

# **PEDIATRIC HYPERTENSION – INSIGHTS INTO ETIOLOGY, DIAGNOSIS AND PROGRESSION OF TARGET ORGAN DAMAGE**

by

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## **Abstract**

**Statement of Problem:** Over the last several decades the prevalence of pediatric hypertension has increased fourfold, thought to be partially attributable to the concurrent rise in pediatric obesity. Hypertensive children are at increased cardiovascular disease risk as they often manifest other cardiovascular disease risk factors such as obesity, dyslipidemia, and insulin resistance. Further, up to 40% have target organ damage in the form of left ventricular hypertrophy at initial diagnosis. Left ventricular hypertrophy, a pathological remodeling of the heart thought to be secondary to increased left ventricular afterload as seen in hypertension, causes arrhythmias, heart failure and myocardial infarction in adults. Its striking prevalence at initial diagnosis suggests that elevated blood pressure detection and hypertension diagnosis in children may be delayed or because other factors, specifically obesity, play a more substantial role in its development among hypertensive children.

**Methods:** We conducted two studies: 1) a pre-post evaluation of a quality improvement initiative to improve elevated blood pressure recognition among children and adolescents seen for primary care. The intervention consisted of a one-time provider educational session and implementation of an ongoing real-time electronic medical record alert; and 2) a prospective, observational study of hypertensive children to investigate the association of obesity and obesity-related risk factors with the presence of left ventricular hypertrophy and with the change in left ventricular mass over a 12-month period of anti-hypertensive therapy.

**Results:** We found that recognition of elevated blood pressure among patients seen for pediatric primary care was poor overall but increased from 12.5% pre-intervention to 42% during the intervention period ( $p < 0.001$ ). Recognition was no different by educational session attendance status. During both pre-intervention and intervention periods, systolic BP

$\geq 120$ mmHg was associated with greater recognition. However, the prevalence ratio (PR) was smaller in the intervention period: intervention PR 1.3, 95% confidence interval (CI) 1.2 – 1.5 ( $p < 0.001$ ) versus pre-intervention PR 2.4, 95% CI 1.4-3.9 ( $p = 0.001$ ). Similar relationships were observed for other cardiovascular disease risk factors. Acute care visit encounters were associated with decreased recognition in the intervention period (PR 0.6, 95% CI 0.5- 0.7;  $p < 0.001$ ).

We also found a high prevalence of cardiovascular disease risk factors among children with hypertension: 51% were overweight/obese and 41% had left ventricular hypertrophy. Children with LVH had greater BMI z-score and BMI percentile, higher serum uric acid level, a lower serum lipoprotein (a) level and a greater pro-B natriuretic peptide level than those without LVH. There was no difference in multiple measures of blood pressure between those children with and without LVH. Children who were obese at both study visits experienced the greatest increase in LVMI over time: mean change in LVMI was  $6.4 \text{ g/m}^{2.7}$  (95% CI 2.4, 10.5) among those overweight or obese at each visit, vs.  $0.95 \text{ g/m}^{2.7}$  (95%CI -3.2, 5.1) among children who were of healthy weight at each visit ( $p = 0.056$ ). Overweight/obese children with and without LVH at baseline demonstrated a larger increase in LVMI compared to healthy weight children. Healthy weight children with LVH were the only ones with decreased LVMI over time. BMI z-score at baseline was positively associated with change in LVMI over time ( $\beta$  4.08, 95% confidence interval 1.54, 6.61,  $p = 0.002$ ) during multivariable regression analyses adjusting for age, sex, race, and LVMI at baseline. The association remained essentially unchanged after sequential adjustment for postulated mediating pathways between BMI z-score and LVMI with the exception of pulse pressure and serum aldosterone. When added to the model, those two risk factors decreased the point estimate and p-value.

**Conclusion/Implications:** Elevated blood pressure in children is largely unrecognized, and those with minimal to no additional cardiovascular disease risk factors are least likely to be recognized in a primary care setting. Real time electronic medical record alerts substantially increase provider recognition of elevated BP in children and hold considerable promise as a means to improve adherence to practice guidelines. These alerts particularly aid in the recognition of elevated blood pressure among those not at obvious cardiovascular disease risk. However, the persistence of under-recognition of elevated BP in children highlights the need for additional strategies to further improve provider recognition.

Hypertensive children referred for subspecialty care demonstrate not only a high prevalence of co-morbid cardiovascular risk factors at baseline, but an increase in both their prevalence and severity over time. Most striking of these cardiovascular risk factors is the presence and substantial degree of overweight and obesity. In fact, adiposity as determined by body mass index z-score was the greatest risk factor for left ventricular hypertrophy and change in LVMI over time. None of the many measures of blood pressure assessed during this study were associated with the presence of LVH or with the change in LVMI over time. And, two risk factors potentially modified by diet - pulse pressure, a marker of intravascular volume, and serum aldosterone, a hormonal regulator of blood pressure – appeared to be the most important partial mediators of the relationship between adiposity and change in LVMI. These findings support the overwhelming public health concern regarding the obesity epidemic and suggest that greater emphasis on overweight and obesity prevention and treatment should be made among hypertensive children.

**Future Directions:** Our work emphasizes the substantial prevalence of cardiovascular disease risk factors among children and adolescents. It also suggests that current population estimates

of the burden of pediatric hypertension may underestimate the true prevalence as a substantial number of children with elevated blood pressure are unrecognized in a primary care setting. A common underlying theme to this increased CVD risk is overweight and obesity. Despite providing standard of care guidance on weight loss and adherence to a heart healthy diet, the children in our study became more overweight/obese and demonstrated an increase in number and severity of CVD risk factors over a year of observation. Enhanced preventive and therapeutic strategies targeting overweight and obesity in children holds significant promise as we work towards primordial and primary prevention of adult cardiovascular disease. Further research should test innovative interventions designed to assist youth with adherence to a heart healthy lifestyle and determine the effect of these interventions on cardiovascular disease risk factors.

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***To my husband, Nick,  
And our three inquisitive and curious children,  
Tom, Nate and Lexi  
Thank you for being my constant inspiration***

“When you're curious, you find lots of interesting things to do.”

-Walt Disney

## **Preface**

They say “it takes a village”. While generally referring to raising children, this concept highlighting the importance of community support perfectly describes how I was able to successfully complete this thesis. From the moment I informed my parents that I was pursuing medicine as a career to the moment I told my husband I wanted to obtain my PhD (while continuing to expand our family), I have been met with nothing but support and encouragement. I have been humbled by the generosity of others - generosity of time, of kindness, of understanding – as I pursued this higher education. This came from people in all aspects of my life: my family, my friends, my mentors and advisors, my thesis committee, my colleagues and the wonderful members of the Division of Pediatric Nephrology. Without the tireless support of these wonderful individuals, I would not have been able to complete my research or this thesis. I therefore dedicate this work to my “village”.

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And, finally, to my husband Nick – you have sacrificed much and been rewarded with little during this journey of mine. You have taken on more than your fair share of responsibility for most everything these last few years without a single complaint. You have stayed up late



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## Chapter 1: Introduction

Hypertension in children is on the rise. Over the last 30-40 years pediatric hypertension in the United States has increased fourfold<sup>1,2</sup>. Currently, up to 4.5%, or 3.34 million children in the United States, are diagnosed with this condition<sup>3,4</sup>. Recent American Heart Association Heart Disease and Stroke statistics suggest the number affected may be higher, with up to 15% of adolescents having abnormal blood pressure when defined as  $>120/80$ <sup>5</sup>.

While the reason for the increase in pediatric hypertension is not entirely clear, many consider it to be a consequence of the coincident obesity epidemic. Since 1980 the prevalence of obesity among children and adolescents has almost tripled<sup>6</sup>. Thirty-two percent of children in the United States are now overweight or obese<sup>7</sup>. Further, when only considering this group of at risk children, the estimated proportion of children afflicted with hypertension is much greater, ranging from 20-47%<sup>8</sup>.

While the hypertension burden and resulting sequelae in adults are widely known, the prevalence of hypertension and target organ damage in children is only just beginning to be recognized. Pediatric hypertension, particularly primary hypertension, is almost exclusively clinically silent. However, up to 40% of hypertensive children have left ventricular hypertrophy, a pathological remodeling of the heart thought to occur in response to an increased left ventricular afterload, at initial diagnosis of hypertension<sup>3,9,10</sup>. Left ventricular hypertrophy is also clinically silent in childhood, but is a well-established precursor for arrhythmias and heart failure in adults.<sup>11</sup> Its striking prevalence at initial diagnosis suggests that elevated blood pressure detection and hypertension diagnosis in children may be delayed or because other factors, specifically obesity, play a more substantial role in its development.

There have been several landmark studies demonstrating the progression, or tracking, of blood pressure from childhood to adulthood<sup>12, 13</sup>. In addition, children who are hypertensive have a high likelihood of becoming adults who are hypertensive, and this likelihood increases with the co-morbid presence of obesity and/or left ventricular hypertrophy. With heart disease the leading cause of death in the United States<sup>14</sup>, decreasing the prevalence of hypertension and ultimately left ventricular hypertrophy in at risk children would greatly aid in decreasing adult cardiovascular disease mortality.

Essential to diminishing the amount of hypertension and target organ damage found in children is the early identification of elevated blood pressure and diagnosis of hypertension. Findings from the Young Finns Study<sup>15</sup> reveals the importance of early diagnosis: the greater the number of ideal cardiovascular health metrics present in childhood, the lower the risk of hypertension and risk for atherosclerosis later in life. This applies to young adults as well, with the Coronary Artery Risk Development in (Young) Adults (CARDIA) study demonstrating that a greater number of healthy behaviors in early adult life can result in a lower cardiovascular disease risk profile in middle age<sup>16</sup>.

This rationale - that early identification of a preventable and treatable condition could lead to increased health and decreased cardiovascular disease mortality - has led several prominent medical organizations including the American Heart Association, the National High Blood Pressure Education Program, National Heart Lung and Blood Institute, the European Society of Hypertension, and the American Academy of Pediatrics to publish guidelines emphasizing the importance of blood pressure screening in childhood<sup>3, 17-20</sup>. These guidelines recommend measuring blood pressure in all children ages 3-17 years at least once during every health care episode to screen for hypertension.

Despite these recommendations calling for blood pressure screening at all health care encounters, on average, health care providers measure blood pressure only two-thirds of the time during well-child visits and one-third of the time during sick visits<sup>21</sup>. In addition, because of the complex steps required to determine normal blood pressure values in children, elevated BP readings are only recognized 15% of the time<sup>22, 23</sup>. If providers are not consistently measuring blood pressure and are not recognizing when it is elevated, then our assessment of the burden of pediatric hypertension is likely modest at best.

To improve the identification of hypertensive children, providers need better tools to assist with identification of elevated blood pressure. In addition, once children are diagnosed with hypertension providers need better methods to identify those at greatest cardiovascular disease risk. Previous work has shown that degree of blood pressure elevation does not predict which child with hypertension may or may not have left ventricular hypertrophy<sup>9</sup>. Several cross-sectional studies and some longitudinal studies in primarily white children have suggested adiposity, not blood pressure, to be most associated with left ventricular hypertrophy<sup>9, 24-27</sup>. If adiposity is indeed more associated with left ventricular hypertrophy, then practice guidelines would need to place more emphasis on both prevention of obesity among children and adolescents with hypertension and treatment of obesity among these children when present alongside left ventricular hypertrophy.

With this background in mind, the goals of this thesis research were to 1) conduct a pre-post evaluation of a quality improvement initiative to improve elevated blood pressure recognition among children and adolescents seen for primary care. Our intervention consisted of a one-time provider educational session and implementation of an ongoing real-time electronic medical record alert; and 2) conduct a longitudinal, prospective observational study



of hypertensive children to investigate the association between obesity and obesity-related risk factors with the presence of left ventricular hypertrophy and with the change in left ventricular mass over a 12-month period of anti-hypertensive therapy.

Improving elevated blood pressure recognition will enhance our ability to identify children at increased cardiovascular disease risk. It will also augment our primordial and primary preventive efforts which are the underpinnings of the contemporary strategy to prevent cardiovascular disease as recommended by the American Heart Association<sup>28</sup>. Further, detailing the association of adiposity with left ventricular hypertrophy among hypertensive children will assist us in focusing our treatment efforts. Ultimately, improving our ability to identify and adequately risk stratify youth at increased cardiovascular disease risk will allow us to optimize the care we provide to our pediatric patients and ultimately decrease the cardiovascular disease morbidity and mortality in adults.

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## **Chapter 2: Hypertension**

### **Objectives:**

*After completing this article, readers should be able to:*

1. Define hypertension in children, and be familiar with the approach to the diagnosis of hypertension.
2. Recognize important signs and symptoms associated with hypertension and its sequelae, and formulate an appropriate differential when presented with a hypertensive child or adolescent.
3. Initiate an appropriate work up, and know when to refer to subspecialty care.
4. Prescribe both non-pharmacologic and pharmacologic anti-hypertensive therapy to hypertensive children, and be familiar with the various classes of anti-hypertensive medications available.

### **Case Study**

Jennifer is a 12-year-old girl who plays field hockey and is in your office for a sports physical. She reports feeling well, denies any complaints and has no significant past medical history. She is not taking any medications. Family history is reviewed and is unchanged, significant only for grandparents on both sides of the family with hypertension, and a paternal grandfather who had a myocardial infarction at 60 years of age, and is still living. She is a straight "A" student, and lives at home with her parents and 2 brothers who are healthy. Review of symptoms significant for menarche several months prior, otherwise negative.

Physical examination shows her height and weight to be both at the 50<sup>th</sup> percentile. Blood pressure was 136/82 initially in triage; repeat was 132/78 by the same automated oscillometric

device five minutes later. She is a normal appearing, young girl who is comfortable and in no apparent distress. The rest of her physical exam is well within normal limits. You repeat her blood pressure by manual auscultation and obtain a blood pressure measurement of 128/77.

## **Introduction**

While once only affecting 1% of all children, pediatric hypertension is on the rise, now affecting almost 5% of all children<sup>3</sup>. One possible explanation for this fourfold increase in prevalence over the last several decades is the concurrent rise in pediatric obesity, which currently affects 17% of US children and adolescents<sup>29</sup>. Blood pressure increases with increasing body mass index, which explains the staggering 20-47% of obese children who are hypertensive<sup>8</sup>. This significant increase makes it much more likely that pediatric providers will find themselves caring for hypertensive children, heightening the need for proper recognition, evaluation and treatment in the primary care setting.

## **Definition**

Pediatric hypertension is defined as the *sustained* elevation of either the systolic or diastolic blood pressure at or above the 95<sup>th</sup> percentile BP for a child's age, sex and height percentile. Essential to this definition is the presence of *sustained* BP elevation, which is why all elevated blood pressure measurements should be confirmed by repeated measurements conducted by manual auscultation, with the average of all measurements used to determine the category of HTN. The severity of the elevation will dictate how many measurements are needed prior to diagnosis and work up<sup>30</sup>. In 2004, *Pediatrics* published updated sex-, age- and height percentile-specific 50th, 90th, 95th and 99th percentile systolic and diastolic BPs for children aged 1 to 17 years<sup>3</sup>. These normative values were compiled from over 60,000 healthy children in the United States, based on their first auscultatory blood pressure measurement obtained during

screening, and should be used to classify children into one of the following blood pressure categories:

1. Normal Blood Pressure: Both systolic and diastolic BPs are *less than the 90th percentile or less than 120/80, whichever is lower.*
2. Prehypertension: Systolic and/or diastolic BP is *between the 90th percentile and the 95th percentile, or between 120/80 and the 95th percentile* if 120/80 happens to be higher than the reported 90th percentile for the individual child based on his/her age, sex, and height percentile.
3. Stage I Hypertension: Systolic and/or diastolic BP *between the 95th percentile and the 99th percentile + 5 mmHg*
4. Stage II Hypertension: Systolic and/or diastolic BP *above the 99th percentile + 5 mmHg*

Adolescents and young adults aged 18-21 years of age should be classified according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommendations:

1. Prehypertension: Systolic and/or diastolic BP  $\geq 120/80$  and  $\leq 139/89$
2. Stage I Hypertension: Systolic and/or diastolic BP  $\geq 140/90$  and  $\leq 159/99$
3. Stage II Hypertension: Systolic and/or diastolic BP  $\geq 160/100$

### **When to screen for hypertension**

All children three years of age and older should have their blood pressure measured during each physician visit, whether the visit is for well child care, urgent care, or emergency care, at a minimum of once yearly. In addition, children less than three years of age should also have their

blood pressure measured at each visit if they have a comorbid condition that places them at increased risk for hypertension (Table 1).

**Table 1: Comorbid Conditions Requiring a BP Measurement in Children < 3 Years of Age**

History of prematurity	Solid organ transplant
History of low birth weight/NICU stay	Malignancy or Bone Marrow Transplant (BMT)
Congenital heart disease	Taking meds known to increase BP
Recurrent UTI, hematuria, proteinuria	Presence of systemic illness associated with HTN
Known renal disease or genitourinary abnormalities	Evidence of increased intracranial pressure
Family history of congenital kidney disease	

Table adapted from *The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555-76<sup>3</sup>*.

Particular attention should be given to children with conditions such as diabetes mellitus, chronic kidney disease, history of Kawasaki disease (with or without current coronary artery aneurysms), kidney or heart transplantation, chronic inflammatory diseases, HIV and nephrotic syndrome as they are at increased cardiovascular risk. As such, in addition to regular blood pressure measurement, they should have additional cardiovascular risk factor assessment conducted at health care encounters.

Any child with a blood pressure measurement at or above the 90<sup>th</sup> percentile (or at or above 120/80 if this is greater than the 90<sup>th</sup> percentile for age) should have their BP re-measured at that visit. The average of three measurements obtained by manual auscultation should be recorded, and the child should be “staged” as defined above. This staging and the presence/absence of symptoms will dictate plans for future follow up:

An average BP in the Pre-hypertensive range: These children should be considered pre-hypertensive, and should be followed closely due to their increased risk of developing sustained hypertension. They should be counseled on weight management, if indicated, and should be

given activity and the Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1) recommendations (see section below on non-pharmacological therapy)<sup>30</sup>. Pre-hypertensive children should have a follow up appointment in 6 months to reassess blood pressure.

An average BP in the range of **Stage I** hypertension: If the child is *asymptomatic*, have him/her return for repeat BP measurements on two additional occasions, 1-2 weeks apart, in the same manner. If Stage I hypertension is confirmed by averaging all BP measurements obtained, perform evaluation within one month. If the child is *symptomatic*, more immediate referral to a pediatric hypertension specialist for initiation of evaluation and treatment is indicated.

An average BP in the range of **Stage II** hypertension: If the child is *asymptomatic*, he/she should undergo evaluation and treatment within 1 week. If *symptomatic*, the child should be referred immediately to the emergency department or an inpatient facility for care.

Pediatric hypertension is largely asymptomatic, however children may initially present in hypertensive crisis with severely elevated blood pressure and symptoms ranging from nausea and vomiting to ataxia, mental status changes, seizures and coma or with symptoms related to the underlying etiology of their hypertension. In addition, some children may experience anxiety during evaluations which may cause elevated BPs that are in the hypertensive range, yet when monitored in their home environment are in the normal range. This phenomenon of “white coat” hypertension can be diagnosed with a 24-hour ambulatory blood pressure monitor that obtains many BP measurements taken in a child’s home environment. Children with white coat hypertension should also be considered at increased risk for the development of sustained hypertension and as such should be followed every 6 months<sup>31-33</sup>

### **Proper Blood Pressure Measurement**

To identify and diagnose a child with hypertension, one must use proper technique when measuring blood pressure. Proper technique begins with applying the correct size cuff to a child's bare arm, and ensuring that his/her arm, feet and back are supported, with the cubital fossa positioned at heart level. To determine the correct cuff size, measure the cuff bladder (felt inside the outer packaging) to the child's arm. The right size cuff will have a bladder width that is at least 40% of the child's mid-arm circumference and a bladder length that encircles 80-100% of the mid-arm circumference. *When in doubt, choose a larger cuff* because a too-small cuff may result in artificially elevated blood pressures.

After the child has been *resting for five minutes*:

1. Locate the child's radial pulse, quickly inflate the sphygmomanometer to 60 mmHg and then slowly continue to inflate in increments of 10 mmHg until the pulse disappears
2. Note the Peak Inflation Level, which is the value at which the pulse disappears + 30 mmHg
3. Deflate the cuff and after 30 seconds inflate the sphygmomanometer to the Peak Inflation Level
4. Deflate by 2-3 mmHg/second to a level that is 10 mmHg lower than the last Korotkoff sound (K5).
  - a. Systolic BP = Onset of Korotkoff sounds (K1)
  - b. Diastolic BP = Disappearance of Korotkoff sounds (K5)

All blood pressure elevations (systolic or diastolic BP  $\geq 90^{\text{th}}$  percentile or  $\geq 120/80$ ) should be confirmed by this technique rather than by an automated device. Automated, or oscillometric, devices (such as the Dynamap), while useful as screening tools, can provide inaccurate blood pressure measurements because they do not directly measure blood pressure, but instead estimate the systolic and diastolic blood pressure based on the point of maximal oscillation (the mean intra-arterial pressure) during cuff deflation. The algorithms utilized to determine these values vary from device to device, leading to non-uniformity of measurement across devices.

Devices that automatically inflate to 30 mmHg above the previous reading can influence each subsequent blood pressure reading. These limitations, and the fact that the normative values that make up the reference tables were obtained via auscultation, form the basis for the recommendation that all blood pressure elevations must be confirmed by manual auscultation.

### Initial Evaluation

*All children* diagnosed with hypertension should undergo an evaluation to investigate for secondary causes of hypertension. While primary hypertension is on the rise, and is the most common cause of hypertension among adolescents, secondary hypertension is common enough to warrant investigation, particularly in younger children and those with Stage II HTN at presentation (Table 2).

**Table 2: Differential Diagnosis of Hypertension among Children, by Age.**

Age Range	Etiology	Most common secondary causes
Birth to 1 year	Secondary (99%)	<u>Cardiac:</u> <ul style="list-style-type: none"> <li>- Coarctation of Aorta</li> <li>- Patent ductus arteriosus</li> </ul> <u>Renal:</u> <ul style="list-style-type: none"> <li>- Renovascular defect</li> <li>- Renal parenchymal disease</li> </ul> <u>Pulmonary:</u> <ul style="list-style-type: none"> <li>- Bronchopulmonary dysplasia</li> </ul> <u>Neurologic:</u> <ul style="list-style-type: none"> <li>- Intraventricular hemorrhage</li> <li>- Pain</li> </ul> <u>Neoplasia</u> <ul style="list-style-type: none"> <li>- Wilms tumor</li> <li>- Neuroblastoma</li> </ul> <u>Endocrine</u> <ul style="list-style-type: none"> <li>- Congenital adrenal hyperplasia</li> <li>- Hyperaldosteronism</li> <li>- Hyperthyroidism</li> </ul>
Age 1 – 12 years	Secondary (70-85%) Primary (15-30%)	<u>Renal:</u> <ul style="list-style-type: none"> <li>- Renal parenchymal disease</li> <li>- Renovascular defect</li> </ul> <u>Cardiac:</u>



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		<ul style="list-style-type: none"> <li>- Coarctation of Aorta</li> </ul>
		<u>Urologic:</u>
		<ul style="list-style-type: none"><li>- Reflux Nephropathy</li></ul>
		<u>Endocrine</u>
		<ul style="list-style-type: none"><li>- Congenital adrenal hyperplasia</li><li>- Hyperaldosteronism</li><li>- Hyperthyroidism</li></ul>
		<u>Neoplasia</u>
		<ul style="list-style-type: none"><li>- Wilms tumor</li><li>- Neuroblastoma</li></ul>
		<u>Miscellaneous</u>

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Age 12 - 18 years	Primary (85-95%) Secondary (5-15%)	Same causes as for 1-12 yrs
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The initial evaluation should start with a focused history and physical examination. In addition to obtaining a complete review of systems to help narrow the differential diagnosis (Table 3 below), particular attention should be paid to the past medical history (including birth history), current medications, family history and social history.

When obtaining the **past medical history**, it is important to inquire about any prior diagnosis or treatment of hypertension, and any recent discontinuation of antihypertensive medications, as beta-blockers and alpha-adrenergic agonists can cause severe rebound hypertension if discontinued abruptly. It is also important to determine if the child has any of the following co-morbid conditions or syndromes associated with hypertension:

**Co-morbid conditions:** diabetes mellitus, thyroid disease, Cushing syndrome, systemic lupus erythematosis/other rheumatologic disorder

**Syndromes:**

*Williams syndrome* – associated with supravalvular aortic stenosis, mid-aortic syndrome, renal artery stenosis, renal anomalies

*Turner syndrome* - associated with coarctation of the aorta, renal anomalies, idiopathic hypertension

*Tuberous sclerosis* - associated with coarctation of the aorta, renal artery stenosis, brain tumors

*Neurofibromatosis* – associated with essential and renovascular hypertension

*Polycystic kidney disease*, both autosomal recessive and autosomal dominant variants

Prior history of urinary tract infections or unexplained fevers may suggest chronic pyelonephritis and renal cortical scars and/or reflux nephropathy. A recent or relatively remote streptococcal infection of the pharynx or skin, or exposure to enterohemorrhagic E.coli, may indicate a resolving/resolved post-infectious glomerulonephritis or hemolytic uremic syndrome, respectively. Henoch-Schonlein purpura can be associated with persistent renal manifestations, including hypertension, even after initial complete resolution of symptoms. Previous hospitalization(s) may reveal information on systemic illnesses, exposure to nephrotoxic medications or evidence of renal injury. Recent injuries should be assessed, as renal or neurologic trauma could lead to hypertension as well as associated pain.

Because prematurity and low birth weight are associated with decreased nephron endowment and hypertension, and umbilical catheter placement can lead to renal artery stenosis and renal vein thrombosis, a detailed **birth history** should also be obtained.

A thorough review of both prescribed and over-the-counter **medications** may reveal the following possible causes for elevated blood pressure:

- Steroids
- Decongestants/cold preparations
- Nonsteroidal anti-inflammatory medications

- Herbal medications/supplements
- Oral contraceptive pills
- Anti-hypertensive medications (Recent discontinuation of these medications)
- Beta-adrenergic agonists/theophylline
- Erythropoietin
- Cyclosporine/tacrolimus
- Attention deficit disorder medications

The **family history** can be helpful in determining etiology, particularly for children with monogenic forms of hypertension (such as Liddle Syndrome, Gordon Syndrome and Apparent Mineralocorticoid Excess) and renal disease, and can also help with risk stratification. As described in the recent Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents<sup>30</sup>, a positive family history of coronary heart disease in a male relative (father, grandfather, sibling or uncle) younger than 55 years or in a female relative (mother, grandmother, sibling or aunt) younger than 65 years is an independent risk factor for cardiovascular disease. This risk is inversely related to the age at the time of event. Children with this family history should be considered at increased cardiovascular risk. **Social history** should focus on the following: Sexual activity (pregnancy, preeclampsia); Diet (consumption of caffeine, licorice, sodium, nutritional supplements); Smoking/drinking/illicit drug history (nicotine, cocaine, amphetamines, anabolic steroids, phencyclidine (PCP), MDMA (ecstasy)); level of physical activity (obesity); Sleep history (snoring, daytime somnolence, difficulty awakening which may be suggestive of obstructive sleep apnea); Psychosocial history (stress, anxiety).

**Table 3: Symptoms That May Be Suggestive of Underlying Etiologies of Pediatric Hypertension**

<b>Organ System</b>	<b>Possible Symptoms</b>	<b>Potential Diagnoses</b>
Endocrine	Weight loss or gain Sweating Flushing Fever Palpitations Muscle cramps Weakness Constipation Fatigue	Thyroid disease Pheochromocytoma Congenital adrenal hyperplasia Cushing syndrome Primary aldosteronism Primary hyperparathyroidism Hypercalcemia Diabetes mellitus
Renal	Dysuria Hematuria Foamy urine (suggestive of proteinuria) Frequency Urgency Flank pain Enuresis Edema Fatigue Hearing loss	Renal parenchymal disease Glomerulonephritis Genitourinary anomalies Chronic pyelonephritis Reflux nephropathy Polycystic kidney disease Wilms Tumor Kidney stones
Cardiovascular	Chest pain Shortness of breath Palpitations Claudication	Coarctation of the aorta Patent ductus arteriosus Mid-aortic syndrome
Rheumatologic	Rash Joint or muscle pain Fever Weight change	Systemic Lupus Erythematosus Collagen vascular disease
Neurologic	Headache Vision changes Vomiting Developmental delay Seizures	Increased intracranial pressure Guillain-Barré syndrome
Gynecologic	Last menstrual period	Pregnancy Pre-eclampsia

After eliciting a detailed history, the **evaluation** should then progress to a detailed physical exam, paying particularly close attention to findings suggestive of underlying etiologies:

**Table 4: Physical Examination Findings Suggesting Hypertension Etiology**

	<b>Findings</b>	<b>Possible etiologies</b>
<b>Anthropometrics</b>		
Weight, height and appropriate percentiles	Growth failure	Chronic renal disease, endocrine disease, other chronic diseases
	Obesity	Primary hypertension, Cushing syndrome (also associated with short stature)
<b>Vital signs</b>		
Blood pressure (4 limb)	Lower BPs in lower extremities compared to upper extremities	Coarctation of the aorta
Heart Rate	Tachycardia	Hyperthyroidism, pheochromocytoma, neuroblastoma, primary hypertension
<b>General exam</b>		
Volume status, overall appearance	Fluid overload or edema	Renal or heart failure
	Moon facies	Cushing's syndrome, steroid use
	Elfin facies	William's syndrome
	Webbed neck, wide spaced nipples, short stature	Turner's syndrome
	Pallor, flushing, diaphoresis	Pheochromocytoma
<b>HEENT</b>		
Including fundoscopic exam	Papilledema	Increased intracranial pressure, hypertensive emergency, hypertensive retinopathy
	Retinal hemorrhage, exudates	Hypertensive emergency, hypertensive retinopathy
	Cotton wool spots, AV nicking	Hypertensive retinopathy
	Contusions, lacerations, palpable skull defect, hemotympanum	Head trauma
	Exophthalmos, thyromegaly	Hyperthyroidism
Cardiovascular	Adenotonsillar hypertrophy	Obstructive sleep apnea
	Heart murmur, diminished femoral pulses	Coarctation of the aorta, patent ductus arteriosus
Pulmonary	Friction rub	Systemic lupus erythematosus, collagen vascular disease
	Accessory muscle use, crackles, wheeze	Heart failure, asthma, bronchopulmonary dysplasia
Abdominal	Hepatomegaly	Heart failure
	Bruit	Renal artery stenosis,

	Mass	arteriovenous fistula Wilms tumor, neuroblastoma, pheochromocytoma
	Palpable kidneys	Polycystic kidney disease, urologic disease, mass
Extremities	Joint swelling	Systemic lupus erythematosis
Neurologic	Altered mental status	Hypertensive encephalopathy
	Mood	Anxiety, white coat hypertension
	Weakness	Monogenic forms of hypertension, hyperaldosteronism
Skin	Cafe au lait spots, axillary freckling, neurofibromas	Neurofibromatosis
	Ash leaf patches, angiofibromas, adenoma sebaceum	Tuberous sclerosis
	Malar rash	Systemic Lupus erythematosis
	Palpable purpura	Henoch-Schonlein purpura, vasculitis

Following the history and physical exam, all children should undergo a **laboratory and imaging evaluation, the details of which are listed in Table 5**. If this initial work up is negative in an older child with Stage I hypertension, particularly if their average blood pressure is close to the 95<sup>th</sup> percentile, the child can be given a diagnosis of primary hypertension. Younger children and those with more markedly elevated blood pressure (Stage II hypertension) should undergo further testing if the initial evaluation is unrevealing in order to exclude secondary causes for hypertension (Table 6).

**Table 5: Initial Laboratory and Imaging Evaluation for All Children with Confirmed Hypertension**

Lab or imaging test	Result	Possible etiology
Urinalysis with microscopy, urine culture	Hematuria, proteinuria, pyuria, bacteria	Occult renal disease, chronic urinary tract infections
BUN and creatinine	Elevated values	Acute kidney injury, chronic kidney disease

Electrolytes, serum calcium	Hyper- or hyponatremia, hyper- or hypokalemia, hypercalcemia	Endocrine or genetic forms of hypertension
Complete blood count	Anemia	Kidney disease, rheumatological disease, chronic disease
Fasting lipids	Elevated total cholesterol, LDL, triglycerides, low HDL	Evaluating for co-morbidity
Fasting glucose	Hyperglycemia	Diabetes mellitus, steroid use
Plasma renin activity	Low or absent plasma renin activity	Endocrine or genetic forms of hypertension
Urine pregnancy test (all post-menarchal females)	Positive test	Pregnancy, pre-eclampsia
Renal and bladder ultrasound	<p>Mass</p> <p>Arteriovenous malformation</p> <p>Bilaterally small kidneys</p> <p>Discrepant kidney sizes (<math>\geq 1.5</math> cm)</p> <p>Bilaterally large kidneys +/- cysts</p> <p>Hydronephrosis, thickened bladder</p> <p>Renal tubers</p> <p>Congenital anomalies</p>	<p>Wilms tumor, neuroblastoma, pheochromocytoma</p> <p>Arteriovenous malformation</p> <p>Chronic kidney disease</p> <p>Past perfusional insults, renal scar, renal artery stenosis, renal hypoplasia, renal vein thrombosis</p> <p>Cystic kidney disease</p> <p>Obstructive uropathy, vesicoureteral reflux, obstructive kidney stone</p> <p>Tuberous sclerosis</p> <p>Horseshoe kidney, pelvic kidney</p>
Echocardiogram	<p>Cardiac abnormalities</p> <p>Left ventricular hypertrophy</p>	<p>Coarctation of the aorta, congenital anomalies, heart dysfunction, pericardial effusion</p> <p>End-organ damage</p>

**Table 6: Additional Tests to Determine Secondary Causes of Hypertension**

<b>Test</b>	<b>Purpose</b>
Urine toxicology screen	Rule out illicit drug use
Plasma and urine steroid levels	Rule out steroid mediated hypertension
Plasma metanephrines	Rule out pheochromocytoma
Polysomnography	Rule out obstructive sleep apnea
24-hour ambulatory blood pressure monitoring	Rule out white coat hypertension
Renal arteriogram with venous renin sampling	Rule out renal artery stenosis

### **Treatment**

Once a child is diagnosed with hypertension and has undergone an evaluation, antihypertensive therapy should be initiated. This therapy should include guidance on lifestyle modification and non- pharmacologic therapy. All children should be counseled on the following heart healthy lifestyle:

1. Weight loss if overweight
2. For children 5 years of age or older: participate in at least 1 hour of moderate-to-vigorous exercise (for example: jogging, baseball) every day of the week, and vigorous activity (for example: running, singles tennis, soccer) on 3 days per week.
3. Decrease sedentary activities such as television watching, video and computer games to less than two hours per day
4. Institute several dietary changes according to the Cardiovascular Health Integrated Lifestyle diet (CHILD-1) and Dietary Approaches to Stop Hypertension (DASH) eating plan<sup>30</sup> such as:
  - a. Increase intake of fresh vegetables, fruits, and low-fat dairy
  - b. Reduce carbohydrate, fat and processed sugar intake
    - i. For 4-18 year olds: aim for 10-30% of total calories to come from protein, 45-65% from carbohydrate, 25-30% from fat
  - c. Limit/avoid sugar-sweetened beverages
  - d. Encourage foods with high dietary fiber content (age + 5 = number of grams/day)
5. Salt restriction



- a. Initially recommend “no added salt” with the ultimate goal of achieving the current recommendation of 1.2 grams per day total for 4- to 8-year-olds and 1.5 grams per day total for children 9 years of age and older<sup>3</sup>
6. Smoking cessation, if applicable

Children who have not experienced normalization of their blood pressure with the above interventions after 6 months should be started on anti-hypertensive medications. In addition, children who initially present with secondary hypertension, symptomatic hypertension, left ventricular hypertrophy, hypertensive retinopathy or who have diabetes mellitus, should be started on anti-hypertensive medications at the time of diagnosis, while implementing the same lifestyle interventions. The pharmacological agent chosen should be targeted to the underlying diagnosis, with attention being paid to existing co-morbidities.

Unless contraindicated, initial therapy with either a *calcium channel blocker* or an *angiotensin converting Enzyme (ACE) inhibitor* could be considered, as these medications are well-tolerated, have a minimal side effect profile, and can be dosed once daily. Beta-blockers, angiotensin receptor blockers and diuretics are also acceptable first line agents for the treatment of hypertension in children. The lowest dose should be started, titrating to effect until the maximum recommended dose is achieved or until the patient experiences side effects. At this point, if blood pressure is not controlled, an additional agent from another class should be added to the regimen in the same manner. Table 7 lists the major classes of antihypertensive agents with several medications from each class.

**Table 7: Oral Medications for the Treatment of Pediatric Hypertension**

<b>Medication Class</b>	<b>Mechanism of Action</b>	<b>Advantages</b>	<b>Disadvantages</b>	<b>Comments</b>	<b>Oral Medications and doses*</b>
Angiotensin Converting Enzyme inhibitor	Prevents conversion of angiotensin I to angiotensin II by inhibiting angiotensin-converting enzymes.  Leads to a decrease in angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion.	Once daily dosing, usually well tolerated  Many agents can be compounded into a suspension	Lab monitoring at initiation and dose increases to monitor for hyperkalemia and increased serum creatinine  Cough and angioedema are known side effects	Contraindicated in aortic stenosis, pregnancy  Can lead to renal failure in individuals with renal artery stenosis  Requires dose adjustment in renal insufficiency	<b><u>Lisinopril</u></b> <b>Start:</b> 0.07 mg/kg/dose once daily; <b>Maximum start dose:</b> 5 mg/dose; <b>Maximum dose:</b> 0.61 mg/kg/dose up to 40 mg/dose. <b>ADULT dose range: Start dose:</b> 10 mg/dose once daily; <b>Usual dose range:</b> 20-40 mg/day; <b>Maximum dose:</b> 80 mg/day <b><u>Enalapril</u></b> <b>Start:</b> 0.08-0.1 mg/kg/day; <b>Maximum start dose:</b> 5 mg/day <b>Maximum dose:</b> 0.6 mg/kg per day up to 40 mg/day <i>(Can be given QD or divided BID)</i> <b>ADULT dose range: Start dose:</b> 2.5-5 mg/dose once daily; <b>Maximum dose:</b> 40 mg/day <i>(QD or divided BID)</i>
Angiotensin-receptor blocker	Competitively binds angiotensin II receptors, blocking the usual effect of vasoconstriction and aldosterone release.	Once daily dosing, usually well tolerated  Losartan can be compounded into a suspension	Lab monitoring at initiation and dose increases to monitor for hyperkalemia and increased serum creatinine	Contraindicated in pregnancy  Can lead to renal failure in individuals with renal artery stenosis	<b><u>Losartan</u></b> <b>Start:</b> 0.7 mg/kg/dose once daily <b>Maximum start dose:</b> 50 mg once daily <b>Maximum dose:</b> 1.4 mg/kg/day up to 100 mg once daily <b>ADULT Start dose:</b> 50 mg once daily; <b>Usual dose range:</b> 25-100 mg/day

			Can cause angioedema		<i>divided QD or BID</i>
$\alpha$ - and $\beta$ -Blocker	<p>Non-selective blocking of beta-adrenergic receptors and selective blocking of alpha (1)-adrenergic receptors.</p> <p>Blocks the following effects of these receptors:  Alpha (1): vasoconstriction, renal sodium reabsorption  Beta (1): Increased cardiac output and renin secretion  Beta (2): Increased renin secretion</p>		<p>May negatively impact athletic performance</p> <p>Heart rate can be dose-limiting</p> <p>Can cause: hyperkalemia, hepatotoxicity, bronchospasm, heart failure, hypo- or hyperglycemia, dyslipidemia</p> <p>Abrupt discontinuation can lead to rebound hypertension</p>	<p>Contraindicated in asthma, heart failure, heart block, pulmonary edema</p> <p>Should avoid use in diabetics</p>	<p><b><u>Labetalol</u></b>  <b>Start dose:</b> 1–3 mg/kg/day divided BID;  <b>Maximum dose:</b> 10–12 mg/kg/day up to 1200 mg/day divided BID  <b><u>ADULT Start dose:</u></b> 100 mg BID; increase by 100 mg/dose every 2–3 days to a <b>Maximum dose</b> of 2.4 g/24 hr <b>Usual dose range:</b> 200–800 mg/24/day divided BID</p>
$\beta$ -Blocker	<p>Blocks beta-receptors.</p> <p>Non-cardioselective beta-blockers competitively block beta1 and beta2 adrenergic receptors.</p>	<p>Propranolol can be administered in a sustained-release formulation, given once daily</p>	<p>May negatively impact athletic performance</p> <p>Heart rate can be dose-limiting</p> <p>Can cause:</p>	<p>Contraindicated in asthma and heart failure (Non-cardioselective agents) and in heart block, pulmonary edema</p>	<p><b><u>Propranolol (Non-cardio selective)</u></b>  <b>Start dose:</b> 1–2 mg/kg/day divided BID or TID; <b>Maximum dose:</b> 4 mg/kg/day up to 640 mg/day divided BID or TID  <b><u>ADULT Start dose:</u></b> 40 mg/dose given BID <b>or</b> 60–80 mg of sustained-release</p>

	Cardioselective beta-blockers preferentially block beta1 receptors, although at higher doses will also block beta2 receptors.	Can be used to treat migraine headaches  Usually well tolerated	hyperkalemia, hepatotoxicity, bronchospasm, heart failure, hypo- or hyperglycemia, dyslipidemia  Abrupt discontinuation can lead to rebound hypertension	Should avoid use in diabetics	capsule once daily. <b>Usual dose range:</b> 160-320 mg once daily; <b>Maximum dose:</b> 640 mg/24 hr. <b>Atenolol</b> <b>(Cardioselective (<math>\beta</math>-1 &gt; <math>\beta</math>-2) Blocker)</b> <b>Start dose:</b> 0.5–1 mg/kg/day divided QD or BID; <b>Maximum dose:</b> 2 mg/kg/day up to 100 mg/day divided QD or BID; <b>ADULT start dose:</b> 50 mg once daily; <b>Maximum dose:</b> 100 mg once daily
Calcium channel blocker	Blocks calcium channels located on muscle cells. Leads to vascular smooth muscle relaxation, arterial vasodilation and decreased cardiac contraction, heart rate and conduction.	Once daily dosing, usually well tolerated  Several agents can be compounded into a suspension  Several agents have extended-release formulations	May cause tachycardia, peripheral edema		<b>Amlodipine</b> <b>Start dose:</b> 0.1 mg/kg once daily; <b>Maximum start dose:</b> 5 mg daily; <b>Maximum dose</b> of 0.6 mg/kg/day up to 10 mg/day. <i>Can also be divided BID.</i> <b>ADULT start dose:</b> 5- 10 mg once daily; <b>Maximum dose:</b> 10 mg once daily
Central $\alpha$ -agonist	Stimulates alpha 2-adrenergic receptors, which	Transdermal formulation available; patch	Can cause: dry mouth, sedation, constipation	Concurrent $\beta$ -Blocker use may exacerbate	<b>Clonidine</b> <b>Start dose:</b> 5–10 mcg/kg/day PO divided Q8–12 hr; increase at 5–7 day

	decreases central sympathetic outflow.	can be changed once weekly.  Oral suspension available.	Abrupt discontinuation can lead to rebound hypertension	rebound hypertension during medication withdrawal.	intervals to 5–25 mcg/kg/day PO divided Q6 hr; <b>Maximum dose:</b> 25 mcg/kg/day up to 0.9 mg/day; <b>ADULT start dose:</b> 0.1 mg BID; increase in weekly intervals by 0.1 mg/day; <b>Usual dose range:</b> 0.1–0.8 mg/day divided BID; <b>Maximum dose:</b> 2.4 mg/day
Diuretic	Thiazides inhibit sodium and chloride reabsorption in the distal convoluted tubule; loop diuretics inhibit sodium, potassium, and chloride transport in the thick ascending limb of the loop of Henle.	Useful as add-on therapy and in children with edema	Lab monitoring after initiation and dose increases to monitor for electrolyte disturbances  May lead to hyperuricemia  May negatively impact athletic performance	Potassium sparing diuretics can lead to hyperkalemia when used with ACE inhibitors and/or angiotensin receptor blockers  Furosemide is contraindicated in anuria and hepatic coma	<b>Hydrochlorothiazide</b> <b>Start dose:</b> 1 mg/kg/day once daily <b>Maximum dose:</b> 3 mg/kg/day up to 50 mg/day given once daily <b>ADULT start dose:</b> 12.5-25 mg once daily; <b>Maximum dose:</b> 100 mg/day divided once daily or BID <b>Furosemide</b> <b>Start dose:</b> 0.5–2.0 mg/kg/dose, can be given once daily to BID; <b>Maximum dose:</b> 6 mg/kg/dose given once daily or BID; <b>ADULT start dose:</b> 20-80 mg/dose given Q6-12 hours; <b>Maximum dose:</b> 600 mg/day

Vasodilator	Directly relax vascular smooth muscle	Oral suspension available (hydralazine)	Can cause: tachycardia, fluid retention; hypertrichosis (minoxidil); lupus-like syndrome (hydralazine)	Requires dose adjustment in renal insufficiency  Generally reserved as add-on therapy for resistant hypertension.  Concurrent use with $\beta$ -Blocker and diuretic recommended to prevent tachycardia and edema	<p><b><u>Hydralazine</u></b> Start dose: 0.75 mg/kg/day divided Q6-12 hours; <b>Maximum start dose:</b> 25 mg/dose; <b>Maximum dose:</b> 7.5 mg/kg/day up to 200 mg/day; <b>ADULT start dose:</b> 10-50 mg/dose given Q6 hours; <b>Maximum dose:</b> 300 mg/day</p> <p><b><u>Minoxidil</u></b> <b>Children &lt; 12 years:</b> <b>Start dose:</b> 0.2 mg/kg/day divided QD-TID; <b>Maximum start dose:</b> 5 mg/day; <b>Maximum dose:</b> 50 mg/day divided QD-TID <b>Children <math>\geq</math> 12 years/ADULT:</b> <b>Start dose:</b> 5 mg/day divided QD-TID; <b>Usual dose range:</b> 10-40 mg/day divided QD-TID; <b>Maximum dose:</b> 100 mg/day divided QD-TID</p>
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Below are recommendations for prescribing classes of antihypertensive agents for certain medical conditions.

### **Diabetes**

Consider: ACE inhibitors, Angiotensin receptor blockers (Offer renoprotection and can decrease proteinuria)

Avoid: Beta-blockers (Can mask signs/symptoms of hypoglycemia)

### **Migraine headaches**

Consider: Beta-blockers, Calcium channel blockers (May offer symptomatic improvement for migraine headaches while controlling blood pressure)

### **Asthma**

Avoid: Beta-blockers since contraindicated for asthma (Can cause bronchospasm)

### **Kidney disease and/or proteinuria**

Consider: ACE inhibitors, Angiotensin receptor blockers (Offer renoprotection and can decrease proteinuria)

### **Athlete**

Avoid: Beta-blockers, diuretics (May negatively impact athletic performance)

### **Sexually active female**

Avoid: ACE inhibitors, Angiotensin receptor blockers (Teratogenic; recommend birth control methods)

### **Obesity**

Consider: ACE inhibitors, Angiotensin receptor blockers (May have beneficial effects on comorbidities such as diabetes and dyslipidemia)

Avoid: Beta-blockers, diuretics

(Beta blockers can lead to weight gain, increased triglycerides and decreased high-density lipoprotein cholesterol concentrations)

(Diuretics can worsen insulin resistance and dyslipidemia. They can also increase sympathetic system nervous system and renin activity, both of which are thought to be increased in obesity-related hypertension)

The goal of anti-hypertensive therapy is achievement of normotension, defined as persistent systolic and diastolic blood pressures below the 95<sup>th</sup> percentile. In children at increased cardiovascular risk (those with chronic kidney disease, diabetes mellitus, post heart or kidney

transplantation, history of Kawasaki disease, chronic inflammatory disease, HIV or nephrotic syndrome) or with end-organ damage (left ventricular hypertrophy or hypertensive retinopathy), the anti-hypertensive goal is lower. These children should be treated to achieve systolic and diastolic blood pressures below either the 90<sup>th</sup> percentile, or 120/80, whichever is lower.

### **Prognosis**

Children with hypertension should be followed closely to evaluate the effectiveness of prescribed anti-hypertensive therapy, and to reinforce medication adherence and heart healthy behaviors. If available, blood pressure measurements obtained by a school nurse can be useful in titrating medication dosages between clinic appointments, and in monitoring therapy.

Hypertensive children should also be intermittently screened for the development of end-organ damage in the form of left ventricular hypertrophy, hypertensive retinopathy and microalbuminuria. Children with left ventricular hypertrophy at diagnosis should have a repeat echocardiogram completed 6-12 months after starting anti-hypertensive medications to ensure their left ventricular mass has decreased with therapy. Children without evidence of left ventricular hypertrophy at diagnosis should also undergo follow up echocardiography as left ventricular hypertrophy can develop relatively quickly, can be seen in children with presumably good blood pressure control and cannot be predicted by the severity of a child's blood pressure elevation. While often clinically silent in childhood, these forms of end-organ damage are associated with significant morbidity and mortality in adulthood. The presence of any one of these entities signifies increased cardiovascular risk and the need for intensified anti-hypertensive treatment to reverse these findings and prevent worsening cardiovascular disease.



Some children will require long-term anti-hypertensive therapy into adulthood to maintain normotension. However, successful implementation of lifestyle modifications has been shown to be effective in lowering blood pressure in both children and adults, and can allow some children to avoid or discontinue pharmacologic treatment. Children with primary, obesity related hypertension in particular may be able avoid or discontinue anti-hypertensive medications with lifestyle modifications. Obese children have been shown to experience significant blood pressure reductions with salt restriction, and weight loss is particularly effective at lowering blood pressure.

Children with secondary hypertension may experience normalization of blood pressure as their underlying disease process resolves, allowing them to discontinue medical therapy. However, when a chronic underlying condition has led to a child's hypertension, complete normalization of blood pressure is less likely and management may require long-term antihypertensive therapy and monitoring.

### **Summary**

Based on the National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents consensus, which was developed from the synthesis of all available scientific evidence (NHBPEP, 2004):

- Pediatric hypertension is defined as an average of systolic **OR** diastolic blood pressure measurements at or above the 95th percentile BP for the child's age, sex and height percentile.
- All children three years of age and older who present for care – well child care, urgent care, emergency care – should have their blood pressure measured during each visit. In

addition, some at risk children under three years of age should also have their blood pressure measured at each provider visit.

- All children with confirmed hypertension should undergo a work up to rule out secondary causes. The age of the child and the severity of the blood pressure elevation will dictate how extensive this work up should be.
- Once a child is diagnosed with hypertension and undergone a work up, anti-hypertensive therapy should be initiated: this includes lifestyle modification for all children and pharmacologic therapy for some children.

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### **Chapter 3: Real Time Electronic Medical Record Alerts Increase High Blood Pressure Recognition in Children**

#### **Abstract**

**Background/Objective:** Pediatric hypertension is increasingly prevalent but remains largely unrecognized. Strategies to increase recognition of elevated blood pressure (BP) will enhance prevention and control efforts. We hypothesized that an electronic medical record (EMR) alert system would increase elevated BP recognition in a pediatric primary care setting.

**Methods:** Quality improvement initiative to improve elevated BP recognition through implementation of an ongoing real-time EMR alert coupled with a one-time provider educational session. Encounters of children 3-21 years of age with an elevated intake BP and no history of hypertension were included. Recognition was defined as provider documentation of a repeat BP; BP noted to be abnormal; or plan to repeat/evaluate BP.

**Results:** Recognition increased from 12.5% to 42% ( $p < 0.001$ ) and was no different by educational session attendance status. During both pre-intervention and intervention periods, systolic BP  $\geq 120$ mmHg was associated with greater recognition. However, the prevalence ratio (PR) of recognition was smaller in the intervention period: intervention PR 1.3, 95% confidence interval (CI) 1.2 – 1.5 ( $p < 0.001$ ) versus pre-intervention PR 2.4, 95%CI 1.4-3.9 ( $p = 0.001$ ). Similar relationships were observed for other cardiovascular risk factors. Acute care visit encounters were associated with decreased recognition in the intervention period (PR 0.6, 95% CI 0.5- 0.7;  $p < 0.001$ ).

**Conclusions:** Real time EMR alerts substantially increase provider recognition of elevated BP in children and hold considerable promise as a means to improve adherence to practice guidelines. Still, under-recognition of elevated BP in children persisted. These results highlight the need for additional strategies to improve provider recognition.

## Introduction

Over the last several decades, pediatric hypertension (HTN) has increased in prevalence, and its importance in the overall cardiovascular (CV) health of children has been emphasized<sup>19</sup>. In addition to being associated with atherosclerosis in childhood, pediatric HTN is one CV disease (CVD) risk factor that has known clinical implications in adulthood. As a result, guidelines published in 2004<sup>3</sup> and 2011<sup>19</sup> highlight annual blood pressure (BP) measurement of all children three years and older as one of the key strategies for CV risk identification and reduction among children to decrease the burden and associated morbidity and mortality of CVD in adults<sup>19</sup>.

Despite these guidelines, routine BP measurement<sup>21</sup>, provider recognition of elevated BP, and diagnosis of pediatric HTN all remain low. We have previously shown that only 13% of elevated BPs measured in an urban academic pediatric primary care setting were recognized as elevated by providers<sup>22</sup>. These results are similar to those obtained in a pediatric emergency department setting<sup>34</sup> and in a large pediatric primary care setting<sup>23,35</sup>.

Recognizing the many demands faced by primary care providers, we hypothesized that real-time electronic elevated BP alerts during clinic visits would increase recognition of elevated BP by eliminating the cumbersome steps for proper classification – specifically, the steps of determining a child’s age- and sex-specific height percentile followed by determining their age-sex- and height percentile- specific BP cutoffs. We also hypothesized that improving provider knowledge of guidelines would contribute to greater recognition. To test these hypotheses, we implemented and evaluated a two component intervention: ongoing real-time electronic medical record (EMR) alerts coupled with a one-time provider educational session.

## Methods

We conducted a pre-post evaluation of a quality improvement and education initiative designed to improve provider recognition of elevated BP in children. The setting was an urban, academic primary care practice staffed by pediatric residents, adolescent medicine fellows, attending physicians, and nurse practitioners. All acute and scheduled (well-child care and follow-up) encounters during the intervention period (1/1/09-6/30/09) and scheduled encounters during the pre-intervention period (1/1/06-6/30/06) of patients 3-21 years of age with an elevated intake BP were included.

The pre-intervention and intervention periods were chosen to capture a different cohort of resident providers, target the same time of year to minimize the impact of resident training level, and occur soon after alert implementation. Encounters were excluded if they were of children with a prior HTN diagnosis (n=105); if BP was <120/80 and no height information was recorded within the previous 6 months (n=15); or if the provider clinic note was missing (n=51). This study was approved by an institutional review board of Johns Hopkins University School of Medicine.

### Blood Pressure Measurement Protocol and Intervention

In the practice, intake BP was measured via oscillometry by a nurse or a nursing assistant prior to the provider encounter. All intake BPs, together with the patient's height and weight, were immediately entered into the EMR and were available to providers at the start of the visit during both periods. Pediatric guidelines for monitoring BP, which included age/sex/height percentile-specific BP norms<sup>3</sup> were readily available in print and on-line.

In September 2008, a real-time electronic alert was incorporated into the existing EMR to notify providers when an intake BP was elevated. All elevated BPs ( $\geq 90^{\text{th}}$  percentile for age/sex/height percentile<sup>19</sup> or  $\geq 120/80$ ) generated an EMR alert that the BP was elevated and should be repeated. This was a hard stop and could only be reconciled by entering: “provider needs to obtain manual repeat” or “manual repeat completed” with the additional BPs entered in the EMR at that time. All BPs obtained by the nursing staff and all responses entered were immediately visible to the provider in the EMR.

In addition to this alert, a 30-minute educational session reviewing current BP measurement guidelines and HTN evaluation was offered to all resident providers who held a weekly continuity clinic at the study site (n=59). This session was taught by the same person (TMB) during the regularly scheduled pre-clinic conference from 1/12/09-1/16/09. Resident providers who were not present for these sessions were provided the educational materials and instructed to review them independently (n=13).

#### Data Collection and Variables

The EMR for each encounter was reviewed manually by a research assistant who collected the following information from the visit: patient age, sex, self-reported race, medical history/co-morbid conditions, family history of CVD [defined as one or more of the following: early myocardial infarction ( $\leq 55$  years for men,  $\leq 65$  years for women), cerebrovascular accident, CVD, HTN, dyslipidemia], presence of hypertensive symptoms (one or more noted: headache, nausea, vomiting, shortness of breath/dyspnea, chest pain, palpitations), anthropometrics, and BP. Body mass index (BMI) and BMI z-score were calculated according to the 2000 Centers for Disease Control and Prevention Growth Charts<sup>36</sup>. Children were categorized as being

overweight/obese if their BMI was  $\geq 85^{\text{th}}$  percentile or  $\geq 25\text{kg/m}^2$  if they were 20 years of age or older.

The intake BPs were indexed to the  $90^{\text{th}}$  percentile by taking the measured BP and dividing it by the  $90^{\text{th}}$  percentile BP for each individual's age/sex/height percentile. A systolic or diastolic BP index  $\geq 1$  indicates an elevated BP. In the instance that BP was repeated in triage (n=93), the average of the two BPs was indexed to the  $90^{\text{th}}$  percentile. In addition, each child's systolic and diastolic BP were categorized as at/above vs. below 120 mmHg and 80 mmHg, respectively.

The outcome variable of the study was recognized elevated BP, defined as recognized if any of the following were documented in the EMR for each encounter: (a) provider repeated BP by manual auscultation; (b) provider assessment included abnormal BP, elevated BP or HTN; (c) provider plan included repeat BP or an evaluation for elevated BP.

### Data Analyses

The overall prevalence of recognition during the intervention period was determined and compared to the prevalence in the pre-intervention time period by chi squared analysis. Elevated BP during patient encounters were dichotomized as recognized vs. not, and patient, clinic and provider characteristics were compared between the two groups using student's t-test for continuous variables and chi squared analyses for categorical variables. To more directly model the prevalence of recognition, univariate log-binomial regression was used to obtain the prevalence ratios of recognition by each characteristic. Multivariable log-binomial regression, adjusting for educational session attendance, was conducted to determine the impact of educational sessions on recognition. In addition, the prevalence of recognition by various characteristics was compared between the pre-intervention and intervention period using chi

squared analyses. Analyses were conducted using Stata 11.0 (StataCorp, College Station, TX). A p-value of <0.05 was considered to be statistically significant.

## Results

During the six month intervention period, there were 1305 encounters with elevated BP (Figure 1) out of 5919 total encounters of 3285 unique patients. Overall, 42% (556/1305) of encounters with an elevated BP were recognized during the intervention period compared to 12.5% (100/803) recognized during the pre-intervention period ( $p < 0.001$ ). The prevalence of recognition remained stable throughout the six month intervention period (Figure 2). In the intervention period, children who were older, non-African American, male, overweight/obese, or with a family history of CVD, a personal history of co-morbid condition(s) or a systolic BP  $\geq 120$  mmHg were more likely to have their elevated BP recognized (Table 8). Complaints of hypertensive symptoms (defined in Table 8 subscript c), lack of a significant medical history, diastolic BP  $\geq 80$  mmHg, provider type, and educational session attendance were not associated with recognition. During the intervention period, elevated BP was less likely to be recognized during an acute care visit than during a scheduled appointment.

Overall, recognition significantly increased from the pre-intervention to the intervention period for each patient, clinic and provider characteristic (Table 9). Within each period, there was no difference in recognition by provider type. Forty-seven of the 59 resident providers attended the educational session; recognition was no different when stratified by educational session attendance (Table 9).

The prevalence ratio (PR) of provider recognition was 2.6-3.7 times greater for each month in the intervention period compared to the pre-intervention period overall (Table 10); this difference persisted after adjusting for educational session attendance ( $p < 0.001$ ). In



addition, compared to scheduled encounters, acute care visit encounters were associated with significantly decreased recognition (Table 10). As observed pre- intervention, a systolic BP  $\geq 120$  mmHg was associated with significantly greater recognition (PR 1.3, 95% confidence interval (CI) 1.2, 1.5;  $p < 0.001$ ); however, the PR was not as large as observed during the pre-intervention period (PR 2.4, 95% CI 1.4, 3.9;  $p = 0.001$ ) (Figure 3). Also, elevated BP encounters for children with increased CV risk (presence of overweight/obesity, higher BMI z-score, family history of CVD) or with a known co-morbidity were associated with greater provider recognition; however, as with systolic BP, the PRs were lower in the intervention period (Figure 3).

Several variables not associated with elevated BP recognition pre-intervention were significantly associated with increased recognition in the intervention period: older age, male sex, and non-AA race (Figure 3). Absence of significant medical history was no longer predictive of recognition in the intervention period (pre-intervention PR 0.4, 95% CI 0.2, 0.7,  $p = 0.002$ ; intervention PR 1.1, 95% CI 0.8, 1.5,  $p = 0.7$ ).

Several sensitivity analyses were conducted. In this study, we used the average of all intake BPs to determine if a child's BP was elevated. Because providers may disregard the first measurement and instead use the most recent measurement in their assessment, we examined recognition prevalence using only the most recent intake BP. Of the 93 encounters in which a BP was repeated prior to the provider encounter, 17 (18%) BPs were normal on repeat. Re-categorizing these BPs as "recognized" and excluding the five encounters with repeat BPs  $< 120/80$  and no height measurement in the EMR, the rate of recognition increased slightly to 44% (573/1300).

The pre-intervention period did not include acute care encounters. To determine how inclusion of these encounters in the intervention period may have influenced our results, we

calculated the prevalence of recognition after excluding acute care encounters. In this analysis, the prevalence of recognition increased to 49% ( $p=0.003$ , compared to pre-intervention period).

## **Discussion**

In this study of clinic encounters of patients 3-21 years of age without prior history of HTN in an urban, academic primary care center, we demonstrated that implementation of an automated EMR alert significantly increased provider recognition of elevated BP. The educational session that focused on proper BP measurement and elevated BP recognition and evaluation did not impact recognition as demonstrated in adjusted and stratified analyses. Recognition increased soon after implementation and was sustained throughout the six month study period; there was no evidence of “alert fatigue”, i.e. no decline in recognition after an initial peak. Many of the same characteristics associated with recognition in the pre-intervention period<sup>22</sup> were also associated in the intervention period; however, the magnitude of these associations significantly decreased. Overall, these results support the hypothesis that the complex steps required to recognize elevated BP in children hinder recognition. Electronic alerts can replace the cumbersome process in which providers manually compare a patient’s BP to the age/sex/height percentile BP tables.

As shown previously, patient characteristics that increase the risk of high BP were associated with greater recognition of elevated BP<sup>22</sup>. Children with a greater BMI z-score or categorized as overweight/obese, those with a family history of CVD, and those with co-morbid conditions such as diabetes or kidney disease were more likely to have their elevated BP recognized than were children without these characteristics. Interestingly, recognition was less influenced by the presence of these CV risk factors in the intervention period. While many remained positively associated with recognition, the magnitude was significantly decreased. In

fact, having no significant medical history neither increased nor decreased the probability of recognition, whereas previously this patient characteristic was associated with a 60% decrease in recognition. Similarly, healthy weight children with elevated BP were much less likely to have their elevated BP recognized than overweight/obese children in the pre-intervention period. After implementation of the EMR alert, the PR of recognition increased from 0.4 to 0.8, providing evidence that these children were less likely to be missed. These findings imply that the alert may have helped bridge the gap between those with and without obvious CV risk factors, allowing for enhanced recognition of elevated BP in those who would not otherwise appear to be at risk.

During the intervention period, elevated BP recognition was less dependent on extremely elevated BP. While systolic BP at or above the commonly recognized threshold of 120 mmHg was 1.3 times more likely to be recognized than elevations below 120 mmHg, this “advantage” was less prominent than in the pre-intervention period when such a BP extreme was associated with a 2.4 times increase in recognition.

Several patient characteristics were associated with elevated BP recognition in the intervention period that were not associated pre-intervention. Males and AA children were more likely to have their elevated BP recognized than females and non-AA, respectively. Greater recognition of HTN in these patient groups has been shown in adults<sup>37</sup>. The racial differences in recognition may reflect greater physician awareness of CV risk in minority racial groups as suggested by Banerjee et al.<sup>37</sup> The lack of an association prior to alert implementation may have been due to the poor rate of recognition overall or reduced statistical power because there were fewer clinical encounters with elevated BP in the pre-intervention period than the intervention period.

Another notable finding is that the increase in recognition was sustained over the course of the six months study period. One of the main concerns providers have with computerized alerts is that they will become desensitized to alerts over time and less likely to notice and/or respond to them<sup>38</sup> or more likely to override built-in hard stops<sup>39, 40</sup>. Results from our study dispel this concern.

While increasing provider awareness and education are essential elements of increasing recognition of elevated BP, this study suggests that simplification of a non-intuitive process is critical to achieving improved recognition in a pediatric population. A systematic review of studies evaluating the impact of provider education on clinical practice in the management of HTN found only one randomized controlled trial utilizing formal CME training that resulted in a decrease in systolic BP but no long term change in diastolic BP, BMI, or pattern of BP medication use. Other randomized controlled trials found no change in BP control with formal CME or educational materials<sup>41</sup>.

While recognition of elevated BP did increase, over 55% of encounters with elevated BP in the intervention period remaining unrecognized. With the increased prevalence of HTN and other CV risk factors and the mounting evidence that the origins of CVD are in childhood, further improvements in recognition are needed. While many of these children likely do not have HTN, as that is determined by the sustained elevation of BP over time, having intermittently elevated BP increases one's risk for the ultimate development of HTN. A child with a BP >95<sup>th</sup> percentile that normalizes on repeat measurement has a greater chance of developing HTN (1.4% incidence per year) than a child with normal BP (0.3% per year) or one with confirmed pre-hypertension (1.1% per year). Having a BP >95<sup>th</sup> percentile that decreases only to the pre-

hypertensive range increases one's risk for developing HTN to an even greater degree (6.6% per year)<sup>42</sup>.

Our study has limitations. First, recognition of elevated BP was defined by information obtained from completed provider clinic notes. It is possible that not all recognized elevations were documented in the EMR. In addition, 51 encounters did not have a transcribed clinic note to review, which may have influenced our results. Second, this study was unable to capture how many times a BP was not obtained. It is routine practice in this clinic to measure BP during all health care encounters, but we are unable to confirm whether or not this occurred. Finally, this study is a pre-post evaluation, not a randomized trial. Such a trial would likely be a cluster randomized trial. Given the nature of the intervention, which is a system change, such a trial would be logistically difficult and likely impractical because of cost and feasibility considerations. Finally, the intervention period included data from both scheduled clinic and acute care encounters, as opposed to the pre-intervention period, in which data collection focused solely on scheduled clinic encounters. Still, we conducted a sensitivity analysis that excluded acute care encounters in the intervention period. This analysis revealed an increase in recognition prevalence from 42% to 49% and suggests that the intervention may enhance recognition to a greater degree during regular scheduled visits.

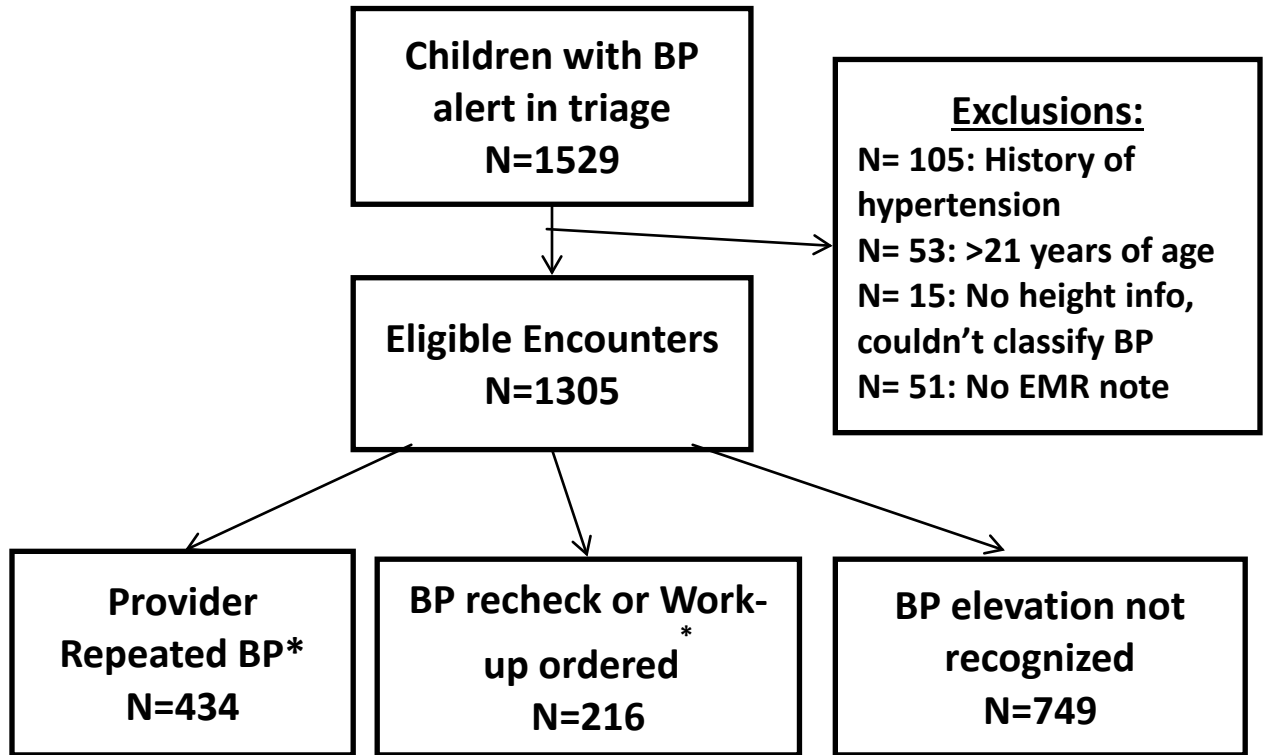
Our study also has several strengths. To our knowledge, it is the first study that directly compares the impact of an electronic alert on recognition of elevated BP in a pediatric primary care population. Second, the study was conducted in a large, urban, academic center that serves a high risk community. Third, it is likely that all encounters with elevated BP were detected. There was no reliance on chart screening to identify instances of elevated BP. Rather, monthly reports were generated listing each encounter where an alert occurred.

Fourth, recognition was based on thorough chart review of clinic notes and did not rely on billing codes or administrative data.

### **Conclusion**

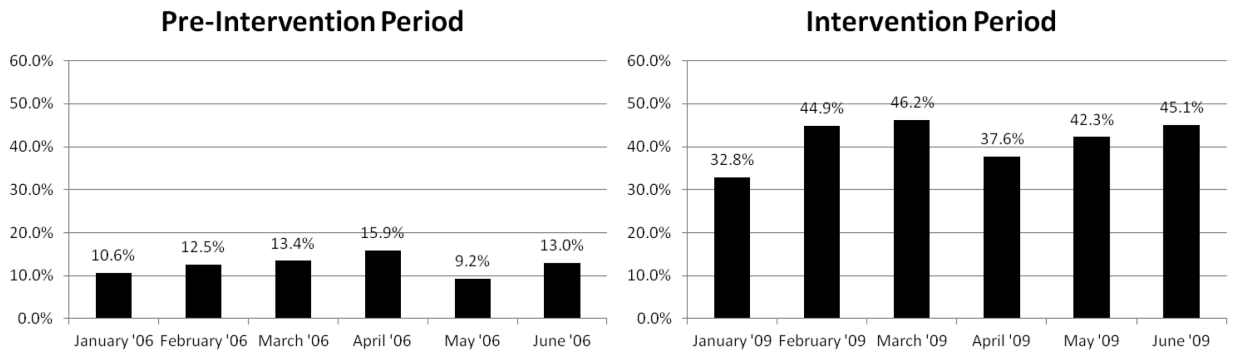
In conclusion, real time EMR alerts can substantially increase provider recognition of elevated BP in children and hold considerable promise as a means to improve adherence to practice guidelines. Still, under-recognition of elevated BP in children persists. Additional strategies to improve provider recognition are needed.

**Figure 1: Flow Diagram of Included Encounters and Provider Recognition in the Intervention Period**

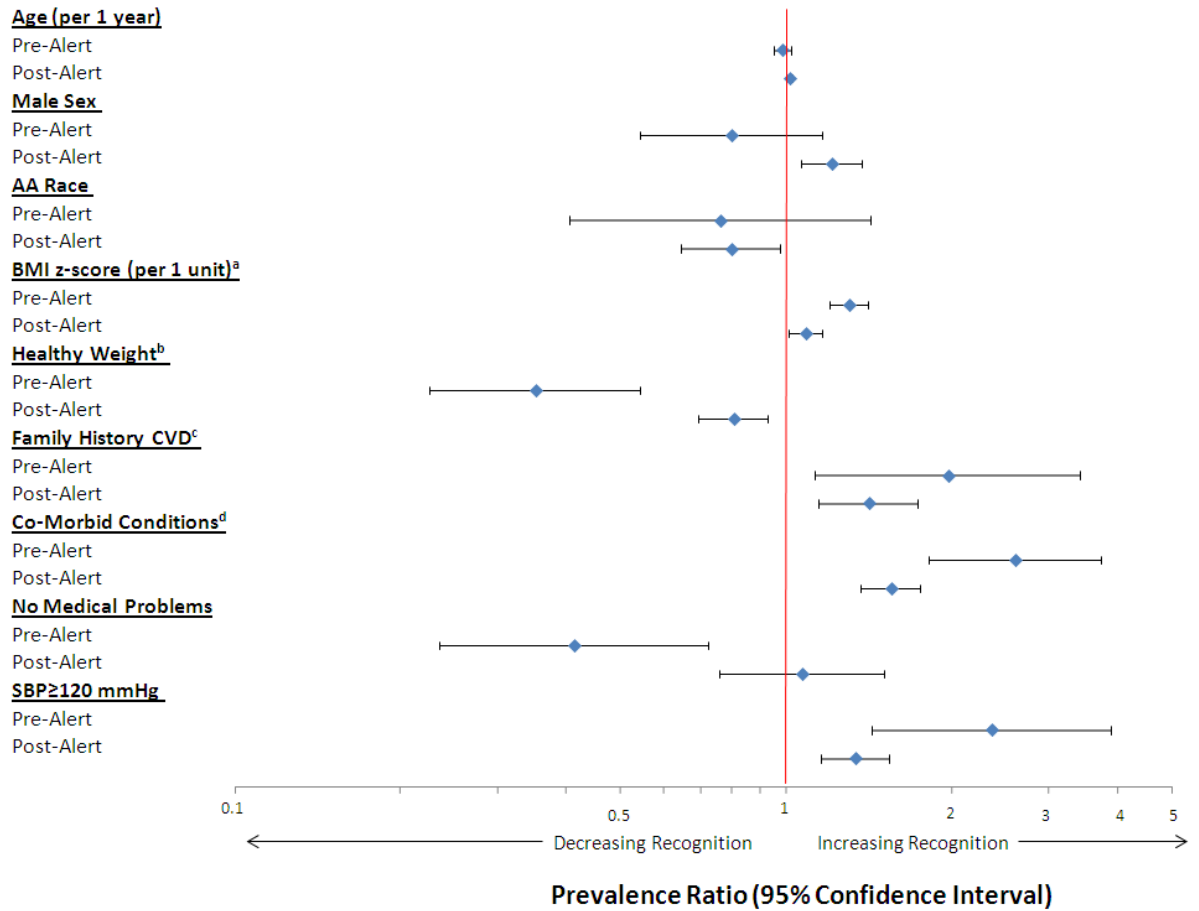


\*Some providers repeated BP *and* planned an additional BP measurement/ordered an evaluation

**Figure 2: Percent of Elevated Blood Pressure Measurements Recognized by Providers during the Pre-Intervention and Intervention Periods**



**Figure 3: Prevalence Ratios of Elevated Blood Pressure Recognition by Various Characteristics during the Pre-Intervention and Intervention Periods**



AA=African American; BMI= Body Mass Index; CVD=cardiovascular disease

<sup>a</sup>BMI z-score is the standard deviation score determined using Centers for Disease Control growth charts.

<sup>b</sup>Healthy Weight defined as a BMI < 85<sup>th</sup> percentile and < 25 kg/m<sup>2</sup> if ≥ 20 years of age; compared to being overweight/obese which is defined as a BMI ≥ 85<sup>th</sup> percentile or ≥ 25 kg/m<sup>2</sup> if ≥ 20 years of age

<sup>c</sup>Family history of CVD defined as any of the following: early myocardial infarction, cerebrovascular accident, cardiovascular disease, high cholesterol, hypertension

<sup>d</sup>Co-Morbid conditions include past medical history of any of the following: obesity, metabolic syndrome, insulin resistance, diabetes mellitus, kidney disease or prematurity



**Table 8. Characteristics of Encounters with Recognized Elevated Blood Pressure, Pre-Intervention and Intervention Periods**

Characteristic	Pre-Intervention							Intervention						
	Overall (n=803)		Blood Pressure Elevation				p-value	Overall (n=1305)		Blood Pressure Elevation				p-value
	Mean or %	SD or n	Recognized (n=100)		Unrecognized (n=703)			Mean or %	SD or n	Recognized (n=556)		Unrecognized (n=749)		
			Mean or %	SD or n	Mean or %	SD or n	Mean or %			SD or n	Mean or %	SD or n		
Age (yrs)	12.6	5.1	12.2	4.8	12.7	5.1	0.36	12.9	5.9	13.3	5.7	12.6	5.9	0.02
African American	93.0%	747	91.0%	91	93.3%	656	0.40	93.2%	1216	91.6%	509	94.4%	707	0.05
Male Sex	43.6%	350	38.0%	38	44.4%	312	0.24	41.2%	538	45.9%	255	37.8%	283	0.004
Body Mass Index (kg/m <sup>2</sup> )	24.6	17.5	30.4	44	23.7	8.2	0.14	25.4	8.6	25.9	8.5	25	8.7	0.12
Overweight or obese <sup>a</sup>	51.3%	388	75.0%	72	47.8%	316	<0.001	55.1%	454	60.5%	245	49.9%	209	0.003
Acute Care Visit	N/A							34.6%	437	24.5%	132	42.0%	305	<0.001
Family History CV disease <sup>b</sup>	6.0%	48	11.1%	11	5.3%	37	0.04	24.1%	105	31.0%	61	18.5%	44	0.003
Complaints of hypertensive symptoms <sup>c</sup>	12.2%	98	11.1%	11	12.4%	87	0.87	18.6%	243	18.9%	105	18.4%	138	0.83
Presence of co-morbid conditions <sup>d</sup>	20.4%	164	40.0%	40	17.6%	124	<0.001	22.6%	295	31.1%	173	16.3%	122	<0.001
No Significant Medical History	26.7%	214	13.0%	13	28.6%	201	0.001	96.2%	1255	96.4%	536	96.0%	719	0.77
SBP <sup>e</sup> ≥ 120 mmHg	67.5%	542	83.0%	83	65.3%	459	<0.001	64.0%	835	70.3%	391	59.3%	444	<0.001
DBP <sup>e</sup> ≥ 80 mmHg	65.8%	46	9.1%	9	5.3%	37	0.16	8.0%	104	9.0%	50	7.2%	54	0.26
SBP index <sup>f</sup>	1.02	0.06	1.07	0.08	1.02	0.06	<0.001	1.01	0.07	1.02	0.06	1.01	0.07	0.001
	N=719		N=93		N=626			N=712		N=353		N=359		

DBP index <sup>f</sup>	0.84	0.14	0.97	0.14	0.83	0.14	0.02	0.89	0.13	0.88	0.13	0.89	0.12	0.78
	N=714		N=92		N=622			N=712		N=353		N=359		
Resident Clinic								63.6%	830	65.1%	362	62.5%	468	0.35
- Resident	N/A							60.1%	499	58.8%	213	61.1%	286	0.52
Provider														
attended														
education														
session														

<sup>a</sup>Body Mass Index (BMI)  $\geq 85^{\text{th}}$  percentile or BMI  $\geq 25 \text{ kg/m}^2$  if age  $\geq 20$

<sup>b</sup>Family history of cardiovascular (CV) disease includes any of the following: early myocardial infarction, cerebrovascular accident, cardiovascular disease, high cholesterol, hypertension

<sup>c</sup>Defined as the presence of any of the following in the encounter note: headache, nausea, vomiting, shortness of breath, chest pain, palpitations

<sup>d</sup>Co-morbid conditions include past medical history of any of the following: obesity, metabolic syndrome, insulin resistance, diabetes mellitus, kidney disease or prematurity

<sup>e</sup>Systolic Blood Pressure, Diastolic Blood Pressure

<sup>f</sup>The systolic/diastolic blood pressure index (SBP index/DBP index) is defined as the measured systolic or diastolic blood pressure (BP) divided by the age/sex/height percentile-specific 90<sup>th</sup> percentile systolic or diastolic BP; an index  $\geq 1$  indicates a BP at or above the 90<sup>th</sup> percentile.

**Table 9. Prevalence of Recognized Elevated Blood Pressure in the Pre-Intervention and Intervention Periods Stratified by Patient, Clinic and Provider Characteristics**

Characteristic	Pre-Intervention Period				Intervention Period				Pre vs. Post
	Number of encounters with elevated BP		% recognized		Number of encounters with elevated BP		% recognized		p-value <sup>b</sup>
	N	%	N	p-value <sup>a</sup>	N	%	N	p-value <sup>a</sup>	
<b><u>Patient Demographics</u></b>									
<b>Age</b>									
≥ 12 years	452	12.0%	54	0.67	753	45.4%	342	0.02	<0.001
< 12 years	351	13.1%	46		552	38.8%	214		<0.001
<b>Sex</b>									
Male	350	10.9%	38	0.24	538	47.4%	255	0.004	<0.001
Female	453	13.7%	62		767	39.2%	301		<0.001
<b>Race</b>									
African American	747	12.2%	91	0.40	1216	41.9%	509	0.05	<0.001
Non-African American	56	16.1%	9		89	52.8%	47		<0.001
<b><u>Medical History</u></b>									
<b>Family History of Cardiovascular Disease<sup>c</sup></b>									
Yes	48	22.9%	11	0.04	105	58.1%	61	0.003	<0.001
No	753	11.7%	88		330	41.2%	136		<0.001
<b>Presence of Co—Morbid Conditions<sup>d</sup></b>									
Yes	164	24.4%	40	<0.001	295	58.6%	173	<0.001	<0.001
No	639	9.4%	60		1010	37.9%	383		<0.001
<b>Past Medical History</b>									
Any	589	14.8%	87	0.001	50	40.0%	20	0.77	<0.001
None	214	6.1%	13		1255	42.7%	536		<0.001

<b>Clinical Measurements</b>									
<b>Adiposity</b>									
Overweight/Obese <sup>e</sup>	388	18.6%	72	<0.001	454	54.0%	245	0.003	<0.001
Healthy Weight <sup>f</sup>	369	6.5%	24		370	43.2%	160		<0.001
<b>Blood Pressure</b>									
SBP≥120 mmHg	542	15.3%	83	<0.001	835	46.8%	391	<0.001	<0.001
SBP<120 mmHg	261	6.5%	17		470	35.1%	165		<0.001
DBP≥80 mmHg	46	19.6%	9	0.16	104	48.1%	50	0.26	0.001
DBP<80 mmHg	752	12.0%	90		1201	42.1%	506		<0.001
<b>Provider Characteristics</b>									
<b>Provider Type</b>									
Nurse Practitioner	173	9.3%	16	0.28	247	42.9%	106	0.40	<0.001
Fellow/Attending	78	10.3%	8		228	38.6%	88		<0.001
Resident	549	13.7%	75		830	43.6%	362		<0.001
<b>Educational Session Attendance</b>									
Resident attended <sup>g</sup>	N/A				499	42.7%	213	0.52	
Resident did not attend	N/A				331	45.0%	149		
<b>Clinic Characteristic</b>									
<b>Clinic Type</b>									
Resident Clinic	549	13.7%	75	0.11	830	43.6%	362	0.35	<0.001
Non-resident clinic	251	9.6%	24		475	40.8%	194		<0.001

<sup>a</sup>Comparing prevalence of recognition by each characteristic within each time period (pre-intervention or intervention period); <sup>b</sup>Comparing prevalence of recognition pre-intervention to intervention period, by individual stratum of characteristics; <sup>c</sup>Family history of any of the following: early myocardial infarction, cerebrovascular accident, cardiovascular disease, high cholesterol, hypertension; <sup>d</sup>Co-morbid conditions include past medical history of any of the following: obesity, metabolic syndrome, insulin resistance, diabetes mellitus, kidney disease or prematurity; <sup>e</sup>Body Mass Index (BMI) ≥85<sup>th</sup> percentile or BMI≥25 kg/m<sup>2</sup> if age≥20; <sup>f</sup>BMI<85<sup>th</sup> percentile and <25kg/m<sup>2</sup> if ≥20 years of age; <sup>g</sup>47/59 resident providers attended the educational session.

**Table 10. Prevalence Ratio (PR) of Recognized Elevated Blood Pressure during the Pre-Intervention and Intervention Periods by Month, Unadjusted and Adjusted for Education Session Attendance**

Variable	Unadjusted			Adjusted for Education Session Attendance		
	PR	95% Confidence Interval	P-value	PR	95% Confidence Interval	P-value
Study Period						
- Pre-Intervention	ref			ref		
- Intervention						
○ Month 1	2.6	1.8, 3.9	<0.001	2.6	1.8, 3.9	<0.001
○ Month 2	3.6	2.9, 4.5	<0.001	3.6	2.8, 4.5	<0.001
○ Month 3	3.7	3.0, 4.7	<0.001	3.7	2.9, 4.7	<0.001
○ Month 4	3.0	2.4, 3.8	<0.001	3.0	2.3, 3.8	<0.001
○ Month 5	3.4	2.7, 4.3	<0.001	3.4	2.7, 4.3	<0.001
○ Month 6	3.6	2.9, 4.6	<0.001	3.6	2.8, 4.5	<0.001
Acute care visit	0.6	0.5, 0.7	<0.001	0.6	0.5, 0.7	<0.001

## Chapter 4: The Association Between Adiposity and Left Ventricular Mass in Children with Hypertension

### Abstract

**Background/Objective:** Left ventricular hypertrophy is highly prevalent at initial diagnosis of hypertension in children, however degree of blood pressure elevation does not predict its presence. We hypothesized that obesity and obesity-related risk factors are associated with left ventricular mass index in hypertensive children, and that the association between adiposity and left ventricular mass index is mediated by blood pressure dependent and independent pathways.

**Methods/Results:** We observed 49 treated hypertensive children for one year. At baseline, 51% were overweight/obese and 41% had left ventricular hypertrophy. Those with left ventricular hypertrophy had greater body mass index z-score but did not have greater clinic or 24-hour ambulatory blood pressures than those without left ventricular hypertrophy. Over time, measures of adiposity and prevalence of cardiovascular risk factors increased while blood pressure was unchanged. Children who were obese at both study visits experienced the greatest increase in left ventricular mass index over time: mean change was  $6.4 \text{ g/m}^{2.7}$  (95% confidence interval 2.4, 10.5) among those overweight/obese at each visit, vs.  $0.95 \text{ g/m}^{2.7}$  (95% confidence interval -3.2, 5.1) among those of healthy weight at each visit ( $p=0.056$ ; Figure 1). Overweight/obese children with and without left ventricular hypertrophy at baseline demonstrated a larger increase in left ventricular mass index compared to healthy weight children. Healthy weight children with left ventricular hypertrophy were the only ones with decreased left ventricular mass index over time. Body mass index z-score at baseline was

associated with change in left ventricular mass index ( $\beta$  4.08, 95% confidence interval 1.54, 6.61,  $p=0.002$ ) after adjusting for age, sex, race, and left ventricular mass index at baseline. After adjustment for each postulated mediating pathways between body mass index z-score and left ventricular mass index in separate analyses, only pulse pressure and serum aldosterone appeared to partially mediate this relationship.

**Conclusions:** Hypertensive children demonstrate not only a high prevalence of co-morbid cardiovascular risk factors at baseline, but an increase in both their prevalence and severity over time. Of these, body mass index z-score was the greatest risk factor for left ventricular hypertrophy and increasing left ventricular mass index over time. These findings support the overwhelming public health concern regarding the obesity epidemic and suggest that greater emphasis on overweight/obesity prevention and treatment should be made among hypertensive children.

## Introduction

The prevalence of cardiovascular disease (CVD) risk factors in children continues to rise. In the United States, it is estimated that 4.5% of children have hypertension<sup>3</sup>, almost a third are overweight or obese<sup>7</sup>, and nearly 20% have dyslipidemia<sup>43</sup>. Overall, at least 24.5 million of the 74.2 million children in the United States<sup>4</sup> have one or more of these CVD risk factors. A recent systematic review and meta-analysis suggests that obesity may account for much of this increased risk<sup>44</sup>. In fact, while increased sodium intake, decreased potassium intake and suboptimal diet overall are known to raise blood pressure (BP), the striking increase in the prevalence of hypertension over the last several decades has been attributed to the coincident epidemic rise in obesity<sup>6</sup>.

While children with obesity, hypertension and dyslipidemia are typically asymptomatic, they manifest alterations to their cardiovascular system previously thought only to occur in adulthood. Left ventricular hypertrophy (LVH), a pathological remodeling of the heart associated with arrhythmias, heart failure, myocardial infarction and death in adults<sup>3,9</sup>, is a common manifestation of early CVD in children<sup>3</sup>. Hypertension has been considered the main cause of LVH, presumably as a response to increased left ventricular afterload. As such, echocardiography is recommended for all hypertensive children to investigate for this form of target-organ damage, the presence of which necessitates initiation or escalation of antihypertensive pharmacological therapy.

Among children with hypertension, LVH is common, with up to 41% having LVH at initial diagnosis<sup>3,9</sup>. Interestingly, neither BP measured in clinic nor in the ambulatory/home setting is



consistently associated with LVH in hypertensive children<sup>9,45</sup>. Further, LVH can occur in normotensive children<sup>46,47</sup>, is more prevalent among children with the metabolic syndrome than without<sup>48</sup>, and is independently associated with obesity<sup>9,44,47,49</sup>. These findings suggest that mechanisms independent of BP may also be responsible for the development of LVH among hypertensive children. Identifying these risk factors will aid risk stratification and targeted treatment efforts.

We investigated the association between adiposity as assessed by body mass index (BMI) z-score and left ventricular mass index (LVMI) among hypertensive children. We hypothesized that obesity and obesity-related risk factors are associated with LVMI in hypertensive children. We also hypothesized that adiposity leads to increased LVMI via several pathways: BP dependent pathways, mediated by elevated BP itself and by hormonal regulators of BP; and BP independent pathways, mediated by metabolic dysregulation, increased intravascular volume and inflammation.

## **Methods**

### Study Design:

We conducted a prospective, observational study of hypertensive children referred for care at the pediatric nephrology clinic at Johns Hopkins University. Hypertensive children 3-22 years who either had a systolic or diastolic BP  $\geq 95^{\text{th}}$  percentile for their age/sex/height<sup>3</sup> or who were on antihypertensive medication for the treatment of hypertension at the time of their clinic visit were eligible. Children with a history of congenital heart disease, cancer or chronic kidney disease stage 2 or greater were ineligible. The Johns Hopkins University School of Medicine Institutional Review Board approved this study.

### Data Collection and Variables:

All enrolled children provided informed consent or assent when <18 years. Each participant underwent a standardized assessment at baseline and 12-month follow-up in the Pediatric Clinical Research Unit. At each assessment, demographic and clinical information were collected. Children provided a 3-day diet history that was reviewed for accuracy and enhanced recall regarding additional pertinent details (e.g. condiments, serving sizes) at each visit by a registered research dietician.

All children underwent anthropometric measurements including height, measured to nearest 0.1 cm using a wall mounted stadiometer and weight, measured to the nearest 0.1 kg using a calibrated balance scale. Waist circumference measurements were taken 1 cm above the patients' navel on exhale, using a Gulick tape measure which applies known tension. Standard hip circumference measurement was taken at the widest girth around the hip and buttocks. All measurements were taken in triplicate according to research protocol and the mean recorded to the nearest 0.1 cm.

Each participant's *Clinic Blood Pressure (CBP)* was measured by manual auscultation after 5 minutes of rest in the right arm with a calibrated aneroid sphygmomanometer according to standardized methods<sup>50</sup>. Mid-arm circumference in cm was used to select the appropriate cuff size. Three seated measurements were taken 30 seconds apart and then averaged together for one composite measurement for the visit. Individuals responsible for CBP measurement undergo training and are required to pass certification evaluations yearly.

All children also underwent *24-hour oscillometric ambulatory BP Monitoring (ABPM)* according to research protocol<sup>51</sup> with BP measurements obtained every 20 minutes over a 24-hour period of time (Spacelabs 90201). As above, their mid-arm circumference was used to select an appropriate cuff size. Awake and Sleep cutoffs were determined by diary. Systolic and diastolic BP dip was calculated as  $([\text{mean wake BP} - \text{mean sleep BP}] / \text{mean wake BP} \times 100)$ . As BP norms for children vary based on age/sex/height, to compare BP elevations between children each child's systolic and diastolic BP (clinic and 24-hr ABPM BPs) was divided by his/her age/sex/height specific 95<sup>th</sup> percentile BP<sup>3, 51</sup>. This calculation provides a 95<sup>th</sup> percentile BP index, with values  $\geq 1$  indicating measurements  $\geq 95^{\text{th}}$  percentile (i.e. in the hypertensive range). Clinic and 24-hour ABPM pulse pressure were also calculated (systolic BP – diastolic BP in mmHg).

In addition, as part of the cohort protocol, all children underwent a complete echocardiographic examination. Images from the standardized two-dimensional guided M-mode assessment for left ventricular mass (LVM) were digitally recorded. Three measurements were taken for each subject and averaged by a single study cardiologist (KWH). LVM was calculated based on diastolic measurements of the left ventricular dimension, intraventricular septum and left ventricular posterior wall using a validated equation as recommended by the American Society of Echocardiography<sup>52, 53</sup>. LVMI was then calculated by dividing the LVM by the participant's height in meters<sup>2,7</sup>; an individual was determined to have LVH if his/her LVMI was  $\geq 95^{\text{th}}$  percentile for their age and sex<sup>54</sup>.

Laboratory Assessments: All children had a random blood sample drawn at both their baseline and 12-month assessments. Serum aldosterone (ng/dL) and plasma renin activity (ng/mL/h)

were measured at Quest Diagnostics using liquid chromatography tandem mass spectrometry (LC/MS/MS), with an analytical sensitivity of 1.0 ng/dL and 0.03 ng/mL/h respectively. High sensitivity C-reactive protein (hsCRP; mg/dL) was determined using highly-sensitive immunoturbidimetry and hemoglobin A1c (%) was measured by high performance liquid chromatography. Serum uric acid concentration (mg/dL) was determined by enzymatic spectrophotometry. Additional laboratory assessments included 25-hydroxyvitamin D (ng/mL); lipids (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides; all mg/dL); lipoprotein (a) (nmol/L) and pro-B natriuretic peptide (pg/ml). Children provided a 24-hour urine collection; sodium excretion in mg was calculated by multiplying the total urine volume by the measured sodium concentration.

#### Demographic and Clinical Characteristics:

Children were categorized as African American (AA) or non-AA based on self-report. Body mass index (BMI) was calculated as  $\text{kg/m}^2$  and age-sex specific BMI percentiles and z-scores were determined<sup>55, 56</sup>. Children were defined as overweight/obese if their BMI percentile was  $\geq 85^{\text{th}}$  percentile<sup>57</sup>. Age/Sex/Race-adjusted waist-circumference percentile norms were used to categorize children as  $\geq 90^{\text{th}}$  percentile<sup>58</sup> or below. The waist-hip ratio was calculated as the waist circumference divided by the hip circumference (both in cm).

Metabolic syndrome was defined as having  $\geq 3$  of the following: systolic or diastolic BP  $\geq 90^{\text{th}}$  percentile; BMI  $> 97^{\text{th}}$  percentile; triglycerides  $> 110$  mg/dL; HDL  $< 40$  mg/dL; waist circumference  $> 90^{\text{th}}$  percentile for boys,  $\geq 90^{\text{th}}$  percentile for girls<sup>59</sup>.

#### Statistical analyses:

Demographic and clinical variables were compared between children with and without LVH using student's t-tests with unequal variances for continuous variables that were normally distributed, Wilcoxon Rank Sum for continuous variables not normally distributed and Fisher's exact tests for categorical variables. As several variables of interest had missing values, felt to be missing at random, we conducted multiple imputation utilizing all available information on related covariates. This imputed dataset was used to conduct the analyses detailed below. There were no missing data for LVMI or BMI and BMI z-score. Analyses using the dataset with missing data were compared with those conducted using the imputed dataset to assess the appropriateness of imputation.

To assess for longitudinal associations between variables and LVMI over time, delta variables were calculated (12-month follow-up measurement - baseline measurement) for LVMI and variables of interest. Because the distribution of delta LVMI measurements did not deviate significantly from a normal distribution, we used linear regression to quantify the association between change in LVMI and characteristics at baseline and change over time, adjusting for age, sex, and race.

To investigate the association between adiposity and LVMI over time, we conducted linear regression analysis with baseline BMI z-score as the independent variable and delta LVMI as the dependent variable. These analyses were initially adjusted for age, race, and sex, and then further adjusted for LVMI at baseline in a second model to serve as the base model for subsequent analyses described below.

We chose baseline BMI z-score as the independent variable instead of other markers of adiposity because this was felt to best represent degree of adiposity among children. Further, because BMI and waist circumference values defining overweight and obesity in children change with increasing age<sup>58, 60</sup> using z-scores allow us to compare values between children of varying ages.

To investigate the relative contribution of the hypothesized mediating pathways between adiposity and LVMI, and to determine if adiposity, as ascertained by BMI z-score, was independently associated with LVMI, we conducted several additional linear regression analyses. These separate analyses started with the base model as the foundation and further adjusted for the variables hypothesized to mediate the relationship between adiposity and LVMI. In these analyses, we expected to see an attenuation of the association between BMI z-score and LVMI for variables that mediate the relationship between adiposity and LVMI. For risk factors that do not mediate this association, we expected unchanged or similar point estimates and p-values to describe the association between BMI z-score and LVMI despite the addition of the variable to the model.

A two-sided P value <0.05 was considered statistically significant. Statistical analyses were conducted using STATA 11.2 software (StataCorp LP, College Station, TX). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Johns Hopkins University<sup>61</sup>.

## **Results**

### *Participant Characteristics*

Forty-nine children 3-19 years of age completed both baseline and 12-month assessments out of 53 enrolled (92% retention; 2 disenrolled, 2 lost to follow-up). Forty-one percent had LVH at baseline. The average length of time between the follow-up assessments was 12.8 months. Over the course of follow-up, the mean (standard deviation (SD)) change in LVMI was 2.89 g/m<sup>2.7</sup> (8.4 g/m<sup>2.7</sup>). Of the measures of adiposity, the mean change in BMI was 1.6 kg/m<sup>2</sup> (2.1 kg/m<sup>2</sup>), mean change in BMI z-score was 0.11 (0.32), and the mean change in waist circumference was 4.6 cm (5.9 cm). The percentage of children classified as overweight/obese was 51% at baseline and 57.1% at follow-up (p=0.69). BP changed to a minimal degree over the course of the study: the average change in clinic SBP was -0.14mmHg (12.5), average change in clinic SBP index was -0.02 (0.09), average change in awake SBP was 0.52mmHg (9.5) and average change in awake SBP index was -0.001 (0.07). Forty-four children were prescribed antihypertensive medications at baseline, with 43 prescribed anti-hypertensive medications at follow-up. The majority of children reported participating in at least 30 minutes of physical activity three times a week: 41 at baseline and 44 at follow up. The prevalence of LVH at follow-up was 53.1% (vs. 40.8% at baseline; p=0.31).

### *Baseline Characteristics*

As one would expect, children with LVH had greater LVMI compared to those without LVH (Table 11a). There were no age, sex or race differences between the two groups, but there was a greater proportion of children with a positive OSA screen (defined when >30% positive responses on validated questionnaire<sup>62, 63</sup>) among those with LVH. Children with LVH also had a greater BMI z-score, but did not have evidence of increased visceral adiposity as represented by waist circumference or waist-hip ratio when compared to children without LVH. Children with

LVH also had a higher serum uric acid level, a lower serum lipoprotein (a) level and a greater pro-B natriuretic peptide level than those without LVH. High sensitivity CRP and urinary sodium excretion values were non-significantly higher in those with LVH (1.1 mg/dL vs. 0.40 mg/dL for hsCRP; 4.2 grams vs. 3.5 grams for urinary sodium excretion).

There was no difference in BP between those with and without LVH when measured at rest by manual auscultation or by 24-hour ABPM (Table 11b). The median plasma renin activity was also no different between the groups. Serum aldosterone, however, was higher amongst children with LVH who were prescribed an Angiotensin Converting Enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) when compared to those without LVH who were also prescribed one of those medications.

#### *Longitudinal Associations*

In linear regression analyses that separately assessed each independent variable, age, waist circumference at baseline, and change in hemoglobin A1c were associated with change in LVMI over time while adjusting for age, sex and race (Table 12). Children who were overweight or obese at both study visits experienced the greatest increase in LVMI over time: mean change in LVMI was  $6.4 \text{ g/m}^{2.7}$  (95% CI 2.4, 10.5) among those overweight or obese at each visit, vs.  $0.95 \text{ g/m}^{2.7}$  (95%CI -3.2, 5.1) among children who were of healthy weight at each visit ( $p=0.056$ ; Figure 4). In addition, when stratified by weight status (healthy weight vs. overweight/obese) and LVH status at baseline, overweight/obese children with and without LVH demonstrated a larger increase in LVMI compared to healthy weight children. In fact, healthy weight children with LVH were the only ones to demonstrate a decrease in LVMI over time (Figure 5).



### *Mediator Analyses*

Baseline adjusted analyses revealed a significant relationship between BMI z-score at baseline and change in LVMI over time ( $\beta$  4.08, 95% CI 1.54, 6.61,  $p=0.002$ ; Table 13).

Sequential adjustment for BP, markers of metabolic dysregulation, and markers of inflammation (hsCRP and 25-hydroxy vitamin D) revealed essentially no change in the point estimate or  $p$ -values between BMI z-score and change in LVMI. The models adjusting for serum aldosterone with ACEi/ARB use and pulse pressure resulted in a decrease in both the point estimate and  $p$ -value, suggesting partial mediation.

### **Discussion**

In this year-long observational study of hypertensive children, we demonstrated a high burden of co-morbid CVD risk factors at baseline, and an increase in both their prevalence and severity over time. Most striking was the presence and substantial degree of overweight and obesity; over 50% of the cohort was both overweight and obese, much more than the prevalence in the United States population overall (32%<sup>7</sup>). These CVD risk factors, specifically uric acid, measures of adiposity, lipids, hemoglobin A1c, and hsCRP, along with target organ damage felt to be secondary to hypertension itself, increased/worsened over time despite relatively good BP control as evidenced by the mean BP index being  $<1$  at baseline and decreasing over time. Over time, adiposity, not BP, was demonstrated as the greatest risk factor for LVH and increasing LVMI among these hypertensive children. These findings support the overwhelming public health concern regarding the obesity epidemic and suggest that greater efforts are needed to prevent and treat overweight/obesity in hypertensive children.

While several other studies in children have described the impact of CVD risk factors on target organ damage, ours is the first to report longitudinal data on a racially diverse population of hypertensive children without kidney disease. Litwin et al. demonstrated that among European children with incident primary hypertension, successful treatment of hypertension was not independently associated with decrease in LVMI. In fact, there was no difference in the prevalence of LVH between those children who “responded” to antihypertensive therapy and those who did not. Instead, adiposity had the strongest association with LVMI over time, with decreasing waist circumference being the main predictor of decreasing LVMI.

Adult studies also provide evidence that adiposity may be more important in determining LVM than BP. Obese adults who lost weight after bariatric surgery also had concomitant reductions in BP, LVM and relative wall thickness. Interestingly, their BP reduction was not associated with decreased LVM or improved LV structure<sup>64</sup>.

Normotensive children also provide evidence for the greater role of adiposity on LVM when compared to BP. A dietary intervention trial of Finnish children followed yearly from seven months of age to adolescence revealed the strongest determinant of LVM to be an adolescent’s concurrent weight<sup>26</sup>. While children in the intervention group enjoyed significant improvements in diet, lipids, BP and endothelial function, they did not experience significant changes in weight, LVM or LVH<sup>26, 27</sup>. So, while improved diet quality was able to decrease BP among these normotensive children, lower BP did not impact LVM or the presence/absence of target organ damage in the form of LVH.

One of the indications for initiation or intensification of antihypertensive medication among hypertensive children is the presence of LVH. Recommendations suggest aiming for a more aggressive BP treatment goal of <90<sup>th</sup> percentile when LVH is present<sup>3</sup>. Given these recommendations, the pattern of change in LVMI among healthy weight children with and without LVH as demonstrated in Figure 5 is not surprising. Particularly given the age related changes in LVMI over time, those children without LVH could be expected to have an increase in LVMI over time; and as long as this increase did not indicate the development of LVH, this could be considered a normal finding. Children with LVH, however, would be expected to demonstrate a decrease in LVMI with successful pharmacological treatment, as the healthy weight children with LVH experienced.

Conversely, the pattern of change in LVMI among children who were overweight/obese is concerning. While also not unexpected that overweight/obese children without LVH could have an increase in LVMI, they demonstrated an increase that was 2.5 times higher than experienced by the healthy weight children without LVH. Further, those overweight/obese children with LVH experienced almost as large of an increase as those without LVH, not the expected decrease over time.

Perhaps the most striking finding in our study was the strong independent association between adiposity and change in LVMI over time that remained despite sequential adjustments for multiple mediating pathways. The two variables that partially mediated this association, serum aldosterone and pulse pressure, are potentially modifiable risk factors for increasing LVMI. The adipocyte is an endocrine organ that secretes neurohumoral factors that influence cardiac remodeling directly and contribute to intravascular volume expansion. These factors

lead to increased, and possibly inappropriate, aldosterone secretion. In the setting of excess sodium intake, this excess aldosterone excretion contributes to the target organ damage found in hypertensive individuals<sup>65, 66</sup> and can cause increased intravascular volume. The role of this neurohumoral pathway was also demonstrated in the bariatric surgery intervention study described earlier, where the authors concluded that the effect of weight loss on cardiac geometry was primarily mediated by the associated decrease in intravascular volume and reversal in hormonal abnormalities, not by a decrease in BP<sup>64</sup>.

The strong association between BMI z-score and change in LVMI that remains despite adjusting for these factors suggests either an independent relationship between adiposity and LVMI or, more likely, an interaction of LVMI with many or all of these mediators. Lending further support to this complex association are the multiple studies that describe different patterns of abnormal cardiac geometry among obese hypertensive compared to non-obese hypertensive individuals<sup>67</sup>. Specifically, obese hypertensive individuals tend to exhibit eccentric hypertrophy<sup>67</sup>, a geometric pattern associated with a greater dietary sodium intake and larger intravascular volume<sup>68, 69</sup>. Non-obese hypertensive individuals tend to have concentric hypertrophy, which is associated with more severely elevated BP in adults<sup>67, 68, 70</sup>.

Our study has several limitations. These include its relatively small sample size and observational design, which makes us unable to infer causality. As children were recruited from a pediatric nephrology clinic, there may be a selection bias in that included children may have more severe hypertension than those who might have been recruited from a non-referral based office setting. In addition, the majority of the children were non-fasting at the time of their study visit. As a result we were unable to include data regarding fasting insulin or glucose and

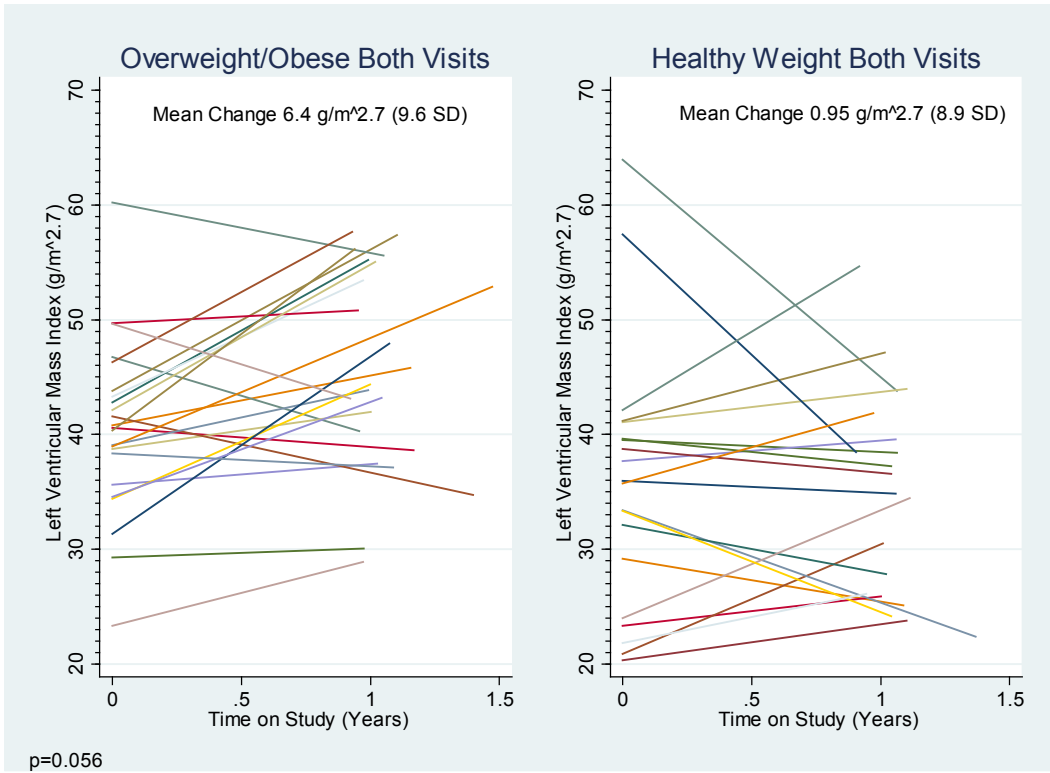
were unable to assess the homeostatic model assessment of insulin resistance (HOMA-IR). We were therefore unable to fully ascertain the degree of metabolic dysfunction among the children in our cohort.

Our study also has several strengths. It provides data on a racially diverse population of hypertensive children at considerable CVD risk. It's longitudinal, prospective design allows us to minimize information bias and evaluate the relationship of various mediators of obesity and LVH on the change in LVMI over time. The standardized echocardiograms read by a study cardiologist provide us with a robust estimate of the left ventricular size and prevalence of LVH. Our use of 24-hr ABPM provides a more precise assessment of BP than one set of clinic BP measurements<sup>71, 72</sup>.

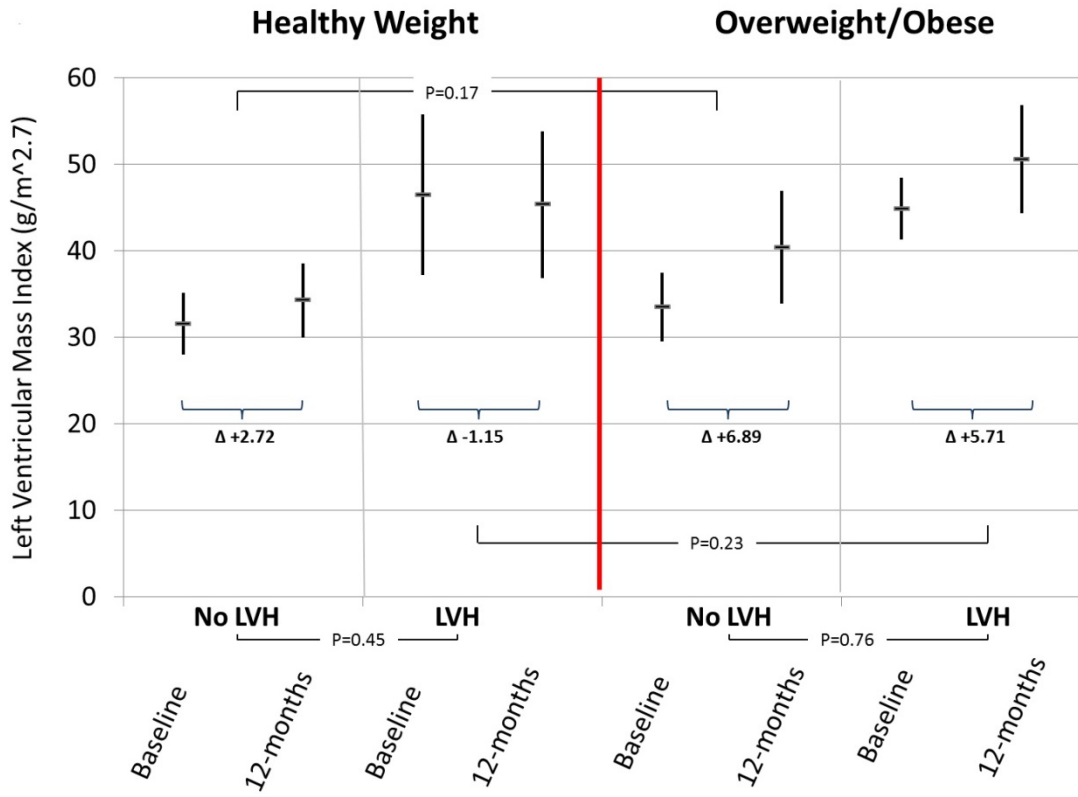
#### **Perspectives:**

In sum, our study emphasizes the substantial contribution of obesity on CVD risk among hypertensive children and suggests that the presence of overweight/obesity should be elevated in importance when risk stratifying children with hypertension. Despite providing standard of care guidance on weight loss and adherence to a heart healthy diet, the children in our study became more overweight/obese and demonstrated an increase in number and severity of CVD risk factors. Successful treatment of these modifiable risk factors, known to be associated with increased CVD morbidity and mortality in adults, could potentially improve both pediatric and adult cardiovascular health by decreasing LVMI. Enhanced preventive and therapeutic strategies targeting overweight and obesity in children holds significant promise as we work towards primordial and primary prevention of adult CVD.

Figure 4: Mean Change in Left Ventricular Mass Index by Weight Status at Baseline



**Figure 5: Mean Change in Left Ventricular Mass Index by Weight and Left Ventricular Hypertrophy Status at Baseline**



**Table 11a. Baseline Characteristics of 49 Hypertensive Children and Adolescents with and without Left Ventricular Hypertrophy – Demographics, Anthropometrics and Obesity Related Laboratory Measurements**

Characteristic	Overall		LVH (N=20)		No LVH (N=29)		P-value <sup>a</sup>
	Mean, Median or N	SD, IQR, or %	Mean, Median or N	SD, IQR, or %	Mean, Median or N	SD, IQR, or %	
LVMI (g/m <sup>2.7</sup> )	37.7	9.5	45.4	7.4	32.3	6.6	<0.0001
<b><u>Demographics</u></b>							
Age (years)	13.8	3.9	14.3	4.1	13.4	3.8	0.48
Male	29	59%	14	70%	15	52%	0.25
African American	19	39%	2	25%	14	48%	0.14
<b><u>Medical History</u></b>							
Positive OSA Screen	10	21%	7	37%	3	10%	0.04
Duration of HTN (mo)	39.4	32.3	49.2	40.6	32.6	23.5	0.11
<b><u>Measures of Adiposity</u></b>							
BMI (kg/m <sup>2</sup> )	25.3	7.6	27.8	9.0	23.5	6.0	0.07
BMI z-score	1.2	0.98	1.5	0.7	0.9	1.1	0.03
Overweight/obese <sup>b</sup>	25	51%	13	65%	12	41%	0.15
Waist circumference (cm)	81.5	18.6	85.5	20.1	78.7	17.3	0.22
Waist-hip ratio	0.88	0.08	0.88	0.08	0.88	0.08	0.73
<b><u>Inflammatory Markers</u></b>							
HsCRP (mg/L)	0.5	0.2,1.4	1.1 N=18	0.4, 2.1	0.4 N=28	0.2, 1.2	0.13
25-OH vitamin D (ng/mL)	25	10.8	26.2 N=19	10.1	24.2 N=29	11.3	0.53
<b><u>Markers of Metabolic Dysregulation</u></b>							
Hemoglobin A1C (%)	5.2	0.39	5.1 N=17	0.42	5.3 N=28	0.37	0.31
Non-HDL cholesterol (mg/dL)	105.9	32.8	102.8 N=18	23.9	107.9 N=29	37.6	0.57
Lipoprotein (a) (nmol/L)	55	17, 100	43 N=19	5,75	65 N=28	28.3, 137.5	0.053
Metabolic syndrome <sup>c</sup>	11	23%	5	25%	6	21%	0.74
Serum uric acid	5.6	1.7	6.4	1.9	5.0	1.4	0.02



(mg/dL)			N=16		N=25		
<b><u>Dietary Risk</u></b>							
<b><u>Factors and</u></b>							
<b><u>Markers of</u></b>							
<b><u>Intravascular</u></b>							
<b><u>Volume</u></b>							
Dietary Sodium intake (mg/24 hours)	3282	1100	3161 N=14	953	3350 N=25	1188	0.59
Urinary Sodium Excretion (mg/24-hours)	3765	2321	4215 N=14	2642	3512 N=25	2137	0.40
Pro-B natriuretic Peptide (pg/ml)	16	10,54	29 N=19	10,84	10 N=28	10,38	0.04

<sup>a</sup>Student's t-test with unequal variances for normally distributed continuous measures, Wilcoxon Rank sum for non-normally distributed continuous measures, Fisher's exact test for categorical measures

<sup>b</sup>Defined as BMI  $\geq 85^{\text{th}}$  percentile

<sup>c</sup>Defined as having  $\geq 3$  of the following: systolic or diastolic BP  $\geq 90^{\text{th}}$  percentile; BMI  $> 97^{\text{th}}$  percentile; triglycerides  $> 110$  mg/dL; HDL  $< 40$  mg/dL; waist circumference  $> 90^{\text{th}}$  percentile for boys,  $\geq 90^{\text{th}}$  percentile for girls<sup>59</sup>.

Abbreviations: BMI=body mass index; HDL=high-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; HTN=hypertension; IQR=interquartile range; LVH=Left Ventricular Hypertrophy; LVMI=left ventricular mass index; OSA=obstructive sleep apnea; SD=standard deviation.

**Table 11b. Baseline Clinic Blood Pressure, 24-hour Ambulatory Blood Pressure and Related Measures in Children with and without Left Ventricular Hypertrophy**

Characteristic Mean (SD), Median (IQR) or n (%)	Overall		LVH N=20		No LVH N=29		P- value <sup>a</sup>
	Mean, Median, or N	SD, IQR, or %	Mean, Median, or N	SD, IQR, or %	Mean, Median, or N	SD, IQR, or %	
<b>Systolic BP</b>							
Clinic Systolic BP (mmHg)	122	11.7	121 N=11	12.3	123 N=24	11.7	0.69
Clinic 95 <sup>th</sup> Systolic BPi <sup>b</sup>	0.97	0.08	0.93 N=11	0.08	0.98 N=24	0.08	0.1
Awake Systolic BP (mmHg)	128	10.9	126 N=18	9.4	129 N=27	11.8	0.34
Awake 95 <sup>th</sup> Systolic BPi	0.97	0.08	0.95 N=18	0.06	0.99 N=27	0.09	0.11
24-hour Systolic BP (mmHg)	123	10.5	122 N=18	9.9	124 N=27	11	0.63
24-hour 95 <sup>th</sup> Systolic BPi	0.98	0.07	0.97 N=18	0.07	0.99 N=27	0.08	0.32
Systolic Dip <sup>c</sup> (%)	9.7	5.5	9.3 N=17	4.1	10.0 N=27	6.3	0.68
<b>Diastolic BP</b>							
Clinic Diastolic BP (mmHg)	73	9.6	75 N=11	10.8	73 N=24	9.2	0.59
Clinic 95 <sup>th</sup> Diastolic BPi <sup>b</sup>	0.89	0.11	0.89 N=11	0.14	0.89 N=24	0.1	0.98
Awake Diastolic BP (mmHg)	72	7.9	70 N=18	7.1	73 N=27	8.3	0.15
Awake 95 <sup>th</sup> Diastolic BPi	0.88	0.1	0.85 N=18	0.09	0.89 N=27	0.1	0.11
24-hour Diastolic BP (mmHg)	67	7.3	66 N=18	7.4	68 N=27	7.2	0.38
24-hour 95 <sup>th</sup> Diastolic BPi	0.88	0.1	0.86 N=18	0.1	0.89 N=27	0.09	0.29
Diastolic Dip <sup>c</sup> (%)	15.4	11.4	13.7 N=17	7.3	16.5 N=27	13.2	0.37
<b>Pulse Pressure</b>							
Clinic Pulse Pressure	49.1	9.4	46.5 N=11	12.4	50.3 N=24	7.7	0.36
Awake Pulse Pressure	56.2	7.8	56.4 N=18	8.6	56.1 N=27	7.5	0.89

**BP Control**

Systolic and Diastolic Wake BP <95 <sup>th</sup> percentile	27 (60%)	60%	13 N=18	72%	14 N=27	52%	0.22
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**Hormonal****Regulators of BP**

Plasma Renin Activity (ng/mL/h)	4.13	2.37,	7.28	2.56,	3.68	2.4,	0.14
• On ACEi/ARB	10.73	5.36,	10.73	8.77,	10.75	4.7,	0.56
		18.95	N=13	18.95	N=8	20.0	
• Not on ACEi/ARB	2.89	1.35,	2.1	0.94,	2.91	2.2,	0.20
		3.78	N=7	2.96	N=20	3.9	
Serum aldosterone (ng/dL)	2.5	1,6	3	2,6	2.5	1,7	0.47
			N=20		N=28		
• On ACEi/ARB	2	0.5, 6	2	2,9	0.5	0.5,	0.03
			N=13		N=8	1.5	
• Not on ACEi/ARB	4	2,6	4	1,5	4	2,	0.60
			N=7		N=20	8.5	

<sup>a</sup>Student's t-test with unequal variances for normally distributed continuous measures, Wilcoxon Rank sum for non-normally distributed continuous measures, Fisher's exact test for categorical measures

<sup>b</sup>BPI=BP index; defined as the measured BP/95<sup>th</sup> percentile BP for age/sex/height; value  $\geq 1$  denotes BP  $\geq 95^{\text{th}}$  percentile.

<sup>c</sup>BP Dip=1- (BP during sleep/BP while awake)\*100%

Abbreviations: ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; BP=blood pressure; IQR=interquartile range; LVH=Left Ventricular Hypertrophy; LVMI=left ventricular mass index

**Table 12. Association of Baseline Characteristics, Change in Baseline Characteristics and Change in Left Ventricular Mass Index, Adjusted for Age, Sex and Race**

Characteristic <sup>b</sup>	Baseline Variables			Delta Variables <sup>a</sup>		
	$\Delta$ LVMl (g/m <sup>2.7</sup> )	95% Confidence Interval	p-value	$\Delta$ LVMl (g/m <sup>2.7</sup> )	95% Confidence Interval	p-value
<b><u>Demographics</u></b>						
Age (years)	1.01	0.37, 1.64	0.003			
Race (AA vs. non-AA)	-0.10	-5.20, 5.0	0.97			
Sex (Male vs. Female)	0.08	-4.98, 5.14	0.97			
<b><u>Measures of Adiposity</u></b>						
BMI z-score	2.57	-0.04, 5.18	0.053	3.75	-4.23, 11.73	0.35
Overweight/Obese <sup>c</sup>	4.44	0.49, 9.37	0.08			
Waist Circumference (cm)	0.21	0.06, 0.36	0.008	0.18	-0.25, 0.61	0.40
<b><u>Blood Pressure</u></b>						
Awake Systolic BPi <sup>d</sup>	-1.04	-32.02, 29.9	0.95	11.8	-20.6, 44.17	0.46
Awake Diastolic BPi <sup>d</sup>	-17.39	-40.33, 5.56	0.13	-1.21	-26.5, 24.09	0.92
Awake Pulse Pressure	0.38	-0.002, 0.77	0.051	0.14	-0.14, 0.42	0.32
<b><u>Hormonal Regulators of BP</u></b>						
Serum aldosterone (ng/dL)	-0.05	-0.25, 0.16	0.65	0.03	-0.17, 0.22	0.78
Plasma renin activity (ng/mL/h)	0.14	-0.04, 0.32	0.12	-0.02	-0.16, 0.12	0.81
<b><u>Inflammatory Markers</u></b>						
hsCRP (mg/L)	-0.66	-2.26, 0.94	0.40	0.56	-0.35, 1.48	0.22
25-OH Vitamin D (ng/mL)	0.13	-0.13, 0.39	0.3	-0.26	-0.53, 0.003	0.053
<b><u>Markers of Metabolic Dysregulation</u></b>						
Hemoglobin A1c (%)	-5.79	-12.60, 1.01	0.09	5.54	0.29, 10.78	0.039
Non-HDL cholesterol (mg/dL)	-0.03	-0.12, 0.05	0.4	0.03	-0.09, 0.16	0.59
Lipoprotein (a) (nmol/L)	-0.008	-0.04, 0.019	0.55	0.01	-0.05, 0.07	0.75
Serum Uric Acid (mg/dL)	0.30	-1.79, 2.4	0.77	-0.20	-4.28, 3.88	0.92
<b><u>Dietary Risk Factors and Markers of Intravascular Volume</u></b>						
Urinary Sodium Excretion (mg/24-hrs)	0.0003	-0.0009, 0.001	0.65	-0.0003	-0.001, 0.0007	0.52

Pro-B natriuretic Peptide (pg/ml)	0.019	-0.05, 0.08	0.56	-0.05	-0.12, 0.03	0.24
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<sup>a</sup>Delta Variables are the change values for each characteristic listed. They represent the difference in measurement between the two study visits (value at 12-month follow-up – value at baseline). Δ represents a delta variable.

<sup>b</sup>Each characteristic individually assessed in a separate model that adjusted for age, sex and race.

<sup>c</sup>Defined as BMI ≥85<sup>th</sup> percentile

<sup>d</sup>BPI=BP index; defined as measured BP/95<sup>th</sup> percentile BP for age/sex/height; value ≥1 denotes a BP ≥95<sup>th</sup> percentile.

Abbreviations: AA=African American; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; BMI=body mass index; BP=blood pressure; HDL=high-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; LVMI=left ventricular mass index.

**Table 13. Association of Baseline Body Mass Index z-score with Change in Left Ventricular Mass Index – Investigating for Mediating Pathway**

<b>Multivariable Models</b>	<b>Adjusting for the following variables:</b>	<b>Δ LVMI by BMI z-score at baseline</b>	<b>95% Confidence Interval</b>	<b>P-value</b>
Model 1	Age, race, sex	2.57	-0.04, 5.18	0.053
Model 2 (Base Model)	Age, race, sex, LVMI at baseline	4.08	1.54, 6.61	0.002
<b><u>Blood Pressure:</u></b>				
Model 3a	Model 2 covariates + Awake SBPi <sup>a</sup> at baseline and follow-up	3.86	1.25, 6.47	0.005
<b><u>Metabolic Dysregulation:</u></b>				
Model 3b	Model 2 covariates + non-HDL cholesterol at baseline and follow-up	3.72	1.09, 6.35	0.007
Model 3c	Model 2 covariates + Hemoglobin A1c at baseline and follow-up	3.94	1.43, 6.45	0.003
<b><u>Inflammation:</u></b>				
Model 3d	Model 2 covariates + hsCRP at baseline and follow-up	4.21	1.40, 7.02	0.004
Model 3e	Model 2 covariates + 25-hydroxy vitamin D at baseline and follow-up	3.78	1.19, 6.37	0.005
<b><u>Hormonal Regulators of Blood Pressure:</u></b>				
Model 3f	Model 2 covariates + serum aldosterone at baseline and follow-up	4.15	1.55, 6.76	0.003
Model 3g	Model 3f covariates + ACEi/ARB use at baseline and follow-up	3.74	0.95, 6.53	0.01
<b><u>Increased Intravascular Volume:</u></b>				
Model 3h	Model 2 covariates + pulse pressure at baseline and follow-up	3.17	0.26, 6.07	0.03

<sup>a</sup>SBPi= systolic blood pressure index, defined as awake SBP/95<sup>th</sup> percentile awake SBP.  
Abbreviations: ACEi=angiotensin converting enzyme inhibitor; ARB=Angiotensin II Receptor Blocker; BMI=body mass index; hsCRP=high sensitivity C-Reactive Protein; LVMI=Left Ventricular Mass Index; non-HDL=Non-High Density Lipoprotein.

## Chapter 5: Conclusions

This thesis research describes the breadth and significance of pediatric hypertension and how this previously adult-predominant condition has now solidified itself as a common pediatric problem. While the reported prevalence of diagnosed hypertension has increased to one in 25 children<sup>3</sup>, this may be an underestimate. We have previously shown that provider recognition of elevated blood pressure in children cared for in a primary care setting is exceedingly poor<sup>22</sup> and others have shown provider adherence to recommended blood pressure screening to be less than optimal<sup>21</sup>. Further, we have also shown that a substantial proportion of children with incident hypertension already have evidence of target organ damage in the form of left ventricular hypertrophy (LVH) at initial diagnosis and that the severity of their hypertension is not associated with its presence<sup>9</sup>. These studies suggest that elevated blood pressure detection and hypertension diagnosis in children may be delayed or that other factors, specifically obesity, also has a more substantial role in the development of target organ damage, specifically LVH, among hypertensive children.

To further expand on our prior work we conducted two separate studies. The first study determined the impact of an intervention combining education and technology on provider recognition of elevated blood pressure in a pediatric primary care clinic. In the second study, we examined the longitudinal association of obesity and obesity-related risk factors with LVH and left ventricular mass in children with hypertension.

During implementation of our intervention, recognition of elevated blood pressure increased more than three-fold (12.5% to 42%,  $p < 0.001$ ), but still remained poor with more than half of elevated blood pressure encounters remaining unrecognized. We were surprised to find

that recognition was no different by educational session attendance status, but unsurprised to discover that recognition was lower during acute care encounters when compared to scheduled clinic encounters (prevalence ratio (PR) 0.6, 95% confidence interval (CI) 0.5- 0.7;  $p < 0.001$ ). Encounters of children with a co-morbid CVD risk factor or more obviously elevated blood pressure were more likely to be recognized in both the pre-intervention and intervention periods. However, after implementation of automated alerts, recognition was less influenced by the presence or absence of these risk factors.

In our prospective, observational study of children with established hypertension, we found a high prevalence of co-morbid cardiovascular disease (CVD) risk factors. More than half of the children were overweight/obese and 41% had LVH. These CVD risk factors, in addition to serum uric acid, lipids, hemoglobin A1c, and hsCRP, increased or worsened over time despite relatively good BP control.

Children who were overweight or obese at both study visits experienced the greatest increase in left ventricular mass index (LVMI) over time: mean change in LVMI was  $6.4 \text{ g/m}^{2.7}$  (95% CI 2.4, 10.5) among those overweight or obese at each visit, vs.  $0.95 \text{ g/m}^{2.7}$  (95%CI -3.2, 5.1) among children who were of healthy weight at each visit ( $p=0.056$ ). Overweight/obese children with and without LVH at baseline demonstrated a larger increase in LVMI compared to healthy weight children. In fact, healthy weight children with LVH were the only ones with decreased LVMI over time.

We also demonstrated that baseline BMI z-score was positively associated with an increase in LVMI over time ( $\beta$  4.08, 95% CI 1.54, 6.61,  $p=0.002$ ) during multivariable regression



analyses adjusting for age, sex, race, and LVMI at baseline. This association remained essentially unchanged after sequential adjustment for all postulated mediating pathways between BMI z-score and LVMI, with the exception of pulse pressure and serum aldosterone. When added to the model, those two risk factors decreased the point estimate, suggesting they were partial mediators of this relationship. The strong relationship between BMI z-score and change in LVMI that persisted despite adjusting for each of these factors suggests either an independent relationship between adiposity and LVMI or, more likely, an interaction of LVMI with many or all of these mediators.

Overall, our work documents a substantial burden of CVD risk factors among our most vulnerable population – children and adolescents. It has been estimated that at least 24.5 million of the 74.2 million children in the United States<sup>4</sup> have one or more CVD risk factor, which include diagnoses such as hypertension, dyslipidemia and obesity. These estimates rely on proper identification and diagnosis conducted in a busy clinical practice. As we have shown, even with education and real-time electronic alerts, pediatricians under-recognize elevated blood pressure in routine practice. This finding suggests that current population estimates may also underestimate the prevalence of pediatric hypertension nationally.

A common underlying theme to this increased CVD risk is overweight and obesity. The prevalence of hypertension in children has increased over the last several decades along with the known substantial increase in overweight and obesity among youth<sup>6</sup>. In addition, all of the CVD risk factors screened for in children have known biological pathways associating them with increased body mass. Our work shows that hypertensive children referred for subspecialty care demonstrate not only a high prevalence of co-morbid CVD risk factors at baseline, but an

increase in both their prevalence and severity over time. Most striking of these CVD risk factors is the presence and substantial degree of overweight and obesity. In fact, among the hypertensive children in our study, adiposity as determined by body mass index z-score was the greatest risk factor for both LVH and change in LVMI over time. LVH, a form of target organ damage in hypertension defined by a LVMI  $\geq 95^{\text{th}}$  percentile, has been thought to occur via exposure to increased LV afterload as seen in hypertension. In our study, no measure of blood pressure was associated with its presence. Additionally, none of the measures of inflammation or metabolic dysregulation played an important mediating role between adiposity and LVMI over time. Markers of intravascular volume and hormonal regulation of blood pressure did appear to partially mediate this relationship. With these risk factors potentially modifiable by diet – specifically with sodium restriction – this finding emphasizes the importance of lifestyle modification in the treatment of hypertension in children.

While not surprising that adherence to a heart healthy lifestyle, one that includes good diet quality and regular physical activity, would improve a child's CVD risk profile, adherence remains a challenge. Our work also shows that despite standard of care counseling regarding lifestyle modifications, the hypertensive children enrolled gained weight over time and manifested an increase in CVD risk factors despite good blood pressure control. In addition, overweight and obese hypertensive children experienced greater increases in their left ventricular mass over time when compared to healthy weight counterparts. And of the children who should have demonstrated a decrease in LVMI over time – those with LVH – only those with healthy weight met this therapeutic goal.

With the significant burden of CVD risk factors in children and the now well recognized tracking of hypertension and CVD risk factors from childhood to adulthood, primordial and primary prevention remains of paramount importance. With overweight and obesity a common denominator for many if not all of these risk factors, we must find ways to engage and empower youth to follow a heart healthy lifestyle. Primordial prevention remains the cornerstone of efforts to improve not only the CV health of our children and adolescents, but also decrease CVD morbidity and mortality in adults.

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## CURRICULUM VITAE

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Date of Version

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2000 to 2003	The Children's Hospital at Montefiore Bronx, NY	Intern & Resident Pediatrics
2003 to 2004	The Children's Hospital at Montefiore Bronx, NY	Chief Resident Pediatrics
2004 to 2005	Johns Hopkins University Baltimore, MD	Research Fellow Pediatric Nephrology
2004 to 2006	Johns Hopkins Bloomberg School of Public Health Baltimore, MD	MHS Clinical Epidemiology
2005 to 2008	Johns Hopkins University Baltimore, MD	Clinical and Research Fellow Pediatric Nephrology
2010 to Present	Johns Hopkins Bloomberg School of Public Health Baltimore, MD	PhD candidate Clinical Investigation

#### **D. Professional Experience**

2003 to 2004	Chief Resident Department of Pediatrics The Children's Hospital at Montefiore
2008 - Present	Assistant Professor Department of Pediatrics Johns Hopkins University School of Medicine
2011 – Present	Medical Director Pediatric Hypertension Program Johns Hopkins University School of Medicine

## II. RESEARCH ACTIVITIES

### A. Peer Reviewed Scientific Articles

1. Fadrowski, JJ, Frankenfield, D, Amaral, S, Brady, T, Gorman, GH, Warady, B, Furth, SL, Fivush, B, Neu, AM. Children on long-term dialysis in the US: findings from the 2005 ESRD Clinical Performance Measures Project. *Am J Kidney Dis* 50(6):958-66, 2007. PMID:18037097
2. Brady, TM, Fivush, B, Flynn, JT, Parekh, R. Ability of Blood Pressure Parameters to Predict Left Ventricular Hypertrophy in Children with Primary Hypertension. *J Pediatr* 152(1):73-8,78.e1, 2008. PMID:18154904  
Subject of Editor's Perspective: Daniels, SR. Hypertension and left ventricular hypertrophy. *J Pediatr* 152(1): A2, 2008.
3. Brady, TM, Solomon, BS, Neu, AM, Siberry, GK, Parekh, RS. Patient, Provider and Clinic Level Predictors of Unrecognized Elevated Blood Pressure in Children. *Pediatrics* 2010 Jun; 125 (6): e1286-e1293. PMID:20439598  
Subject of Research Highlight: Mearns, BM. Pediatrics: Raised blood-pressure measurements are under-recognized in children. *Nat Rev Cardiol*. 2010 Oct;7(10):540.
4. Brady, TM, Fivush, B, Parekh, R, Flynn, JT. Racial Differences among Children with Primary Hypertension. *Pediatrics* 2010 Nov;126(5):931-7. (doi:10.1542/peds.2009-2972). PMID:20956429
5. Loeffler, L, Navas-Acien, A, Brady, T, Miller, E, Fadrowski, J. Uric Acid Level and Elevated Blood Pressure in U.S. Adolescents. National Health and Nutrition Examination Survey 1999-2006. *Hypertension*. 2012 Apr;59(4):811-7. Epub 2012 Feb 21. PMID:22353609
6. Brady, T, Schneider, M, Flynn, J, Cox, C, Samuels, J, Saland, J, White, C, Furth, S, Warady, B, Mitsnefes, M. Carotid Intima Media Thickness in Children with Chronic Kidney Disease: Results from the CKiD study. *Clinical Journal of the American Society of Nephrology*. 2012. (doi: 10.2215/CJN.03130312). Epub September 14, 2012. PMID:22977209
7. Eakin, M, Brady, T, Kandasamy, V, Fivush, B, Riekert, K. Disparities in Antihypertensive Medication Adherence in Adolescents. *Pediatric Nephrology*. 2013 Aug;28(8):1267-73. (doi: 10.1007/s00467-013-2455-2). Epub 2013 Mar 20. PMID: 23512259
8. Pruetto, C, Fivush, B, Flynn, J, Brady, T. Effects of Obesity and Race on Left

Ventricular Geometry in Hypertensive Children. *Pediatric Nephrology*. 2013 Aug; 28(10):2015–2022. (doi: 10.1007/s00467-013-2507-7). PMID:23703719

9. Kogon, A, Pierce, C.B., Cox, C, Brady, T.M., Mitsnefes, M, Warady, B.A., Furth, S.L., Flynn, J.T. Proteinuria is a Major Factor in Uncontrolled BP in Pediatric CKD. *Kidney International*. 2013 Sep 18. (doi: 10.1038/ki.2013.352). Epub ahead of print. PMID: 24048375
10. Scholl UI, Goh G, Stölting G, de Oliveira RC, Choi M, Overton JD, Fonseca AL, Korah R, Starker LF, Kunstman JW, Prasad ML, Hartung EA, Mauras N, Benson MR, Brady T, Shapiro JR, Loring E, Nelson-Williams C, Libutti SK, Mane S, Hellman P, Westin G, Akerström G, Björklund P, Carling T, Fahlke C, Hidalgo P, Lifton RP. Somatic and germline CACNA1D calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism. *Nat Genet*. 2013 Aug 4. (doi: 10.1038/ng.2695). Epub 2013 Aug 4. PMID: 23913001

#### **B. Peer Reviewed Scientific Articles, Submitted**

1. Brady, T.M., Neu, A.M., Appel, L., Miller, E.R., Siberry, G., Solomon, B. Real Time Electronic Medical Record Alerts Increase High Blood Pressure Recognition in Children. *Submitted, Pediatrics*.

#### **C. Peer Reviewed Scientific Articles, In Preparation**

1. Reader, L.D., Fadrowski, J.J., Loeffler, L.F., Holmes, K.W., Appel, L., Miller, E.R., Brady, T.M. Association of Uric Acid and Left Ventricular Hypertrophy in Pediatric Hypertension. *In Preparation*.
2. Brady, T.M., Fivush, B.A., Holmes, K.W., Miller, E.R., Appel, L. The Role of Adiposity on Left Ventricular Mass amongst Hypertensive Children. *In Preparation*.

#### **D. Invited Review Articles/Editorials**

1. Brady, TM, Siberry, G, Solomon, B. Pediatric Hypertension: A Review of Proper Screening, Diagnosis, Evaluation and Treatment. *Contemporary Pediatrics* 25(11): 46-56, 2008.
2. Brady, TM, Feld, L. Pediatric Approach to Hypertension. *Seminars in Nephrology*, 2009 Jul; 29(4):379-88. PMID:19615559
3. Brady, TM, Parekh, RS. Metabolic Syndrome: Signs and Symptoms Running Together. *Pediatric Transplantation*, 2010 Feb;14(1): 6-9. PMID:20078837

4. Brady, TM. Hypertension. *Pediatrics in Review*, 2012; 33:541-552. PMID: 23204396
5. Brady, TM. Hypertension. *Decision Support in Medicine*. <https://www.decisionsupportinmedicine.com/DSM/a/articles/29/A/4255>.
6. Brady, TM, Flynn, JT. Hypertensive Crisis. *Decision Support in Medicine*. <https://www.decisionsupportinmedicine.com/DSM/a/articles/29/A/2365>.
7. Brady, TM, Redwine, KM, Flynn, JT; for the American Society of Pediatric Nephrology. Screening Blood Pressure Measurement in Children: Are We Saving Lives? *Pediatric Nephrology*, 2013; Dec 11. [Epub ahead of print]. PMID: 24326788.

#### **E. Abstracts (\* presented)**

1. \*Brady, TM, Flynn, JT: Racial Background Has No Effect on the Characteristics of Primary Hypertension in Children. Poster presented at the Eastern Society for Pediatric Research Annual Meeting, March 2005.
2. \*Brady, TM, Flynn, JT: Racial Background Has No Effect on the Characteristics of Primary Hypertension in Children. *PAS* 2005: 57: 463.
3. \*Brady, TM, Flynn, JT: Characteristics of Primary Hypertension in Children of Different Racial Groups. *American Journal of Hypertension* 18: A223, May 2005.
4. Brady, TM, Parekh, RS, Fivush, BA, Flynn, JT: Ambulatory Blood Pressure Systolic Loads Predict Left Ventricular Hypertrophy in Hypertensive Children. *Journal of the American Society of Nephrology* 16: 797A, 2005.
5. \*Brady, T, Fivush, B, Flynn, J, Parekh, R. Ability of Blood Pressure (BP) Parameters to Predict Left Ventricular Hypertrophy (LVH) in Children With Primary Hypertension (HTN). *Journal of the American Society of Nephrology* 17: 427A, 2006.
6. \*Brady, T, Frankenfield, D, Gorman, G, Neu, A, Fivush, B. Achievement of Adult Serum Albumin Targets in Hemodialysis (HD) and Peritoneal Dialysis (PD) Pediatric Patients. *Journal of the American Society of Nephrology* 17: 410A, 2006.
7. \*Brady, TM, Siberry GK, Neu, AM, Levy, J, Solomon, B, Parekh, RS.

Prevalence and Predictors of Unrecognized High Blood Pressure (BP) in Children. Platform presentation at the Pediatric Academic Society Annual Meeting, Toronto, Canada, May 2007. E-PAS2007:615550.7.

8. \*Brady, TM, Siberry GK, Neu, AM, Levy, J, Solomon, B, Parekh, RS. Prevalence and Predictors of Unrecognized High Blood Pressure (BP) in Children. Poster Presentation at the National Kidney Foundation of Maryland Annual Scientific Session, May 2007.
9. \*Brady, TM, Siberry GK, Neu, AM, Levy, J, Solomon, B, Parekh, RS. Patient, Clinic and Provider Predictors of Unrecognized High Blood Pressure (BP) in Children. Journal of the American Society of Nephrology 18: 628A, 2007.
10. \*Brady, TM, Siberry GK, Neu, AM, Solomon, B, Parekh, RS. High Blood Pressure in Children: Factors Associated with Lack of Recognition. Journal of the American Society of Nephrology 19: 620A, 2008.
11. \*Pruette, CS, Fivush, B, Flynn, J, Brady, TM. Racial Differences in Left Ventricular Hypertrophy among Children with Primary Hypertension. Platform Presentation at the Eastern Society for Pediatric Research Annual Meeting, March 2009.
12. \*Pruette, CS, Fivush, B, Flynn, J, Brady, TM. Racial Differences in Left Ventricular Hypertrophy among Children with Primary Hypertension. Platform Presentation at the Pediatric Academic Society Annual Meeting, Baltimore. E-PAS2009:2530.6.
13. \*Brady, TM, Fivush, B, Parekh, R, Flynn, J. Impact of Race/Ethnicity on Ambulatory Blood Pressure (ABP) Among Children with Primary Hypertension (PHTN). Journal of the American Society of Nephrology 20: 722A, 2009.
14. \*Brady, TM, Fivush, B, Parekh, R, Flynn, J. Racial/Ethnic Differences among Children with Primary Hypertension (PHTN). Journal of the American Society of Nephrology 20: 721A, 2009.
15. \*Pruette, CS, Fivush, B, Flynn, J, Brady, TM. Left Ventricular Hypertrophy (LVH) Among African-American (AA) and Non-AA Children with Primary Hypertension (PHTN). Journal of the American Society of Nephrology 20: 724A, 2009.
16. \*Brady, T, Schneider, M, Flynn, J, Cox, C, Kimball, T, Furth, S, Warady, B, Mitsnefes, M. Correlates of carotid artery intima media thickness (cIMT) in children with Chronic Kidney Disease (CKD): a report from the Chronic Kidney

Disease in Children (CKiD) cohort study. Oral Poster Presentation at the Fifteenth Congress of the International Pediatric Nephrology Association, September 2010. *Pediatric Nephrology* 25: 776, 2010.

17. \*Brady, T, Schneider, M, Flynn, J, Cox, C, Kimball, T, Mentser, M, White, C, Furth, S, Warady, B, Mitsnefes, M. Carotid Intima Media Thickness (cIMT) in Children with Chronic Kidney Disease (CKD): Results from the Chronic Kidney Disease in Children (CKiD) cohort study. Poster presentation at the American Society of Nephrology Annual Meeting, November 2010.
18. \*Loeffler, L, Miller, E, Brady, T, Fadrowski, J. Uric Acid Level and Hypertension in U.S. Adolescents. Platform Presentation at the American Society of Nephrology Annual Meeting, November 2010.
19. \*Pruette, CS, Fivush, B, Flynn, J, Brady, TM. Left Ventricular Hypertrophy (LVH) Among African-American (AA) and Non-AA Children with Primary Hypertension (PHTN). *Clinical and Translational Science* 4: P23, 2011.
20. \*Kogon, A, Pierce, C, McDermott, K, Brady, T, Mitsnefes, M, Warady, B, Furth, S, Flynn, J. Factors Associated with Longitudinal Blood Pressure Changes in Pediatric Patients with Chronic Kidney Disease. Platform Presentation at the American Society of Pediatric Nephrology Annual Meeting, May 2011.
21. \*Pruette, C, Fivush, B, Flynn, J, Brady, T. Left Ventricular Geometry in Children with Primary Hypertension: Prevalence and Predictors. Poster Presentation at the American Society of Hypertension Annual Meeting, May 2011.
22. \*Kogon, A, Pierce, C.B., Brady, T.M., Mitsnefes, M, Warady, B.A., Furth, S.L., Flynn, J.T. Factors Contributing to the Development and Control of Elevated Blood Pressure in Pediatric CKD Patients. Oral abstract presentation at the American Society of Nephrology Annual Meeting, November 2011.
23. \*Brady, T.M., Neu, A.M., Siberry, G., Solomon, B. Increased Provider Recognition of Elevated Blood Pressure in Children. Poster Presentation at the American Society of Nephrology Annual Meeting, November 2012.
24. \*Reader, L.D., Fadrowski, J.J., Loeffler, L.F., Miller, E.R., Holmes, K.W., Brady, T.M. Association of Uric Acid and Left Ventricular Hypertrophy in Pediatric Hypertension. Oral Poster Presentation, Medical Student Research Day, Johns Hopkins University School of Medicine, January 2013.

25. \*Brady, T.M., Holmes, K.W., Boynton, S., Pruetto, C., Fadrowski, J.J., Miller, E.R. Diurnal Blood Pressure (BP) and BP Variability is not associated with Left Ventricular Hypertrophy among Hypertensive Children. Poster Presentation at the American Society of Pediatric Nephrology Annual Meeting, May 2013.
26. \*Reader, L.D., Fadrowski, J.J., Loeffler, L.F., Miller, E.R., Holmes, K.W., Brady, T.M. Association of Uric Acid and Left Ventricular Hypertrophy in Pediatric Hypertension. Poster Presentation at the American Society of Pediatric Nephrology Annual Meeting, May 2013.
27. \*Thompson W.R., Holmes K.W., Jennings J., Brady T.M. Ventricular Strain is Abnormal in Children with Hypertension. Poster Presentation at the American Heart Association Scientific Sessions Meeting, November 2013.
28. \*T. Brady, K. McDermott, M. Schneider, C. Cox, B. Warady, S. Furth, M. Mistnefes. Cystatin C Independently Predicts Change in Left Ventricular Mass index Over Time in Children with Chronic Kidney Disease. Journal of the American Society of Nephrology 24: 430A, 2013.
29. \*T. Brady, K. McDermott, M. Schneider, C. Cox, B. Warady, S. Furth, M. Mistnefes. Cystatin C Independently Predicts Abnormal Systolic and Diastolic Function Over Time in Children with Chronic Kidney Disease (CKD). Platform Presentation at the American Society of Pediatric Nephrology Annual Meeting, May 2014.
30. C.S. Pruetto, T.M. Brady, S. Mendley, B. Fivush, D. Roter, A. Green, K. Riekert. Patient-Provider Communication on Medication Adherence in Adolescents with Chronic Kidney Disease. Submitted to the American Society of Pediatric Nephrology Annual Meeting, May 2014.
31. \*Reader, L.D., Fadrowski, J.J., Loeffler, L.F., Miller, E.R., Holmes, K.W., Brady, T.M. Uric Acid Is Not Associated With Change In Left Ventricular Mass Index Among Hypertensive Children. Poster Presentation at the American Society of Pediatric Nephrology Annual Meeting, May 2014.
32. Habli, M., Brady, T.M., Eschenbacher, M., Rodriguez, Z., DeFranco, E.A., Kamath-Rayne, B.D. Neonatal Hypertension and Antenatal Exposure to NSAIDs. Submitted to the American Society of Nephrology Annual Meeting, November 2014.
33. Pruetto, C.S., Brady, T.M., Mendley, S., Fivush, B., Roter, D., Green, A., Eakin, M.A., Riekert, K.A. Medication Adherence in Adolescents with Chronic Kidney



Disease or Kidney Transplantation: Self- Report Vs. Provider Perception.  
Submitted to the American Society of Nephrology Annual Meeting,  
November 2014.

34. Sethna, C.B., Mariani, L.H., Weyant, R.J., Brady, T.M., Meyers, K.E.C., Gibson, K.L., Wickman, L.T., Gadegbeku, C.A. Hypertension and Blood Pressure Variability in NEPTUNE. Submitted to the American Society of Nephrology Annual Meeting, November 2014.
35. Brady, T.M., Fivush, B., Holmes, K., Miller, E.R. The Relationship between Adiposity and Left Ventricular Mass in Children with Hypertension. Submitted to the American Society of Nephrology Annual Meeting, November 2014.

## **F. Research/Grant Support**

### **1. Completed**

2002	American Society of Pediatric Nephrology Travel Grant Awarded to attend the American Society of Nephrology Annual Meeting and Exhibition Philadelphia, PA
2003	American Society of Pediatric Nephrology Travel Grant Awarded to attend the American Society of Nephrology Annual Meeting and Exhibition San Diego, CA
2003	American Society of Pediatric Nephrology Travel Grant Awarded to attend the Pediatric Academic Society Annual Meeting Seattle, WA
8/1/2004- 6/30/2005	NIH/NIDDK T32 DK07732 Renal Disease Epidemiology Training Grant PI: Michael J. Klag, MD, MPH Role: Pediatric Nephrology Fellow \$45,048
2005	Eastern Society for Pediatric Research Travel Grant Awarded to attend the Eastern Society for Pediatric Research Annual Meeting

Old Greenwich, CT

7/1/2005-  
6/30/2006

NIH/NIDDK  
T32 DK07732  
Renal Disease Epidemiology Training Grant  
PI: Michael J. Klag, MD, MPH  
Role: Pediatric Nephrology Fellow  
\$46,992

2006

National Kidney Foundation Travel Grant  
Awarded to attend the NKF Clinical Meeting  
Chicago, IL  
\$400

7/1/2006-  
6/30/2007

*Prospective Study of Barriers Impeding Recognition  
of Elevated Blood Pressure in Children*  
National Kidney Foundation of Maryland  
Mini-Grant Award  
Role: Principal Investigator  
\$5,400

7/1/2006-  
6/30/2008

*Prospective Study of Barriers Impeding Recognition  
of Elevated Blood Pressure in Children*  
American Kidney Fund Clinical Scientist in Nephrology  
Fellowship Award  
Role: Pediatric Nephrology Fellow, Principal Investigator  
\$113,500

7/1/2006-  
6/30/2008

*Prospective Study of Barriers Impeding Recognition  
of Elevated Blood Pressure in Children*  
National Institutes of Health  
Loan Repayment Program Award  
\$70,000

7/1/2008-  
6/30/2009

*Longitudinal Study of Left Ventricular Hypertrophy  
Regression in Children with Primary Hypertension*  
National Kidney Foundation of Maryland  
Professional Development Award  
Role: Principal Investigator  
\$40,000

7/1/2008-  
6/30/2009

*Longitudinal Study of Left Ventricular Hypertrophy  
Regression in Children with Primary Hypertension*

	<p>Thomas Wilson Sanitarium for the Children of Baltimore City  Grant Award  Role: Principal Investigator  \$20,000</p>
7/1/2008 – 6/30/2009	<p><i>Improving the Diagnosis and Treatment of Children  with Elevated Blood Pressure and Hypertension</i>  Johns Hopkins Children’s Center  Special Studies Project  \$9,970</p>
9/1/2008 – 8/30/2011	<p><i>Longitudinal Study of Left Ventricular Hypertrophy  Regression in Children with Primary Hypertension</i>  American Society of Nephrology  Norman Siegel Research Scholar Grant  Role: Principal Investigator  \$180,000 direct support</p>
9/1/2010 – 8/31/2012	<p>National Institutes of Health/ Johns Hopkins Institute  for Clinical and Translational Research  KL2 Clinical Research Scholar Award  5KL2RR025006  \$130,000 annual direct support</p>
7/1/2011 – 6/30/2012	<p><i>Empowering and Enabling Hypertensive Children and  Families to Improve their Health</i>  Johns Hopkins Children’s Center  Special Studies Project  \$10,000</p>
1/1/2011- 12/31/2012	<p><i>Metabolic Determinants of Left Ventricular Mass in  Children with Primary Hypertension</i>  American Heart Association  Clinical Research Program  11CRP5270013  \$50,000 annual direct support</p>
7/1/2011- 6/30/2013	<p><i>Metabolic Determinants of Left Ventricular Mass in  Children with Hypertension</i>  National Institutes of Health  Loan Repayment Program Award  \$70,000</p>

## 2. Ongoing

- 9/1/2011 –  
5/31/2016                      *Doctor-Teen Communication & Antihypertensive Adherence among Teens with CKD*  
NIH NIDDK  
R01DK092919  
Total Costs= \$2,231,744  
P.I. Kristin Riekert, PhD  
Role: Co-investigator
- 7/1/2013-  
6/30/2014                      *Feasibility of a Texting Intervention among Children and Young Adults*  
National Kidney Foundation of Maryland  
Mini-Grant Award  
Role: Principal Investigator  
\$10,000
- 1/1/2014-  
12/30/2014                      Clinician Scientist Award  
Johns Hopkins University School of Medicine  
\$80,000

## 3. Pending

- 7/1/2014-  
6/30/2018                      *Promoting Heart Healthy Behaviors in Youth*  
NIH NHLBI  
1K23 HL119622-01  
Total Direct Costs=\$743,445  
Role: Principal Investigator

## III. CLINICAL ACTIVITIES

### A. Licensure and certification

- Medical License**            2002 – State of New York, License No. 228732  
2004 – District of Columbia, License No. MD035032  
2004 – State of Maryland, License No. D0062035
- Board Certifications**    '03, '13 - Diplomate, American Board of Pediatrics  
'10                                - Diplomate, American Board of Pediatrics, Sub-board  
Pediatric Nephrology

## **B. Service Responsibilities**

2008 – Present	Pediatric Nephrology Attending/Consult Service 8-12 Weeks/Year
2008 – Present	Harriet Lane Kidney Center Outpatient Clinic 2 Half-day Sessions/Month
2008 – Present	Harriet Lane Kidney Center Hypertension Clinic 1 Half-day Session/Month

## **C. Clinical Program Building**

2011 – Present	<i>Pediatric Hypertension Program</i> Medical Director Develop and oversee a multi-disciplinary pediatric hypertension clinic which provides specialized renal nursing and dietician services. This clinic provides a comprehensive evaluation and treatment approach that includes the use of 24-hour ambulatory blood pressure monitoring, echocardiography interpretation, obstructive sleep apnea screening, home blood pressure monitors and weight loss support. Pediatric focused educational materials and support for successful lifestyle modifications are provided.
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## **IV. EDUCATIONAL ACTIVITIES**

### **A. Clinical Instruction**

2003-2004	Morning Conference – 3 conferences/ year Responsible for presenting didactic lectures to housestaff and medical students on core topics in pediatrics
2003-2004	Weekly medical student walk rounds Pediatric Ward Teams Responsible for case-based teaching of medical students
2003-2004	Chairman’s Rounds Once per week Responsible for preparing conference for faculty, housestaff and medical students

2003-2004	Professor's Walk Rounds Twice per week Responsible for preparing presentation for housestaff and medical students
2003-2004	Mock Codes 4 times per month Responsible for preparing and running mock code for housestaff and medical students
2005-2008	Board Review 4-6 times per year Responsible for preparing and giving lectures on relevant nephrology topics for pediatric residents and pediatric nephrology fellows
2006	Renal Physiology Course Small Group Leader 2 hour session First-year Medical Students
2007, 2009	Harriet Lane Clinic Continuity Clinic Lecture Series Lecture – "Pediatric Hypertension" Johns Hopkins University Baltimore, MD
2008 – Present	Pediatric Nephrology Attending Teaching Rounds 8-12 weeks per year Responsible for 1-2 hour teaching rounds daily for residents
2008 – Present	Nephrology Rotation Core Lecture Series 1 lecture/month Pediatric Housestaff
2009, 2011	Pediatric Noon Clinical Conference "Hypertensive Urgencies and Emergencies in Children – Assessment and Management" Johns Hopkins University Baltimore, MD
2009	Pediatric Noon Clinical Conference "The Ups and Downs of Blood Pressure: Hypertension in Children" Sinai Hospital

Baltimore, MD

2009 Pediatric Noon Clinical Conference  
 “Nephrotic Syndrome”  
 Johns Hopkins University  
 Baltimore, MD

2010 Pediatric Noon Clinical Conference  
 “Renal Tubular Acidosis”  
 Johns Hopkins University  
 Baltimore, MD

2010, 2013 Neonatal Intensive Care Unit Lecture Series  
 “Neonatal Hypertension”  
 Johns Hopkins University  
 Baltimore, MD

2012 Emergency Department Lecture Series  
 “Hypertensive Crises”  
 Johns Hopkins University  
 Baltimore, MD

2012-2014 Pediatric Intensive Care Unit Lecture Series  
 “Hypertensive Crises”  
 Johns Hopkins University  
 Baltimore, MD

2012, 2013 Clinical Epidemiology Course – Small Group Leader  
 First Year Medical Students  
 Johns Hopkins University School of Medicine  
 Baltimore, MD

**B. CME Instruction**

2006 Pediatric Trends  
 “Chronic Kidney Disease Presenting as Constipation”  
 Johns Hopkins University  
 Baltimore, MD

2006 Pediatric Case Management Conference  
 “Obstructive Uropathy”  
 Johns Hopkins University  
 Baltimore, MD

- 2007 Platform Presentation  
 “Prevalence and Predictors of Unrecognized High Blood Pressure in Children”  
 American Society of Pediatric Nephrology Annual Meeting  
 Toronto, Canada
- 2008 Pediatric Trends  
 “Vesicoureteral Reflux Presenting as Fever and Malaise”  
 Johns Hopkins University  
 Baltimore, MD
- 2008 Pediatric Noon Research Conference  
 “Pediatric Hypertension: Patient Characteristics, Target Organ Damage and Effectiveness of BP Screening”  
 Johns Hopkins University  
 Baltimore, MD
- 2010 Oral Poster Presentation  
 “Correlates of carotid artery intima media thickness in children with Chronic Kidney Disease: a report from the Chronic Kidney Disease in Children (CKiD) cohort study.”  
 The Fifteenth Congress of the International Pediatric Nephrology Association  
 New York, NY
- 2013 Pediatric Trends  
 “Hypertensive Crisis”  
 Johns Hopkins University  
 Baltimore, MD

**C. CME Instruction, Alternative Media**

- 2008 Brady, TM, Siberry, G, Solomon, B. Pediatric Hypertension: A Review of Proper Screening, Diagnosis, Evaluation and Treatment. *Contemporary Pediatrics* 25(11): 46-56, 2008. CME activity.
- 2012 Brady, TM. Hypertension. *Pediatrics in Review*, 2012; 33:541-552. CME activity.

**D. Mentoring**

- 2009-2012 Cozumel Pruetter, MD, MHS



Assistant Professor Pediatrics  
2012 Recipient of the Francis Schwentker Award for Excellence in Research, based on the manuscript “Effects of Obesity and Race on Left Ventricular Geometry in Hypertensive Children”.

2010-2012 Darcy Weidemann, MD  
Pediatric Nephrology Fellow  
Resident QI Project  
Elevated BP Recognition in a Primary Care Setting

2012-present Lauren Reader  
Medical Student (M’15)  
Johns Hopkins University School of Medicine  
Scholarly Concentration Project: “Association of Uric Acid and Left Ventricular Hypertrophy in Pediatric Hypertension”  
Research abstract selected for Oral Presentation at Medical Student Research Day and as a Poster Presentation at the American Society of Pediatric Nephrology annual meeting

## **V. ORGANIZATIONAL ACTIVITIES**

### **A. University and Hospital Committees / Positions Held / Sub-Committees**

#### **1. Children’s Hospital at Montefiore**

2003 – 2004 Representative, Radiology Task Force

2003 – 2004 Children’s Hospital at Montefiore (CHAM) Quality Improvement Committee

2003 – 2004 CHAM 8 & 9 Quality Performance Improvement Subcommittee

2003 – 2004 Adolescent Inpatient Unit Quality Performance Improvement Subcommittee

2003 – 2004 CHAM 8 & 9 Inpatient Review Committee

2003 – 2004 Adolescent Inpatient Unit Review Committee

2003 – 2004 Intern Selection Committee

#### **2. Johns Hopkins University, Division of Pediatric Nephrology**

- 2005-Present            Advocacy Committee  
Participated in and helped organize several fund-raising and patient activities for the Johns Hopkins Department of Pediatric Nephrology.
- 2008-Present            Fellow Applicant Selection  
Actively involved in interviewing applicants and selecting candidates for the Johns Hopkins Pediatric Nephrology Fellowship Program
- 2012-Present            Pediatric Nephrology Division QI Project Co-Leader  
Responsible for designing, implementing and disseminating the results of the project: "Tracking and Improving Pneumococcal Vaccination Rates, January 1, 2013 through June 30, 2013", followed by an expansion of the project to include all children with CKD, July 1, 2013 through June 30, 2014.

**3. Johns Hopkins University, Department of Pediatrics**

- 2006-2009                Computerized Alerts Committee  
Active participant involved in the conception, development, and testing of computerized alerts designed to notify providers of elevated blood pressure in the Harriet Lane Clinic.
- 2012-Present            Intern Applicant Selection  
Actively involved in interviewing applicants and selecting candidates for the Johns Hopkins Pediatric Residency Program

**B. Abstract Reviewer/ National Meetings**

- 2009, 2010                American Society of Nephrology Abstract Reviewer

**C. Professional Affiliations/ Committees/ Positions Held/ Sub-Committees**

- 2000-04, '07-08,        American Academy of Pediatrics  
2013-Present                *2013-Present: Section on Nephrology*  
    *2013-Present: PREP Nephrology Editorial Board*
- 2005-Present            American Society of Nephrology
- 2005-Present            American Society of Pediatric Nephrology  
    *2009-Present: Research Committee*  
    *2014-Present: Guideline Task Force*

2005-Present	International Pediatric Hypertension Organization
2008-2010	National Kidney Foundation
2008-2011	Mid-Atlantic Renal Coalition <i>2008-2011: Pediatric Nephrology Network Consortium</i>
2009-Present	CKiD (Chronic Kidney Disease in Children) Cohort Study Consortium <i>2009-Present: Cardiovascular Sub-Committee</i>
2010-2012	International Pediatric Nephrology Association
2010-Present	American Kidney Fund Clinical Scientist in Nephrology Committee
2013-Present	NEPTUNE (NEPhrotic Syndrome STUdy NETwork) Pediatric Working Group <i>2013–Present: Cardiovascular Outcomes Committee</i> <i>2013-Present: Recruitment and Retention Committee</i>
2014-Present	National Kidney Foundation of Maryland <i>Medical Advisory Board Member</i>
2014-Present	Association for the Advancement of Medical Instrumentation <i>Sphygmomanometer Committee</i>

## **VI. RECOGNITION**

### **A. Honors**

1992 - 1996	Dean's List Boston College, Chestnut Hill, MA
1996	Magna Cum Laude Boston College, Chestnut Hill, MA
1996	William J. Kenealy, S.J. Award Awarded for distinction in academics and social concern
1996	Order of the Cross and Crown Awarded for high academic standing and an established record of

service and leadership on campus

- 2003-2004 Chief Residency, Pediatrics  
Children's Hospital at Montefiore  
Bronx, NY
- 2006 Recipient of the Pearl M. Stetler Fellowship Award  
Research funding for woman physician
- 2007 American Society of Pediatric Nephrology  
Trainee Research Award  
Best Clinical Abstract
- 2011 NEMA Research  
Clinical Research Award  
Awarded to the individual in the Johns Hopkins Bloomberg School  
of Public Health GTPCI program with the highest score on the  
Comprehensive Exam
- 2013 Super Doctors Rising Star  
Washington, DC-Baltimore-Northern Virginia
- 2013 Leadership Program for Women Faculty  
Selected as a participant in this highly regarded program designed  
to promote leadership development among women and academic  
medicine career building.

#### **B. Invited Presentations/Lectures**

- 2004 Pediatric Grand Rounds  
"Common Pediatric Problems: What Should We Do? An Evidence  
Based Medicine Approach"  
The Children's Hospital at Montefiore  
Bronx, NY
- 2006 Adult Nephrology Grand Rounds  
"Challenging Pediatric Nephrology Cases"  
Johns Hopkins University  
Baltimore, MD
- 2007 Pediatric Grand Rounds  
"Prevalence and Predictors of Unrecognized High Blood Pressure  
in Children"

Johns Hopkins University  
Baltimore, MD

2007 American Kidney Fund  
Board of Trustees Meeting  
Research Platform Presentation  
Rockville, MD

2008 Pediatrics for the Practitioner  
“The Ups and Downs of Blood Pressure: Hypertension in Children”  
Johns Hopkins University  
Baltimore, MD

2009 Pediatric Grand Rounds  
“Hypertension in Children”  
Franklin Square Hospital Center  
Baltimore, MD

2009 Pediatric Grand Rounds  
“Risk Factors for and Sequelae of Pediatric Hypertension”  
Johns Hopkins University  
Baltimore, MD

2009 Adult Nephrology Grand Rounds  
“Pediatric Hypertension: Further Evidence that Children are not  
Little Adults”  
Johns Hopkins University  
Baltimore, MD

2010 Pediatric Grand Rounds  
“Pediatric Hypertension: Who is at risk?”  
Georgetown University Medical Center  
Washington, DC

2010 Pediatric Grand Rounds  
“Pediatric Hypertension: Who is at risk?”  
Virginia Hospital Center  
Arlington, VA

2010 Pediatric Grand Rounds  
“Pediatric Hypertension: Who is at risk?”  
Uniformed Services University of the Health Sciences

Bethesda, MD

2011 Pediatric Trends  
 “Pediatric Hypertension”  
 Johns Hopkins University  
 Baltimore, MD

2012 Pediatric Grand Rounds  
 “Hypertension in Children and Adolescents”  
 St. Agnes Hospital  
 Baltimore, MD

2012-2014 Pediatrics for the Practitioner  
 Session Workshop  
 “Hypertension”  
 Johns Hopkins University  
 Baltimore, MD

2013 Pediatric Grand Rounds  
 “The Skinny on Obesity Related Hypertension in Children”  
 Johns Hopkins University  
 Baltimore, MD

2013 Pediatric Grand Rounds  
 “The Skinny on Obesity Related Hypertension in Children”  
 Sinai Hospital of Baltimore  
 Baltimore, MD

2013 Dean’s Presentation  
 “Heart Health in Children with High Blood Pressure”  
 Johns Hopkins University  
 Baltimore, MD

2013 Pediatric Grand Rounds  
 “The Skinny on Obesity Related Hypertension in Children”  
 Greater Baltimore Medical Center  
 Baltimore, MD

2013 American Society of Pediatric Nephrology  
 Workshop: "Urine the Know" Best of Pediatric Nephrology in  
 2012-2013  
 “Carotid intima-media thickness in children with CKD: results from  
 the CKiD study”

Washington, DC

2013 Student Health and Wellness Center  
"Adolescent Hypertension"  
Johns Hopkins University  
Baltimore, MD

### **C. Editorial Appointments**

#### **1. Clinical Guideline Review Activities**

2011 Kidney Disease: Improving Global Outcomes (KDIGO) - "KDIGO Clinical Practice Guideline for Management of Blood Pressure in CKD."

#### **2. Journal Peer Review Activities**

2014 - Present Frontiers in Pediatric Nephrology  
Review Editorial Board  
Review Editor

2008 - Present Reviewer for:

- Pediatrics
- Journal of Human Hypertension
- American Journal of Hypertension
- Clinical Journal of the American Society of Nephrology
- Pediatric Transplantation
- International Journal of Pediatrics
- Pediatric Cardiology
- Nutrition, Metabolism & Cardiovascular Diseases
- Pediatric Anesthesia
- Medical Science Monitor

#### **3. Book Chapter Review Activities**

2009 First Aid for the USMLE Step 2 Clinical Knowledge  
7<sup>th</sup> edition  
Renal/Genitourinary chapter

### **D. Media**

1. "High Blood Pressure Affecting Children Now." WJZ Baltimore. May 19, 2009. <http://wjz.com/health/high.blood.pressure.2.1013574.html>

2. "Missing a Threat to Young Hearts." Baltimore Sun. June 1, 2009.
3. "Kids Should Get Hypertension Checks, Too." WBALTV Baltimore. June 2, 2009. <http://www.wbaltv.com/video/19583272/index.html?taf=bal>
4. "More Kids Facing High Blood Pressure." NBC Washington. January 12, 2010. [http://www.nbcwashington.com/shows/health-expo/More Kids Facing High Blood Pressure Washington DC.html](http://www.nbcwashington.com/shows/health-expo/More_Kids_Facing_High_Blood_Pressure_Washington_DC.html)
5. "Doctors Focus on Kids' Blood Pressure." Wall Street Journal. June 29, 2010.
6. "High Blood Pressure in Children." WOLB 1010 AM. Urban Health Radio Program. Breaking it Down: Our Health Our Way. January 26, 2012
7. "Johns Hopkins Expert Sees More Hypertension in Kids." USA Washington. September 17, 2012. <http://www.wusa9.com/news/article/221855/28/Johns-Hopkins-Expert-Sees-More-Hypertension-In-Kids>