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Review Article

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Blood Pressure Trajectories from Childhood to Adolescence in Pediatric Hypertension

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ABSTRACT

It has been known for a long time that elevated blood pressure (BP) in the young may persist and progress into adult hypertension (HTN). Multiple studies have revealed the predicted BP trajectory lines starting from childhood and related them to later cardiovascular (CV) risks in adulthood. As a small baby grows into a tall adult, BP will also naturally increase. Among early-life predictors of adult HTN, birth history, such as prematurity, and low birth weight have been popular subjects in research on pediatric HTN, because body size at birth has been reported to be inversely related to the risk of adulthood HTN. The hypothesis of HTN in prematurely born adolescents has been postulated as a physiological predisposition to postnatal excessive weight gain. Current body weight is a well-known independent predictor of HTN in children, and some studies showed that children demonstrating upward crossing of their weight percentiles while growing into adolescents have significantly increased risk for elevated BP later in life. Recently, reports focused on the adverse effect of excessive catch-up growth in this population are gradually drawing attention. Accordingly, children born prematurely or with intrauterine growth restriction who show rapid changes in their weight percentile should be under surveillance with BP monitoring. Prevention of childhood obesity, along with special care for premature infants or infants small for their gestational age, by providing healthy nutritional guidelines should be cardinal strategies for the prevention of adult HTN and CV risks later in life.

Keywords: Blood pressure; Hypertension; Children; Low birth weight; Infant, premature

INTRODUCTION

It has been recognized for a long time that elevated blood pressure (BP) in the young may persist and progress into adult hypertension (HTN).[1)2)] Longitudinal cohort studies also revealed the predicted BP trajectory lines, starting from childhood, and cardiovascular (CV) risks in adulthood.[3-5)] Consistent with a well-known study reporting significant outcome benefits from lifelong control of systolic BP <120/80 mmHg in adults, the ultimate goal of prevention of HTN is reducing related CV morbidity later in life.[6)] With extended life expectancy and improved quality of life, more strictly controlled BP in younger patients with HTN is recommended. As the individual lifestyles of adulthood are formed by the body habitus from young childhood, it is worthy to perform in-depth review of BP of a much

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younger population, including young adolescents, children, infants, and even neonates born as small for gestational age (SGA).

Children have distinctive features of elevated BP or HTN compared with HTN in adulthood regarding not only the period of HTN but also the underlying diseases causing childhood HTN. Besides, in children, even the initial step to diagnose the HTN itself is tricky, because in the clinical field, the pediatric population includes the population from neonates of less than 1 kilogram and less than 0.5 meter in height to large adolescents weighing more than 100 kg and as tall as 180 cm in height. Naturally, the diagnosis of HTN in children depends on the 95th percentiles for the reference norm of BP in their age group.[7] It is also a highly demanding process to effect the cooperation of very young children during BP measurement for reliable measured data due to higher incidence of white coat HTN compared with adults.[8] There are several reports on the inaccuracy in pediatric outpatient BP measurement.[9] Furthermore, it is also fundamental to define underlying specific diseases secondarily causing HTN in children, including renovascular diseases, coarctation of the aorta, endocrine disease, and monogenic HTN.

Failure in diagnosis of these categories of diseases may mean that we miss the chance to treat HTN early in life. These days, with the increasing incidence of childhood obesity in the United States (U.S.), primary HTN is currently reported as the most common diagnosis of HTN for hypertensive children and adolescents, whereas in other areas, reports of primary HTN in children are still uncommon.[10]

Typically, HTN in very young children is generally considered as a secondary condition caused by an underlying disease.[11] The proportion of secondary HTN compared with primary HTN soars when patient's chronological age is markedly decreased. Considering pediatric growth and development, such as when a small neonate grows into a tall adolescent, there are many factors affecting children's body habitus that relate to BP later on.[12] Infants with prematurity or intrauterine growth restriction (IUGR) are known to be more susceptible to later HTN due to their peculiar labile pathophysiology.[13]

Several theories exist to explain high BP later in adolescents who were born prematurely or with low birth weight (LBW).[10-13] An initial hypothesis of HTN in prematurely born adolescents postulated a physiological predisposition of premature birth toward HTN and CV disease later. These consequences were from poor fetal nutrition leading to IUGR and excessive postnatal weight gain.[14] On the contrary, there also were several studies insisting that they have failed to show an inverse relation between birth weight (BW) and BP. The relationship between BW, catch-up growth, and finally BP seems to be extremely complicated by many additional factors. Current body weight is a well-known independent predictor of HTN in children. Kwok et al.[12] insisted that an inverse relationship between BW and BP was stronger when adjusted for current body weight and postnatal weight gain. As current body weight modulates the association between BW and BP, adjustment for current body size is considered to be very important. LBW may at least in part increase the risk of high BP through increased susceptibility to environmental factors, such as postnatal weight gain.[12] Recently, there also are reports drawing attention to the fact that children demonstrating upward crossing of weight percentiles in various young age groups have significantly increased risk of elevated BP later. In interpreting the discrepant results, we should focus on the differences in study designs and bias that may lead to varied conclusions. The other important proposed mechanism linking BW to elevated BP is the glomerular hyperfiltration theory.[14] A decreased kidney mass and reduction of renal reserve in LBW infant are

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considered, along with enhanced salt sensitivity and the risk of HTN. IUGR may also lead to irreversible postnatal vascular dysfunction and to elevated BP in adolescents. Although many other proposed mechanisms on the pathogenesis of pediatric HTN related to premature born or IUGR have been reported, ongoing debate will persist for the time being because so many factors are reported to affect childhood BP.

In this review, we will introduce the concept of origin of adult HTN from infant or even from fetal life and important BP trajectories in childhood that were found to be consistent with adulthood BP trajectories. We also discuss the risk factors that move an adolescent's own BP trajectory toward the upper one that is known to be highly susceptible to adult HTN. Although the secondary HTN is more frequent and important in childhood HTN, we will set aside any in-depth review of the causes of secondary HTN and will focus on the reviews of BP trajectories and excessive weight as risk factors for later HTN. With an increased life expectancy, studies focused on the reduction of later-life CV risk factors from young ages are gradually increasingly getting attention. In this context, reviewing studies on premature birth or IUGR that are related to later-life HTN and speculating on the pathophysiology of pediatric HTN and expanding consideration to preventive measures against later-life HTN are very important.

INFANCY AND CHILDHOOD TO EARLY-MIDLIFE SYSTOLIC BLOOD PRESSURE TRAJECTORIES

Among the reports insisting that childhood HTN persists over time into adulthood, studies on this perspective using the Bogalusa heart study for nearly about 40 years are well-known[14][15] for predicting HTN by tracking children's BP. In 1983, Webber et al.[14] reported that persistence in tracking for CV risk factors was examined in 2,236 children over a 5-year period and the greatest persistent trend was noted for height and weight. For systolic BP, they reported that more than 30% of children initially high also remained high in the second examination.[14] About 10 years later, Bao et al.[1] showed that among 1,505 individuals, the subjects who were in the highest quintile of their BP during young children aged 5 to 14 were much more likely to develop HTN 15 years later, at 20 to 31 years old at follow-up, by tracking of elevated BP from childhood to adulthood. They also found that the weight gain from childhood to adulthood was an independent predictor of future HTN. The correlations between children's elevated BP and future adult HTN also remained 15 years later, even after controlling for body mass index (BMI). For more than 30 years, many studies tried to show the temporal trend of BP during the children's growth and tried to find cardinal factors affecting positive or negative correlations for BP during the childhood. There was an attempt to find life course trajectories of systolic BP using longitudinal data from eight UK cohorts in the year 2011.[16] Besides a cross-sectional approach that may be affected by environmental factors for systolic BP, the authors tried to find an age-related general pattern of systolic BP progression consisting life course trajectories of multiple UK cohorts that had repeatedly measured systolic BP taken over different but overlapping periods of life. The data comprised 102,580 systolic BP observations of as many as 30,372 individuals spanning from age 7 to 80 years. They found four life course phases of progression of systolic BP: a rapid increase systolic BP coinciding with peak adolescent growth, a more gentle increase in early adulthood, a midlife acceleration from the fourth decade, and deceleration in late adulthood.

A recent important study by Theodore et al.[4] tried to find subgroups at risk of developing adult HTN by identifying four BP trajectory groups in a longitudinal birth cohort from

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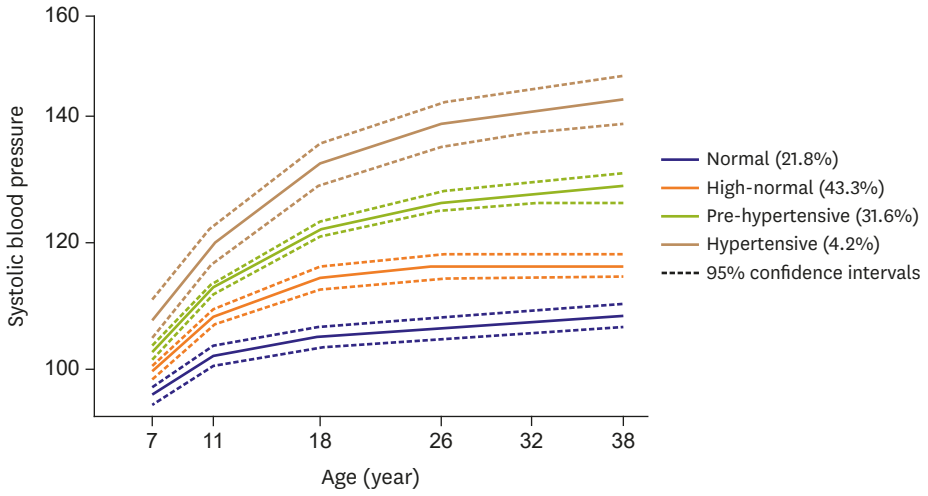

Figure 1. Plot of predicted trajectory lines with 95% confidence intervals for the 4 blood pressure trajectory groups identified in a general population longitudinal birth cohort. Reproduced with permission from Wolters Kluwer, Theodore RF, et al. *Hypertension* 2015;66:1108-15.[4]

the general population. They presented a neat plot of predicted trajectory lines with 95% confidence intervals in 2015 based on Dunedin study in New Zealand (**Figure 1**).[4] The researchers collected BP data at ages 7, 11, 18, 26, and 38 years from a longitudinal birth cohort. They examined the predictors and modifiers of BP trajectories and found harmful BP trajectories that had worse CV outcomes later. They found that these higher BP trajectories were related to LBW. Interestingly, higher BMI and cigarette smoking were the main risk factors, and patients with these risk factors crossed BP trajectory lines toward to higher track during their growth. Similar approaches to tracking BP trajectories in youth were reported thereafter. Sylvestre et al.[17] tried to find sex-specific distinguishing BP trajectories in Canadian youth to find modifiable risk factors on the trajectories for a intervention to maintain normal trajectories. The researchers found that BMI and smoking were associated with higher BP in most trajectory groups, whereas screen-time in both sexes and physical activity in women were related to high systolic BP trajectories only. There are also several reports on the differences of estimated systolic and diastolic BP trajectories according to ethnicity of the population.[18] The authors tried to find the roots of racial differences in early childhood BP trajectories and they concluded that they were not dependent on family socioeconomic status, and racial differences accounts for a proportion of racial differences.[19]

Numerous diseases with a family history may be affected by genetic trends and the upward crossing of BP trajectories during children's growth might be affected by genetic factors. With recent advancement of understanding the genetic influences of diseases, there have been attempts to understand childhood BP influenced by genetics. Howe et al. reported a genetic influence on rates of BP change and systolic BP trajectories.[20] They examined the associations of allelic scores of single-nucleotide polymorphisms (SNPs) for adult BP, height SNPs, and BMI SNPs with trajectories of systolic BP from 6 to 17 years of age using the Avon Longitudinal Study of Parents and Children and the Western Australian Pregnancy Cohort. They interpreted their results as allelic scores of SNPs that were associated with systolic BP at an early age at 6 years of age and were not responsible for the changes in BP through childhood and adolescence. The determinants of systolic BP included height, genetic factors, environmental factors, and obesity. In comparison with young childhood, the adolescent

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period is under adverse influences of environmental factors on young adult health. There is even a report on adverse childhood experiences and BP trajectories from childhood to young adulthood in the Georgia Stress and Heart Study.[21] The long-term effect of adverse childhood experiences in BP trajectories from childhood and young adulthood appeared as a greater increase of BP in young adulthood compared with those without adverse childhood experiences. An interesting study on the association of BP in pregnancy with offspring BP trajectories during childhood and adolescence, and a prospective study design was also reported.[22] In this study, the association between maternal high BP and offspring's trajectory changes during childhood were examined. The differences in BP between offspring of hypertensive and normotensive pregnancies remain consistent across childhood and adolescence according to higher maternal BP in early pregnancy, rather than by pregnancy-related BP changes. In adults, with regard to elevated BP trajectories preceding the onset of HTN, the recent Framingham Heart Study tried to find threshold level above which the BP rise tends to progress into HTN, and they found that the range approximately 120–125 mmHg at certain age ranges after midlife represent vascular remodeling and signal incipient HTN irrespective of age.[23]

As BP is known to be closely related to children's height, it is not unusual to find children BP curves that resemble children growth curves. There are two distinct periods of growth spurt, one of which is during infancy and the other of which is during the adolescent period, when children undergo puberty. Most of the aforementioned reports sharing perspectives on the understanding of how childhood and adolescent HTN correlates with adult HTN make us understand that the easy and systematic rendering of predictors can help us find a window and intervene to prevent childhood HTN and future adult HTN.

FETAL ORIGIN OF ADULT DISEASE HYPOTHESIS

Low birth weight and prematurity relating to later risk of HTN and suggestive pathophysiologic mechanisms

We would like to introduce briefly previous renowned studies on childhood BP. In contrast to adults, children undergo growth and development that start even before birth, that is, during intrauterine life. Measured BP is normally lower in premature and LBW infants compared with that in full-term infants. Remarkably, BP trajectory lines for premature or IUGR infants have a tendency to deviate from expected trajectories of full-term infants during their growth into adolescents. Paradoxically, premature infants are reported to be more frequently hypertensive later.

In children, LBW is considered as a surrogate for poor fetal nutrition. Barker et al. suggested a hypothesis for prenatal programming of BP.[13] They suggested that the intrauterine environment had an important effect on BP and HTN in adults via a relation to the past history of small babies with large placentas. Their explanation includes the prenatal programming of BP as a concept of a permanent alteration of physiology in a LBW infant in a nutrient-poor uterine environment to which fetuses adapt to promote survival, which had a deleterious effect after birth when nutrients are plentiful. Since this report on the early life predictors for pediatric HTN, past history of preterm birth, LBW, and IUGR have been favorite subjects in HTN studies in children for more than 30 years, although interpretation of results is conflicting, according to the studies. Many researchers tried to find confounding variables to explain the varied results for the association of BW and BP.[24-30]

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Collective proposed mechanisms linking BW to elevated BP are as follows: The first one is hyperfiltration theory.[31][32] Since the hyperfiltration theory of fewer nephrons is considered one pathophysiology of HTN in adolescents born as premature birth, a few reports have evaluated the clinical background. A study reported pathological findings of glomerulomegaly and hypertrophy of the juxtaglomerular apparatus and glomerulosclerosis in two adolescents with a past history premature birth.[33] The reduced numbers of nephrons that promote hyperfiltration and HTN in the remaining nephrons are considered to be the ultimate cause of the enlargement and severe injury to the remaining glomeruli. The second proposed mechanism is nephrogenesis theory. Several studies tried to understand the relations of adolescent HTN and premature birth by examining the kidney size, kidney function, and circulating angiotensin levels.[34][35] Usually, nephrogenesis correlates with BW during the third trimester. Studies on nephrogenesis in preterm infants showed nephrogenesis is still ongoing even after preterm birth, with the majority of nephrons normally formed during the third trimester of pregnancy.[36][37] These studies also implied a nephrotoxic effect on postnatal premature infants who began life with an incomplete complement of immature nephrons during the care for prematurity after birth.[38][39] Additionally, salt sensitivity is correlated negatively with kidney length.[40] Premature or LBW infants with small kidneys are suspected to have higher baseline BP and lower glomerular filtration rate. Third, infants with IUGR seem to have irreversible postnatal vascular dysfunction. Rossi et al.[41] studied this to determine that the causes of arterial properties in adolescents depend on the effects of fetal growth restriction or preterm birth. They measured the pulse wave velocity (PWV) between the carotid and radial arteries to assess arterial stiffness in SGA infants and infants born preterm with an appropriate BW and concluded that preterm birth, rather than being SGA at term, was associated with increased BP and arterial stiffness in adolescents. Fourth, the influence of LBW on the endocrine system has been suggested. An inverse association between BW and hormonal levels, such as aldosterone and cortisol, was suggested.[42] A study analyzed the circulating aldosterone and found that male offspring of preeclampsia mothers had higher aldosterone levels than those of non-preeclampsia mothers. Especially, cases with male preterm very LBW infants, maternal preeclampsia was associated with increased circulating aldosterone levels in adolescence mediated by higher BMI.[43] The concept of Barker's fetal programming elaborated innumerable subsequent related papers on the relationship between premature birth or BW and later BP, ultimately yielding conflicting results that are still under debate.

INTRIGUING FACTORS ON THE INVERSE RELATIONSHIP BETWEEN BIRTH WEIGHT AND BLOOD PRESSURE

Soon after Barker's paper on the prenatal programming of BP was published, many papers published data suggesting a definite inverse relation between BW and later HTN. However, as time passed, there also have been many inconsistent results on the relationship of BW and later HTN, as many factors affect childhood BP. One example of a confusing factor in the analysis of published results is the definition of a small baby. The category of premature infants describes neonates born before 37 weeks of gestation with a low body weight, but these criteria for premature infants includes all the infants with SGA, appropriate for gestational age (AGA), and also large for gestational age (LGA). The next category of LBW infant designates infants with just low BW and includes both premature infants and term infants with low BW. The third category of IUGR designates all the infants with low BW for

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their gestational age, and with these criteria, babies might be categorized as premature or full-term infants. When considering the suggestive pathophysiology of renal development, there can be a bias in interpreting the reported results.

We briefly review the major studies on BW and BP. For about 30 years, the majority of papers were related to the inverse relationship between BW and systolic BP. In 1995, a paper reported a cross-sectional and longitudinal study of 1,511 children aged 9 to 11 years, including children whose BP had been measured at 5 to 7 years of age.[29] At 9 to 11 years, their BW was reported as inversely related to BP rather than placental ratio, once current height and BMI were taken into account. Between the ages of 5-9 and 9-11, systolic BP more rapidly increased in the LBW group. The relations between BW and BP were very similar in preterm and term infants. Additional study including the Avon Longitudinal Study of Pregnancy and Childhood, including children aged 3 years, also revealed inverse relations between BW and systolic BP and concluded that accelerated postnatal growth did not underlie the relation.[30] A large analysis based on 1,756 participants in the population-based CV risk in Young Finns Study, who participated during 1980–2011 from age 3–18 years and 34–49 years, revealed definitely elevated BP levels in prematurity with fetal growth restriction.[44] The authors insisted on the heightened need for an early follow-up for BP and the prevention of HTN among premature SGA individuals, as their BP increase with age begins to be steeper as early as the second decade of life.

There are also papers with opposite perspectives that raise questions regarding biases underpinning the hypothesis of the previously reported inverse relationship.[45] Without considering gestational age at birth, when studies use only BW tabulated in quartiles or BW dichotomized as low or normal, significant negative associations between BW and absolute BP were found in the life-course plot for BP on weight at birth and at 13–15 years. When current weight was included, the strength of the relationship increased, and the authors insisted that noticeable postnatal changes in size had a more important effect on BP in children with normal and lower BW groups.

About 10 years later, a study reported a prospective study with 1,708 children on early weight gain, linear growth, and mid-childhood BP.[46] Premature infants younger than <34 weeks of gestational age at birth and their BWs were sub-analyzed to categorized them as SGA, AGA, or LGA. They tried to find the timing of postnatal weight gain in relation to later elevated BP with regard to the contribution of linear growth in 957 participants in Project Viva, a U.S. pre-birth cohort.[46] They checked BW-for-gestational age z-scores along with weight gains in BMI z-scores and height z-scores during several age intervals (birth to 6 months, 6 months to 1 year, and 2–3 years) and BP at 6–10 years of age. Rapid gain in the BMI z-score during the first 6 postnatal months and in the preschool years led to higher systolic and diastolic BP without consistent relations of height z-score change with mid-childhood BP regardless of size at birth. Similar conclusions that early postnatal growth has more impact on the BP than BW itself have been reached in many studies. A prospective study on early weight gain and absolute BP at 3 years old checked BP from term neonates to 3 years of age to minimize the impact of lifestyle on CV risks.[47] Systolic BP was related positively to weight at 2 and 3 years and after adjustment for current size; it was related negatively to weight at birth and 6 months but not at 1 or 2 years. According to this result, postnatal growth to 6 months of age seemed to be more predictive than BW. These kinds of data highlighting the importance of temporal weight gain shed light on the important window for intervention during postnatal life.

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IMPACT OF WEIGHT GAIN AND TIMING OF CATCH-UP GROWTH FOR CHILDREN BORN SMALL FOR GESTATIONAL AGE

Do we need to provide special care for this highly HTN susceptible group, that is, those who were born prematurely or as SGA? Before we discuss this main issue, we should address the catch-up growth of infants born prematurely or born with inappropriately LBW due to IUGR. It is necessary to again clarify the terminology. The term SGA refers to neonates born relatively small for their gestational age, and it does not mean simply that a baby is small. Thus, SGA preterm infants include those who were born with smaller BW compared with normal babies born with appropriate BW for their gestational age. The term IUGR is homologous to intrauterine development that leads to SGA babies. Hence, babies merely born prematurely (before 37 weeks of gestation) but have appropriate BW are not included in the category SGA. Overall, these small infants usually catch up to their normal body weight no later than 7 years of age, unless they have serious underlying diseases.

Children's height growth curve and BP curve both have an upward slant. As BP is independently related to children's height, if inappropriately short infants grow rapidly in height, BP will increase correspondingly. Meanwhile, if children grow fat, there should be additional hormonal changes affecting their BP. Traditionally, many studies on pediatric HTN tried to focus on the timing of small babies' catch-up growth related to this perspective. Hence, excessive weight gain in SGA infants during catch-up growth postnatally may impose similar weight gain on the various stages of childhood growth. There are papers on SGA infants and the adverse outcome of postnatal weight gain in prospective cohort studies showing the effect of early weight gain on absolute BP.[27)47)48)]

Contrary to the fetal programming of small baby syndrome, animal studies have suggested a “growth acceleration theory,” which means accelerated or excessive catch-up growth during crucial periods during development, accompanied by adverse effects on glucose tolerance, obesity, and life span. This growth acceleration theory was also postulated in children aged 13–16 years who were born prematurely and followed up prospectively with ultrasonic measurement of flow-mediated endothelium-dependent dilatation (FMD).[49)] The authors associated lower FMD in adolescents with the highest rate of weight gain in the first 2 weeks after birth as the adverse effect of accelerated growth in the early infantile period on long-term CV health up to 16 years later. Another observational cohort study showed the importance of upward crossing of weight percentiles in relation to an increased risk of high BP at 7 years of age.[27)] This study used the U.S. Collaborative Perinatal Project (USCPP), including 55,908 pregnancies in an observational cohort following the offspring through 7 years. In this post hoc analysis, z-scores were calculated for weight at birth, 4 months, 1 year, 4 years, and 7 years of age and their changes in z-scores. The authors found that children who cross weight percentiles upward during early childhood had increased CV risks. In a Chinese study including children aged 3 to 6 years, greater BW or postnatal weight gain was associated with increased childhood HTN.[50)] The peculiar result of this study compared with previous studies was the adverse health consequences of maternal overnutrition and infantile excessive postnatal weight gain, where greater BW was an indicator of healthy infants. Moreover, China's one-child policy, brought about a very low prevalence of low-BW infants (up to 1%), which limited the statistical power to detect a significant association between low BW and HTN. A recent Brazilian cross-sectional school-based study, in which enrolled adolescents

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(12–18 years) checked BP at an office and at home, analyzed the relations between nutritional status and BW.[26] LBW infants comprised 8.7% of the study cohort, and the study concluded that BW did not influence BP, BMI, or waist circumference of adolescents. The relations between increasing BMI percentile and increasing BP percentile was also studied in other regions in a recent large retrospective cohort including 101,606 subjects aged 3 to 17 years across the U.S.[10] With over a median 3.1 years of follow-up, they observed that the largest increases in BP percentile were found in children who became obese or maintained obesity and 0.3% of subjects developed HTN.

Accordingly, prevention of excessive weight or obesity would be an effective strategy for prevention of childhood HTN. A study reported the relations between timing of height, BMI, and adiposity gains in early life with BP at 48 months in 719 Asian children in Singapore.[51] The authors checked and analyzed the changes of their height, BMI, and abdominal circumference at 5 intervals (0–3, 3–12, 12–24, 24–36, and 36–48 months). The authors thought that faster BMI and adiposity velocities at 36–48 months are predictive of BP and HTN at 48 months of age but not at earlier intervals. Recently, according to another important paper, Lei at al.[48] modeled an optimal catch-up growth trajectory associated with the lower risk of adverse outcomes in postnatal weight gain in infants and children born as SGA infants. They investigated postnatal growth patterns of SGA infants aged 0–7 years using USCPP cohort data. Among five major growth patterns, excessive catch-up growth after birth produced higher risks of obesity and elevated BP at 7 years of age compared with SGA infants and children who exhibited no catch-up growth, slow catch-up growth, regression after 4 months, or appropriate catch-up growth. The optimal growth trajectory for term SGA infants was catch-up growth to about the 30th percentile in the first several months, with modest catch-up growth thereafter, to around the 50th percentile by 7 years. This implies that the importance of postnatal growth patterns of term SGA infants, rather than the SGA condition itself, might be more importantly related to CV risks later in life.[48] In addition, many other papers have addressed increased CV risks, including high BP related with early infantile rapid growth.[52]

Recently, there have been endocrinologic perspectives on the metabolic syndrome that the effect of fetal programming was reportedly weak in far eastern Asia, suggesting potential ethnic differences in the effect of low BW on later HTN. In Korean study on the effect of BW at gestational age on the current height and weight and components of metabolic syndrome in adolescents born as SGA suggested that BW at gestational age was related to current height and weight of adolescents, but not related to individual components of metabolic syndrome.[53] The authors analyzed Korea National Health and Nutrition Examination Survey data to investigate the relations between BW and current weight in adolescents. The population born as SGA was 11.4% when designating the cut-off weight for SGA as below the 10th percentile for their BW. In far eastern countries, the prevalence of metabolic syndrome in adolescents is low compared with western countries, and the authors explained that the cause of this difference was from differences in eating habits or ethnicity. Contradictorily with previous reports, BW was not significantly associated with impaired glucose tolerance, triglyceride or high-density lipoprotein-cholesterol (HDL-C) levels, or HTN in Korean adolescents, which might imply that BW may be a limited contributing factor to the metabolic syndrome in adolescents born as SGA. A series of Japanese studies on low BW and increased CV risks found that preterm SGA children were significantly shorter and inversely associated with systolic BP at school age but did not have unfavorable lipid levels at the age of 9–10 years.[54]

https://doi.org/10.4070/kcj.2018.0448

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Additional study related to the subject to ethnic effect is required, as there are several convincing studies implying a relationship between life-course BMI trajectories and adult CV risk demonstrated in a large longitudinal cohort study from progressively overweight children growing into adults.[55)56)]

PEDIATRIC HYPERTENSION AND LONG-TERM CARDIOVASCULAR RISKS

When considering the effect of childhood HTN, it sounds relatively absurd to couple childhood HTN with CV risks in later in life. However, there already have been innumerable reports highlighting the CV risks of HTN in youth. Among target organ damage due to HTN, left ventricular hypertrophy (LVH), vascular stiffness, and increased carotid-intima thickness are considered as surrogate markers.[57)] As introduced above, a recent representative epidemiologic study in Dunedin, New Zealand, revealed early-life predictors for adult CV outcomes by tracking systolic BP trajectories from childhood to mild-life and analyzing BP data periodically from 7 to 38 years of age.[4)] As CV risk indicators at age 38, this study used the biomarkers non-fasting total cholesterol, HDL-C, triglyceride, glycated hemoglobin, waist and hip girth, and BP to detect metabolic abnormalities. The higher the risk for high BP, the greater risk for CV risk factors; increased BMI and increased daily cigarette consumption were associated with an upward shift in BP trajectories. Recently, many additional papers on BMI during adolescence and its long-term effect an adult CV risks were published. There was a report on a sex-specific association between adolescent categories of BMI with CV and non-CV origins of mortality in midlife. This studied used a nationwide cohort linked to the national death registry to identify CV-related deaths, and it revealed that underweight adolescent females have favorable CV outcomes in adulthood.[58)] The authors suggested that the optimal BMI value related to future CV outcomes might be below the currently accepted BMI.

Another study also reported distinct child-to-adult BMI trajectories associated with different levels of adult CV disease risk.[55)] The study presented six discrete long-term BMI trajectories modeled for participants 6–49 years of age in the CV Risk in Young Finns Study. This study combined CV risk assessment with imaging of carotid intima-media thickness (cIMT) as a marker for subclinical atherosclerosis in adulthood. The increased CV risk in adulthood was associated with trajectories of worsening or persistent obesity. Efforts to prevent childhood obesity were considered to be the most effective way to reduce the risk of adult atherosclerosis. LBW and its relation to the risk of coronary heart disease was assessed with high-resolution ultrasonic assessment of FMD to determine endothelium-dependent and -independent vascular response of the brachial artery in children.[59)] Individuals born with IUGR are known to have altered vascular structure and function, and the study demonstrated impaired FMD in 344 subjects 20–28 years old who were born with LBW. Thus, the authors insisted that LBW is associated with endothelial dysfunction and might be related to atherosclerosis in later life.

A similar study also reported on the impact of being born preterm or SGA on early vascular aging in adolescents.[60)] This was a regional ongoing cohort study in Tyrol, Austria, known as the Early Vascular Aging (EVA) Study Group, designed to evaluate CV risk profiles in adolescents. The researchers conducted a carotid-femoral PWV and cIMT in cohort adolescents. BP was significantly higher in the preterm with AGA group and PWV was significantly higher in the term-SGA group, while no differences in cIMT between study groups were found. The authors suggested that being born preterm or SGA was related to susceptibility to EVA.

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Most recently, a large longitudinal study characterized longitudinal BP trajectories from childhood and the impact of level-independent childhood BP trajectories on adult LVH and remodeling patterns.[61] Enrolled patients were aged 4–9 years and curve parameters of BP showed significant race and sex differences from age 15 years onwards, and the slope of BP parameters differed consistently between the LVH and normal groups. Of note, linear slopes of childhood BP were related more strongly with concentric LVH during the adolescence period of 12–19 years, implying that the impact of BP trajectories on adult LVH and geometric patterns originates in childhood. This also supports the implication that adolescence is a crucial window for early prevention of LVH later in life. Many researchers accumulated a lot of data suggesting that altered organogenesis and function in preterm birth infants provide targets for preventive and therapeutic strategies to minimize development of CV risks later on.[62] While most articles stress the long-term CV risks of IUGR prematurely born adolescents, there also are contrasting papers suggesting that the increased risk of carotid atherosclerosis evaluated with cIMT was reduced if elevated BP during childhood was resolved by adulthood.[63]

CHILDREN GROUPS REQUIRING SPECIAL SURVEILLANCE FOR PEDIATRIC HYPERTENSION

An updated practice guideline for pediatric HTN was published in 2017 by the American Academy of Pediatrics (AAP).[7] This guideline covers extensive areas for the recognition and identification of pediatric patients with HTN and provides strategic recommendations for management of high BP and prevention of CV disease later in life. The guideline used new thresholds for pediatric HTN based on percentile references calculated from a healthy weighted pediatric population that exclude overweight children. After this new guideline was published, a study analyzed the impact of the new AAP guideline on the clinical practice of pediatric HTN.[64] They used 2013–2016 data to determine that application of the new guideline for pediatric HTN resulted in a weighted net estimated increase of 795,000 U.S. youths being reclassified as having HTN. According to this report, youths who were older, male, and obese accounted for a disproportionate number of persons reclassified as having HTN.

Annual BP measurement is recommended for children 3 years of age or older. Furthermore, conditions under which children younger than 3 years should have BP measured include birth history of prematurity (≤32 weeks of gestation), SGA, very low BW, other neonatal complications treated in a neonatal intensive care unit, congenital heart disease, known renal disease, family history of congenital renal disease, solid organ transplant, malignancy, treatment with drugs raising BP, other systemic illnesses associated with HTN, and elevated intracranial pressure. Compared with previous indications for monitoring BP in children, the recommendations highlight the crucial need to suspect and not miss the population of adolescents highly susceptible to HTN. Thus, there should be a high index of suspicion of HTN for adolescents who rapidly gain weight, have the conditions listed above, or have a history of disease that would make them highly susceptible to HTN.

CONCLUSIONS

Although studies on the association between BW and BP give conflicting results, and interpretation of the results is extremely complex, it seems to be obvious that long term adverse risk of adult HTN originates from an age much younger than previously expected.

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Conclusively, children who were born prematurely or suffered IUGR should be under surveillance to monitor their BP trend. More specifically, children with an adverse BP trajectory should be provided with the optimal nutrition guidelines and information on healthy lifestyle management. If children with high BP risk factors show upward crossing of weight percentiles while they are growing into adolescents, additional intervention for the modification of their upward crossing BP trajectory is strongly recommended.

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