseline), 1 hour competitive video game with monetary reward incentive (stress), and 2-hour post-test rest (recovery). Timed collections of urine samples are collected each hour to compute sodium excretion. These studies in healthy adolescents have identified an increase in sodium excretion that parallels the increase in BP during the stress period; They also identified some individuals who have a decrease in sodium excretion during the stress period despite a comparable or even greater increase in BP levels. In designating the different responses as “Excreter” for the increase in stress-induced pressure natriuresis or “Retainer” for the decrease in stress-induced pressure natriuresis, the investigators found a greater prevalence of Retainers among African Americans compared to Caucasians and associations with adiposity.³³⁻³⁵ These investigators recently added another dimension to their investigations on impaired stress-induced pressure natriuresis. Based on findings from laboratory experiments, urinary endothelin-1 (ET-1) excretion was added to their study protocol. Within the vascular system, ET-1 is a potent vasoconstrictor via the ET_A receptor. However, within the kidney ET-1 has diuretic and natriuretic effects presumably via ET_B receptors. In a recent publication, the investigators reported an increase in urinary ET-1 concentration from baseline to the stress period in the Excreters. Urinary ET-1 concentrations were different in the Retainers with higher levels at baseline but during stress the urinary ET1 levels decreased and remained lower during recovery.³⁶ These novel findings in youth indicate that renal ET-1 may contribute to impaired stress-induced pressure natriuresis in the young. In another related study from this group, the investigators sought to determine if there was an association of real-life stress in childhood with measures of cardiovascular injury and ET-1. In their longitudinal cohort study with multiple cardiovascular measures, including BP, PWV, and calculated peripheral resistance index, were obtained during childhood and young adulthood. At the most recent examination in later adolescence and young adulthood 221 healthy participants completed a standard questionnaire on adverse childhood experiences. The questionnaire was designed to capture stressful childhood experiences such as abuse, neglect, and various types of household dysfunction. The participants’ responses were classified as none, mild (1 adverse experience), or moderate/severe (2 or more adverse experiences). Compared to participants with no adverse experiences in childhood, those with moderate/severe adverse childhood experiences had higher diastolic BP, higher peripheral resistance, and higher PWV. There was also a difference in Plasma ET-1 levels that were related to adverse childhood experiences. Compared to those with no adverse experiences, plasma ET-1 was 18% higher in those who reported one adverse experience, and ET-1 was 24% higher among those who reported 2 or more adverse experience in childhood.³⁷ These reports advance clinical insights on the mechanisms of acute stress in childhood, that can be replicated in a laboratory, and also on the cardiovascular consequences of chronic stressful experiences in childhood.

Target Organ Damage (TOD) in Hypertensive Children:

Based on early evidence that an increase in cardiac mass could be found in hypertensive children, the National Heart Lung and Blood Institute sponsored Fourth Report on High BP in children and adolescents recommended including an evaluation for TOD in children with confirmed hypertension, including echocardiographic assessment of left ventricular mass.⁸ Since publication of that 2004 report, several publications, based on cross-sectional studies, have confirmed the frequent presence of LVH among hypertensive children and adolescents.³⁸⁻⁴⁰ Subsequent studies reported evidence of LVH in adolescents with prehypertension. In a cohort that included type 2 diabetics, Urbina et al.⁴¹ reported greater LVMI among prehypertensive adolescents compared to normotensive adolescents. In another study on a cohort of African American adolescents, the effects of prehypertension and obesity on left ventricular mass were examined. The investigators reported significantly higher LVMI among prehypertensive adolescents compared to normotensive adolescents. LVMI was highest, with significantly more LVH, among those with both prehypertension and obesity. In this study, the associations of prehypertension and obesity with LVMI were found to be independent and additive.⁴² The common finding of hypertension among obese adolescents has led to further considerations about the effect obesity on cardiac mass that can be found even in normotensive obese children and adolescents.^{43,44} Moreover, since publication of the Fourth Report in 2004, several new approaches to diagnosing and defining LVH in children and adolescents have been published, which has led to uncertainty on the most accurate method to assess cardiac mass and define LVH.⁴⁵ Due to this uncertainty, the 2017 guidelines on hypertension in children and adolescents have modified recommendations on determination of LVH in hypertensive children and adolescents.²³ A novel advancement is the development of techniques to quantify systolic and diastolic function using 3-dimensional speckle tracking echocardiography. Information on cardiac function, in addition to cardiac structure, could provide additional insights on TOD in hypertensive children and adolescents. Recent reports that applied 3-dimensional speckle tracking technique to quantify systolic and diastolic function describe alterations in hypertensive children.^{46,47} Using this advanced echocardiographic procedure, Navarini et al.⁴⁷ examined 26 hypertensive and 37 children (mean age 14.3 years) and 37 normotensive children (mean age 11.4 years). Myocardial deformation was reduced in hypertensive children compared to controls, with significantly lower global longitudinal strain, global circumferential strain, global radial strain, and global 3-dimensional strain. These findings provide evidence of impaired left ventricular relaxation and longitudinal systolic function in hypertensive children consistent with impaired diastolic and systolic function. The study is limited somewhat by a normotensive control group that was somewhat younger with lower BMI than the hypertensives. These findings need to be replicated in prospective studies and applied with repeat assessments following interventions to lower BP. However, the capacity to pair structural and functional cardiac measures are likely to improve assessment of cardiac TOD in hypertensive children.

Cardiovascular changes in hypertensive children are not limited to the heart. Increased arterial stiffness, a vascular change generally associated with aging, has been detected in pediatric patients with high BP, as well as other conditions associated with cardiovascular disease including obesity, diabetes and dyslipidemia.^{39,48} Compared to normotensive children, measurements of cIMT, a surrogate marker for preclinical

atherosclerosis in adults, are reported to be higher in children with elevated BP, as well as in children with diabetes and familial hypercholesterolemia.^{49,50} BP associated vascular changes have also been detected in adolescents with prehypertension. As reported by Urbina et al.,⁴¹ in a cohort of adolescents, PWV and cIMT were significantly higher among hypertensives compared to normotensive participants, and these vascular measures were also significantly higher in prehypertensive participants compared to normotensives. These findings indicate that the risk for cardiovascular TOD in adolescence may increase at BP levels below the current definition of hypertension in childhood.

Adults with hypertension are at heightened risk of developing impaired cognitive function that can progress to dementia. Recent reports by Lande et al.,^{51,52} describe cognitive function alterations in hypertensive adolescents. The investigators examined 75 untreated children with primary hypertension, age 10-19 years of age, and 75 frequency matched normotensive control children. BP status was confirmed by ABPM in all participants, who then completed a panel of tests to ascertain cognitive function, including tests of general intelligence, attention, memory, executive function, and processing speed. There was no difference in hypertension and control groups in age, sex, maternal education, income, race, ethnicity, obesity, anxiety, or depression. The hypertensive group demonstrated significantly lower performance on neurocognitive test scores compared with normotensive controls on measures of memory, attention, and executive function. In a subsequent study, the investigators sought to determine if there would be an improvement in cognitive function test performance in the hypertensive children following antihypertensive therapy. Following 12 months of standard recommended antihypertensive treatment, BP, ABPM, and cognitive function testing was repeated in both hypertensives (N=55) and controls (N=66). Mean BP levels in the hypertensive group were lower following the 12-month treatment period. The hypertensives improved their cognitive test scores, but the normotensives also improved their scores. With further analyses, it was determined that the hypertensive adolescents who achieved BP control improved their cognitive test scores comparable to the normotensive controls; whereas the hypertensives who did not improve BP control had no improvement in cognitive function scores. These findings provide evidence that the brain is a site of TOD even in hypertensive youth, and indicate that the changes in brain function are potentially reversible with BP reduction.

Guidelines on Evaluation and Management of Childhood Hypertension:

Based upon new findings on high BP in children and adolescents, some of which has been discussed above, the US guidelines on evaluation and management of hypertension in children and adolescents were recently updated.²³ Although, primary care clinicians are now measuring BP in children, it has been apparent that elevated BP levels in children are frequently not recognized, and BP measurement techniques are variable. The new guidelines provide details on correct BP measurement in children and include a simplified BP table for screening. Due to the established association of childhood overweight and obesity with abnormal BP, the BP tables, designating the 90th and 95th percentiles for BP by sex, age, and height are now

based on normal weight children only. The definition of hypertension remains the same for children <13 years of age as BP $\geq 95^{\text{th}}$ percentile, and the definition of elevated BP (previously designated prehypertension) is BP $\geq 90^{\text{th}}$ percentile but <95th percentile. However, for children ≥ 13 years of age, hypertension is defined numerically as $\geq 130/80$ mm Hg; and elevated BP is defined as $\geq 120/<80$ to $<130/80$ mm Hg. The BP levels that define hypertension and elevated BP are concurrent with the updated hypertension guidelines for adults.⁵³ Additional modifications were added including a recommendation of ABPM to confirm hypertension and identify white coat or masked hypertension. An update of the European guidelines on childhood hypertension management, published in 2016, preceded the US guideline update, and the two guidelines are similar in scope.⁵⁴ The European guideline use the same definition of hypertension (and abnormal BP) in children <16 years of age and continue to use the BP tables from the Fourth Report.⁸ These guidelines also adapted the adult definition of hypertension for adolescents. At age ≥ 16 hypertension is defined as BP $\geq 140/90$ mm Hg, and “high normal” is defined as 130/80 to 139/89 mm Hg. The main difference in these two recent guidelines is that adolescent age and BP levels that define hypertension are higher in the European guidelines. The European guidelines also provide additional detail on newer non-invasive techniques to characterize cardiovascular phenotypes associated with abnormal BP and other risk factors. The history of clinical guidelines on management of hypertension in children, as well as adults, is that future updates will be forthcoming as new evidence emerges to support optimal management of abnormal BP in youth.

Summary:

Publications in the past decade provide new insights on the early phase of hypertension beginning in childhood. Prospective cohort studies with repeated examinations of BP and related risk factors from childhood to early adulthood describe BP trajectories that link higher BP in childhood with hypertension and elevated BP in adulthood. These studies identify evidence of TOD in adulthood that are associated with higher BP in childhood. In addition to low birth weight, a marker of likely adverse intrauterine exposure, other childhood exposures including excess adiposity, high dietary salt, and even chronic stress contribute to higher BP in childhood. Emerging findings on BP associated TOD in children with hypertension indicate that the high blood pressure can be more than increased risk for subsequent cardiovascular disease, but indicate that hypertension related cardiovascular injury is already underway. A current research challenge is to determine the BP level or BP percentile in childhood that increases risk for TOD. More optimistic are the findings that when childhood risk factors of elevated BP and obesity are normalized by adulthood the risk for cardiovascular disease becomes comparable to normotensive adults. Overall, the recent advances in pediatric hypertension demonstrate that the early phase of primary hypertension can begin in childhood.

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References:

1. McNiece KL, Poffenbarger TS, Turner JL, Franco KD, Sorof JM, Portman RJ. Prevalence of hypertension and pre-hypertension among adolescents. *The Journal of pediatrics* 2007;150:640-4, 4 e1.
2. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *Jama* 2007;298:874-9.
3. Falkner B, Gidding SS, Ramirez-Garnica G, Wiltrout SA, West D, Rappaport EB. The relationship of body mass index and blood pressure in primary care pediatric patients. *The Journal of pediatrics* 2006;148:195-200.
4. Munter P H, J, Cutler JA, Wildman RP, Welton PK. Trends in blood pressure among children and adolescents. *Jama* 2004;291:2107-13.
5. Din-Dzietham R, Liu Y, Bielo MV, Shamsa F. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation* 2007;116:1488-96.
6. Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988-2008. *Hypertension* 2013;62:247-54.
7. Tu W, Eckert GJ, DiMeglio LA, Yu Z, Jung J, Pratt JH. Intensified effect of adiposity on blood pressure in overweight and obese children. *Hypertension* 2011;58:818-24.
8. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114:555-76.
9. Rosner B, Cook N, Portman R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children: some methodological issues. *American journal of epidemiology* 2008;167:653-66.
10. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *The New England journal of medicine* 2011;365:1876-85.
11. Juhola J, Magnussen CG, Berenson GS, et al. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: the International Childhood Cardiovascular Cohort Consortium. *Circulation* 2013;128:217-24.

12. Ferreira I, van de Laar RJ, Prins MH, Twisk JW, Stehouwer CD. Carotid stiffness in young adults: a life-course analysis of its early determinants: the Amsterdam Growth and Health Longitudinal Study. *Hypertension* 2012;59:54-61.
13. Aatola H, Hutri-Kahonen N, Juonala M, et al. Lifetime risk factors and arterial pulse wave velocity in adulthood: the cardiovascular risk in young Finns study. *Hypertension* 2010;55:806-11.
14. Theodore RF, Broadbent J, Nagin D, et al. Childhood to Early-Midlife Systolic Blood Pressure Trajectories: Early-Life Predictors, Effect Modifiers, and Adult Cardiovascular Outcomes. *Hypertension* 2015;66:1108-15.
15. Hao G, Wang X, Treiber FA, Harshfield G, Kapuku G, Su S. Blood Pressure Trajectories From Childhood to Young Adulthood Associated With Cardiovascular Risk: Results From the 23-Year Longitudinal Georgia Stress and Heart Study. *Hypertension* 2017;69:435-42.
16. Wuhl E, Witte K, Soergel M, Mehls O, Schaefer F. . Distribution of 24-hour ambulatory blood pressure in children: normalized reference values and role of body dimensions. *Journal of Hypertension* 2002;20:1995-2007.
17. Lurbe E, Torro I, Alvarez V, et al. Prevalence, persistence, and clinical significance of masked hypertension in youth. *Hypertension* 2005;45:493-8.
18. Lurbe E, Thijs L, Torro MI, Alvarez J, Staessen JA, Redon J. Sexual dimorphism in the transition from masked to sustained hypertension in healthy youths. *Hypertension* 2013;62:410-4.
19. Macumber I. Ambulatory Blood Pressure Monitoring in Children and Adolescents: a Review of Recent Literature and New Guidelines. *Current hypertension reports* 2017;19:96.
20. Litwin M, Simonetti GD, Niemirska A, et al. Altered cardiovascular rhythmicity in children with white coat and ambulatory hypertension. *Pediatric research* 2010;67:419-23.
21. Niemirska A, Litwin M, Feber J, Jurkiewicz E. Blood pressure rhythmicity and visceral fat in children with hypertension. *Hypertension* 2013;62:782-8.
22. Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. *Hypertension* 2014;63:1116-35.
23. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics* 2017;140.
24. Fraser A, Nelson SM, Macdonald-Wallis C, Sattar N, Lawlor DA. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. *Hypertension* 2013;62:614-20.
25. Jones A, Charakida M, Falaschetti E, et al. Adipose and height growth through childhood and blood pressure status in a large prospective cohort study. *Hypertension* 2012;59:919-25.

26. Gaillard R, Steegers EA, Duijts L, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. *Hypertension* 2014;63:683-91.
27. Wolfenstetter A, Simonetti GD, Poschl J, Schaefer F, Wuhl E. Altered cardiovascular rhythmicity in children born small for gestational age. *Hypertension* 2012;60:865-70.
28. Lurbe E G-VC, Torro MI, Aguilar F, Redon J. . Associations of birth weight and postnatal weight gain with cardiometabolic risk parameters at five years of age. . *Hypertension* 2014;63:1326-32.
29. He FJ, MacGregor GA. Importance of salt in determining blood pressure in children: meta-analysis of controlled trials. *Hypertension* 2006;48:861-9.
30. Marrero NM, He FJ, Whincup P, Macgregor GA. Salt intake of children and adolescents in South London: consumption levels and dietary sources. *Hypertension* 2014;63:1026-32.
31. Cogswell ME Yuan K, Gunn JP, Gillespie C, et al. Sodium intake among US school aged children 2009-2010. *MMWR* 2014;63:789-97.
32. Yang Q, Zhang Z, Kuklina EV, et al. Sodium intake and blood pressure among US children and adolescents. *Pediatrics* 2012;130:611-9.
33. Harshfield GA, Wilson ME, Hanevold C, et al. Impaired stress-induced pressure natriuresis increases cardiovascularload in African American youths. *American journal of hypertension* 2002;15:903-6.
34. Harshfield GA, Wilson ME, McLeod K, et al. Adiposity is related to gender differences in impaired stress-induced pressure natriuresis. *Hypertension* 2003;42:1082-6.
35. Ge D, Su S, Zhu H, et al. Stress-induced sodium excretion: a new intermediate phenotype to study the early genetic etiology of hypertension? *Hypertension* 2009;53:262-9.
36. Mathur S, Pollock JS, Mathur S, Harshfield GA, Pollock DM. Relation of urinary endothelin-1 to stress-induced pressure natriuresis in healthy adolescents. *J Am Soc Hypertens* 2018;12:34-41.
37. Su S, Wang X, Kapuku GK, et al. Adverse childhood experiences are associated with detrimental hemodynamics and elevated circulating endothelin-1 in adolescents and young adults. *Hypertension* 2014;64:201-7.
38. Hanevold C, Waller J, Daniels S, Portman R, Sorof J. The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. *Pediatrics* 2004;113:328-33.
39. Litwin M, Niemirska A, Sladowska J, et al. Left ventricular hypertrophy and arterial wall thickening in children with essential hypertension. *Pediatric nephrology (Berlin, Germany)* 2006;21:811-9.

40. Brady TM, Fivush B, Flynn JT, Parekh R. Ability of blood pressure to predict left ventricular hypertrophy in children with primary hypertension. *The Journal of pediatrics* 2008;152:73-8, 8 e1.
41. Urbina EM KP, McCoy C, Daniels SR, Kimball TR, Dolan LM. Cardiac and vascular consequences of pre-hypertension in youth. *Journal of clinical hypertension (Greenwich, Conn)* 2011;13:332-42.
42. Falkner B, DeLoach S, Keith SW, Gidding SS. High risk blood pressure and obesity increase the risk for left ventricular hypertrophy in African-American adolescents. *The Journal of pediatrics* 2013;162:94-100.
43. Crowley DI, Houry PR, Urbina EM, Ippisch HM, Kimball TR. Cardiovascular impact of the pediatric obesity epidemic: higher left ventricular mass is related to higher body mass index. *The Journal of pediatrics* 2011;158:709-14 e1.
44. Brady TM. The Role of Obesity in the Development of Left Ventricular Hypertrophy Among Children and Adolescents. *Current hypertension reports* 2016;18:3.
45. Sethna CB, Leisman DE. Left Ventricular Hypertrophy in Children with Hypertension: in Search of a Definition. *Current hypertension reports* 2016;18:65.
46. Agu NC, McNiece Redwine K, Bell C, et al. Detection of early diastolic alterations by tissue Doppler imaging in untreated childhood-onset essential hypertension. *J Am Soc Hypertens* 2014;8:303-11.
47. Navarini S, Bellsham-Revell H, Chubb H, Gu H, Sinha MD, Simpson JM. Myocardial Deformation Measured by 3-Dimensional Speckle Tracking in Children and Adolescents With Systemic Arterial Hypertension. *Hypertension* 2017;70:1142-7.
48. Whincup PH, Gilg JA, Donald AE, et al. Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. *Circulation* 2005;112:1789-97.
49. Lande MB, Carson NL, Roy J, Meagher CC. Effects of childhood primary hypertension on carotid intima media thickness: a matched controlled study. *Hypertension* 2006;48:40-4.
50. Meyer AA, Kundt G, Steiner M, Schuff-Werner P, Kienast W. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. *Pediatrics* 2006;117:1560-7.
51. Lande MB, Batsky DL, Kupferman JC, et al. Neurocognitive Function in Children with Primary Hypertension. *The Journal of pediatrics* 2017;180:148-55 e1.
52. Lande MB, Batsky DL, Kupferman JC, et al. Neurocognitive Function in Children with Primary Hypertension after Initiation of Antihypertensive Therapy. *The Journal of pediatrics* 2018;195:85-94 e1.
53. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection,

Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017.

54. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. Journal of hypertension 2016;34:1887-920.

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