

Diagnosis and Medication Treatment of Pediatric Hypertension: A Retrospective Cohort Study

David C. Kaelber, MD, PhD, MPH,^{a,b,c} Weiwei Liu, MS,^{a,d} Michelle Ross, PhD,^{a,e} A. Russell Localio, PhD,^{a,e} Janeen B. Leon, MS, RDN, LD,^{a,c} Wilson D. Pace, MD,^{a,f} Richard C. Wasserman, MD, MPH,^{a,d,g} Alexander G. Fiks, MD, MSCE,^{a,d,h,i,j,k} for the Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER²) Consortium

abstract

BACKGROUND AND OBJECTIVES: Pediatric hypertension predisposes children to adult hypertension and early markers of cardiovascular disease. No large-scale studies have examined diagnosis and initial medication management of pediatric hypertension and prehypertension. The objective of this study was to evaluate diagnosis and initial medication management of pediatric hypertension and prehypertension in primary care.

METHODS: Retrospective cohort study aggregating electronic health record data on >1.2 million pediatric patients from 196 ambulatory clinics across 27 states. Demographic, diagnosis, blood pressure (BP), height, weight, and medication prescription data extracted. Main outcome measures include proportion of pediatric patients with ≥ 3 visits with abnormal BPs, documented hypertension and prehypertension diagnoses, and prescribed antihypertensive medications. Marginal standardization via logistic regression produced adjusted diagnosis rates.

RESULTS: Three hundred ninety-eight thousand seventy-nine patients, ages 3 to 18, had ≥ 3 visits with BP measurements (48.9% girls, 58.6% <10 years old). Of these, 3.3% met criteria for hypertension and 10.1% for prehypertension. Among practices with ≥ 50 eligible patients, 2813 of 12 138 patients with hypertension (23.2%; 95% confidence interval, 18.2%–28.2%) and 3990 of 38 874 prehypertensive patients (10.2%; 95% confidence interval, 8.2%–12.2%) were diagnosed. Age, weight, height, sex, and number and magnitude of abnormal BPs were associated with diagnosis rates. Of 2813 diagnosed, persistently hypertensive patients, 158 (5.6%) were prescribed antihypertensive medication within 12 months of diagnosis (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [35%], diuretics [22%], calcium channel blockers [17%], and β -blockers [10%]).

CONCLUSIONS: Hypertension and prehypertension were infrequently diagnosed among pediatric patients. Guidelines for diagnosis and initial medication management of abnormal BP in pediatric patients are not routinely followed.



^aComparative Effectiveness Research Through Collaborative Electronic Reporting (CER²) Consortium Research Team, Elk Grove Village; Illinois; Departments of ^bInternal Medicine, Pediatrics, Epidemiology, and Biostatistics, Case Western Reserve University, Cleveland Ohio; ^cCenter for Clinical Informatics Research and Education, The MetroHealth System, Cleveland, Ohio; ^dPediatric Research in Office Settings, American Academy of Pediatrics, Elk Grove Village, Illinois; ^eDepartment of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; ^fAmerican Academy of Family Physicians National Research Network, Leawood, Kansas; ^gDepartment of Pediatrics, University of Vermont College of Medicine, Burlington, Vermont; and ^hThe Pediatric Research Consortium, ⁱDepartment of Biomedical and Health Informatics, ^jCenter for Pediatric Clinical Effectiveness, and ^kPolicyLab, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

WHAT'S KNOWN ON THIS SUBJECT: Pediatric hypertension or prehypertension is known to be underdiagnosed from small studies. No studies show whether guideline-based medication treatment is initiated for pediatric patients with hypertension or how antihypertensive medications are used among these patients.

WHAT THIS STUDY ADDS: This study confirms widespread underdiagnosis of pediatric hypertension and prehypertension among 400 000 pediatric patients seen in primary care settings across the United States. For the first time ever we report on antihypertensive medication initiation and use in hypertensive patients.

To cite: Kaelber DC, Liu W, Ross M, et al. Diagnosis and Medication Treatment of Pediatric Hypertension: A Retrospective Cohort Study. *Pediatrics*. 2016; 138(6):e20162195

Pediatric hypertension has an estimated prevalence of 2% to 5% among children, is 1 of the 10 most common chronic diseases in childhood,¹⁻⁵ predisposes children to adult hypertension, and is associated with early markers of cardiovascular disease.⁶⁻¹² Given the estimated several million children and adolescents with abnormal blood pressure (BP) throughout the United States and potential long-term health risks,¹³ timely recognition of pediatric hypertension and treatment, with safe and effective medications, is needed to reduce long-term morbidity and mortality.^{12,14,15} In previous research at a single institution among almost 15 000 patients, clinicians failed to recognize 76% of cases of pediatric hypertension, suggesting the possibility of 1.5 million undiagnosed cases in the United States.¹⁶

Lack of diagnosis prevents the initiation of guideline-based treatments, including lifestyle modification and medication.¹⁴ Antihypertensive medication treatment is specifically recommended for children and adolescents with symptomatic stage 1 hypertension or those who have persistently abnormal BP after 3 to 6 months without pharmacological intervention, and for all children and adolescents with stage 2 hypertension.¹⁴ This study seeks to determine the extent to which national guidelines regarding the diagnosis and initial pharmacological management of pediatric hypertension are being followed in a large number of diverse primary care practices caring for children and adolescents.

METHODS

Study Design and Setting

The participating clinicians, sites, and patients in this retrospective cohort study were part of the Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER²) Consortium, coordinated

by the American Academic of Pediatrics.¹⁷ The network consists of 7 health care organizations, including 196 pediatric primary care sites across 27 states, representing >2000 pediatric primary care clinicians (pediatricians, family physicians, internist-pediatricians, physician assistants, and pediatric and family medicine nurse practitioners) and >1.2 million children. To participate, study sites had to be using an electronic health record (EHR) for the period in which they submitted data. Organizations and sites used different EHRs. We did not investigate the details of EHR tools and functions or other strategies that might have been in place to aid in the recognition and/or management of pediatric hypertension or prehypertension, although we know that some EHR tools and functions were in place at certain sites in the latter part of the 15-year study period.

Patients

This study included children and adolescents between 3 and 18 years of age. Included subjects were primary care patients with ≥ 3 visits, each with BP and height measurements, between 1999 and 2014. Age criteria were selected according to the National Heart, Lung, and Blood Institute's National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents fourth report on the diagnosis, evaluation, and treatment of high BP in children and adolescents ("the fourth report") recommendations for routine BP screening.¹⁴ The average time period over which the ≥ 3 visits occurred was 62 months (range 0.3–173 months).

Data Collection

Data from the study sites' EHRs were extracted and standardized according to the Observational Medical Outcomes Partnership Common Data Model Version 4.0.^{17,18} Data elements used included vital signs (BP,

height, and weight), visit diagnoses (International Classification of Diseases, Ninth Revision [ICD-9] codes), and prescriptions recorded in the EHRs, as well as race and ethnicity, insurance, age, and sex. We identified and excluded outlying height and weight measurements by using a validated algorithm based on exponentially weighted moving averages of growth measurements.¹⁹ Within a given site, EHR data were included only if BP, height, diagnosis codes, and prescriptions all were captured in a given year. If any of these were not recorded, then all data for that practice for that year were excluded. Less than 10% of all observations were excluded based on outlier and incomplete data criteria. Race or ethnicity was available on only 74.1% of patients and insurance data on 69.8% of patients, because these data were not routinely captured in some practice sites. Standard clinical BP measurement protocols were in place at each site.

Antihypertensive medication prescriptions were classified as β -blockers, diuretics, calcium channel blockers, renin-angiotensin-aldosterone system (RAAS) blocking agents, and other. "Other" antihypertensive medications included peripheral α -antagonist, vasodilators, and α -agonists. Combination drugs were counted toward each of their contributing drug classes. Although prescription data came from primary care provider practices' EHRs, the use of medication reconciliation processes in primary care sites should include entering medications prescribed by other providers involved in the care of the patient (eg, specialists), if they were not already part of the primary care practices' EHRs.

Defining Hypertension and Prehypertension

BMI z scores and percentiles were calculated according to Centers for

Disease Control and Prevention growth chart algorithms.²⁰ Age, sex, and height-adjusted systolic and diastolic BP percentiles were calculated based on published formulas.¹⁴ Prehypertension was defined as ≥ 3 systolic and/or diastolic BP measurements ≥ 90 th and < 95 th percentiles for sex, age, and height percentile or $> 120/80$ mm Hg.¹⁴ Stage 1 hypertension was defined as ≥ 3 systolic and/or diastolic BP measurements ≥ 95 th percentile and < 99 th percentile $+ 5$ mm Hg.¹⁴ Stage 2 hypertension was defined as systolic and/or diastolic BP measurements ≥ 99 th percentile $+ 5$ mm Hg.¹⁴ In the rare circumstance that a patient had ≥ 3 systolic and/or diastolic BP measures in > 1 abnormal BP category, they were counted in the most severe category. Diagnosis of prehypertension or hypertension was defined as an abnormal BP-related diagnosis listed on or after the date of the first abnormal systolic and/or diastolic BP. ICD-9 codes for recognized prehypertension or hypertension included elevated BP without hypertension (code 796.2); hypertension (code 401.xx); hypertension, not otherwise specified (code 401.9); hypertension, benign (code 401.1); and hypertension (code 997.91) or heart disease due to hypertension, not otherwise specified (code 402.9).

Statistical Analysis

Confidence intervals (CIs) for overall rates accounted for the clustered sampling (patients within practice sites) and reflect the variability of those rates across sites. Standardized proportions (percentages) of patients with hypertension and prehypertension diagnoses were estimated via logistic regression, with hypertension or prehypertension as the outcome.²¹ Covariates for standardization included sex, age (3–9, 10–14, and 15–18 years), weight (normal, overweight, and obese by BMI percentiles), height (designated as “not tall” and “tall,”

because patients who resemble adults in stature may be more likely to have their hypertension or prehypertension recognized), sex (male or female), number of abnormal BP readings beyond the 3 needed for diagnosis, and number of stage 2 BP readings, all of which were specified a priori. Because we hypothesized that patients who resembled adults in stature may be more likely to have their hypertension or prehypertension recognized, “not tall” was defined as height less than the median heights for 18-year-old boys and girls in the Centers for Disease Control and Prevention Growth Chart,²⁰ and “tall” was greater than or equal to these heights. Data on patient race or ethnicity and health insurance were commonly missing, and because we could not conduct formal imputation of missing data because missingness varied by site, we performed no analyses that involved race and ethnicity or health insurance.

To complete multivariable analysis of associations of patient-level factors and diagnosis while controlling for possible confounding effects of site, sparse data made the elimination of small sites necessary.^{22–24} Therefore, we restricted analyses to practice sites with ≥ 50 hypertensive or prehypertensive children. To evaluate the extent of variation in the treatment of hypertension across sites, we fit 2 models that included age (categorized) as a covariate and practice site as a random effect, by using 2 approaches: adaptive quadrature (16 integration points), as implemented in Stata version 14 (Stata Corp, College Station, TX),²⁵ and integrated nested Laplace approximations²⁶ as implemented in R version 3.1.2 (The R Project for Statistical Computing, Vienna, Austria).²⁷

The Institution Review Board (IRB) at the American Academy of Pediatrics approved this study and the IRB at the Children’s Hospital

of Philadelphia determined that this study was not human subjects research. Additional local IRBs also reviewed and approved this study.

RESULTS

From the ≤ 15 -year study period at some sites and from a total population of > 1.2 million pediatric patients, 398 079 patients were between 3 and 18 years of age and had ≥ 3 visits with BPs and heights measured over 3 032 430 visits. From this eligible population, 13 080 children (3.3%) met criteria for hypertension and 40 076 (10.1%) for prehypertension. After smaller practice sites were dropped to allow multivariable modeling, the sample included 12 138 children in 44 sites with hypertension and 38 874 children in 77 sites with prehypertension (Table 1, Fig 1).

Hypertension Underdiagnosis Analysis

Among the 12 138 children with hypertension, 2813 (23.2%; 95% CI, 18.2%–28.2%) had an EHR diagnosis of hypertension or abnormal BP. Of the 4996 children with stage 2 hypertension, 1612 (32.4%; 95% CI, 26.6%–38.3%) had a diagnosis. Children who were older, heavier, tall, or male, who had ≥ 1 BP measurement in the stage 2 BP range, or who had additional readings beyond the 3 needed for diagnosis were more likely to be diagnosed with hypertension (Table 2).

Prehypertension Underdiagnosis Analysis

Among the 38 874 children with prehypertension, 3990 (10.3%; 95% CI, 8.2%–12.2%) had an EHR diagnosis of hypertension or abnormal BP. Children who were older, heavier, tall, or male, who had ≥ 1 BP in the stage 2 BP range, or who had additional readings beyond the 3 needed for diagnosis were more likely to be diagnosed with prehypertension (Table 3).

TABLE 1 Characteristics of HTN and preHTN Substudy Populations

	Study Population, N = 398 079	HTN Substudy Population			preHTN Substudy Population	
		HTN, N = 12 138	HTN With Diagnosis, N = 2813	Anti-HTN Prescription, N = 158	preHTN, N = 38 874	preHTN With Diagnosis, N = 3990
Average age, y (SD)	9.4 (4.0)	9.1 (3.8)	10.3 (3.9)	11.3 (3.7)	10.8 (4.1)	11.6 (3.9)
Average BMI percentile (SD)	63.8 (28.9)	76.3 (27.2)	84.1 (23.7)	82.1 (23.9)	73.6 (26.9)	81.9 (23.7)
Female, %	48.9	52.6	46.1	40.5	40.1	31.0
Male, %	51.1	47.4	53.9	59.5	59.9	69.0
Normal, % ^a	68.1	45.5	30.4	36.7	52.0	35.7
Overweight, %	15.8	16.8	15.5	16.5	18.6	18.0
Obese, %	16.1	37.7	54.0	46.8	29.4	46.3
Caucasian, %	42.2	43.3	32.5	27.2	43.6	33.4
African American, %	25.8	33.1	42.6	39.2	31.1	40.8
Other, %	6.3	6.7	4.9	4.4	6.4	4.1
American Indian or Alaskan, %	0.3	0.2	0.1	0.0	0.3	0.3
Asian or Pacific Islander, %	1.5	1.6	0.8	0.6	1.4	0.7
Mixed racial group, %	0.6	0.5	0.7	0.6	0.5	0.8
Missing race, %	23.3	14.6	18.4	27.9	16.9	20.0
Hispanic or Latino, %	7.3	8.2	9.0	12.7	6.9	8.5
Not Hispanic or Latino, %	54.0	64.9	60.2	54.4	58.5	56.0
Missing ethnicity, %	38.7	26.9	30.8	32.9	34.6	35.5
Public insurance reported, % ^b	32.4	44.3	54.4	52.5	36.1	45.5
Public insurance not reported, %	37.4	40.0	30.1	26.6	43.7	35.2
Missing insurance, %	30.2	15.7	15.5	20.9	20.2	19.4

HTN, hypertension; preHTN, prehypertension; SD, standard deviation.

^a Recorded at third BP measurement.

^b Public insurance reported refers to those who ever indicated public insurance in the data, versus those who never indicated public insurance. Those who had no insurance data collected are not listed.

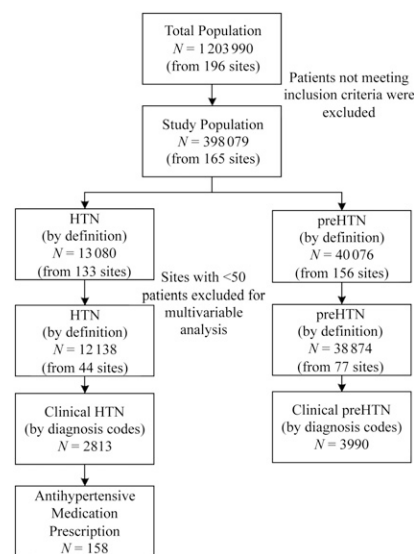


FIGURE 1 Study population and subsample populations. HTN, hypertension; preHTN, prehypertension.

Antihypertensive Medication Analysis Among Hypertensive Patients

Among children with diagnosed hypertension and who continued to have high blood pressure readings ($n = 2813$), 158 (5.6%; 95% CI, 4.5%–6.7%) were treated with

antihypertensive medicine within 12 months of diagnosis. Stage 2 hypertension (5.8% vs 3.2%), but not age, sex, or BMI percentile, increased the chances of an antihypertensive medication prescription. The most common antihypertensive medication categories were RAAS inhibitors (angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers) (35% of children), followed by diuretics (22%), calcium channel blockers (17%), and β -blockers (10%) (Fig 2). The average age of the first prescription was 13.7 years. Variation across sites in medication initiation achieved statistical significance ($P = .029$); however only 1 site had much higher treatment rate (15% [13/85]) than others.

DISCUSSION

This study documents the underdiagnosis of pediatric hypertension and the medication undertreatment of pediatric hypertension in a sample of pediatric primary care practice

sites caring for almost 2% of the pediatric population across the United States. The 3.3% prevalence of hypertension is consistent with pediatric hypertension studies measuring multiple blood pressures over multiple visits, documenting prevalence ranging from 2% to 5%.^{1–5} The low diagnosis rate (24%) is consistent with a smaller study from 1 health system.¹⁶ Some underdiagnosis may be explained by the fact that identifying hypertensive children is complicated by the variation in normal BP ranges across sex, height percentile, and age, with hundreds of abnormal BP threshold values for pediatric patients.¹⁴ When abnormal BP identification becomes a core functionality in pediatric EHRs,²⁸ recognition of abnormal BPs and hypertension or prehypertension may improve.²⁹

Several factors were associated with higher rates of hypertension or prehypertension diagnosis. Children who were overweight or obese, male, or tall or who had a greater number of or higher abnormal BPs were

TABLE 2 Standardized Percentages of Children With Diagnosis of Hypertension

Demographic Factor, <i>n</i> = 12 138	Standardized Percentage (95% CI)	Overall Within-Factor Difference, <i>P</i>
Age category, y		<.001
3–9	20.3 (19.4–21.1)	
10–14	29.6 (28.2–31.0)	
15–18	27.2 (23.4–31.1)	
Weight, %		<.001
Normal	18.2 (17.2–19.1)	
Overweight	23.1 (21.4–24.8)	
Obese	28.8 (27.6–30.0)	
Height, %		<.001
Not tall	23.0 (22.3–23.7)	
Tall	31.7 (27.2–36.1)	
Sex, %		<.001
Female	20.7 (19.8–21.6)	
Male	26.2 (25.2–27.2)	
Stage 2 range BP readings, %		<.001
No	19.3 (18.4–20.2)	
Yes	27.9 (26.8–29.1)	
No. of abnormal BP readings >3, %		<.001
No extra readings	18.0 (17.2–18.9)	
1 extra reading	24.9 (23.5–26.4)	
2 extra readings	30.9 (28.5–26.4)	
≥3 extra readings	37.1 (34.7–39.5)	

All estimates are standardized (adjusted). Models using logistic regression and predictive margins for standardization included age, weight, height, sex, presence of BP readings in stage 2 range, and number of abnormal BP readings >3. All models also include clinical practice site as a covariate because variation across sites in the rate of diagnosis and the characteristics of patients induces confounding by practice. Estimates therefore can be interpreted as the adjusted percentage of children who received a diagnosis of hypertension within practice sites (and averaged across practice sites), controlling for their individual differences.

TABLE 3 Standardized Percentages of Children With Diagnosis of Prehypertension

Demographic Factor, <i>n</i> = 38 874	Standardized Percentage (95% CI)	Overall Within-Factor Difference, <i>P</i>
Age category, y		<.001
3–9	9.3 (8.8–9.7)	
10–14	11.0 (10.6–11.5)	
15–18	11.7 (10.6–12.9)	
Weight, %		<.001
Normal	7.7 (7.4–8.1)	
Overweight	9.5 (8.9–10.2)	
Obese	14.7 (14.1–15.3)	
Height, %		.011
Not tall	10.2 (9.9–10.5)	
Tall	11.7 (10.6–12.8)	
Sex, %		<.001
Female	8.2 (7.7–8.6)	
Male	11.7 (11.3–12.1)	
Stage 2 range BP readings, %		<0.001
No	9.4 (9.1–9.7)	
Yes	19.4 (18.1–20.6)	
No. of abnormal BP readings >3, %		<.001
No extra readings	8.3 (7.9–8.7)	
1 extra reading	11.4 (10.8–12.0)	
2 extra readings	13.7 (12.7–14.8)	
≥3 extra readings	18.0 (16.6–19.4)	

All estimates are standardized (adjusted). Models using logistic regression and predictive margins for standardization included age, weight, height, sex, presence of BP readings in stage 2 range, and number of abnormal BP readings >3. All models also include clinical practice site as a covariate because variation across sites in the rate of diagnosis and the characteristics of patients induces confounding by practice. Estimates therefore can be interpreted as the adjusted percentage of children who received a diagnosis of prehypertension within practice sites (and averaged across practice sites), controlling for their individual differences.

more likely to be diagnosed with hypertension and prehypertension. The more abnormal the value and the more frequent the abnormal value, the more likely pediatric providers

were to recognize the disease. In addition, if a child is overweight or obese, the pediatric provider may be more likely to look for and recognize existing hypertension

or prehypertension, which could be ameliorated by weight loss. The difference in rates of diagnosis by patient sex could be related to the fact that absolute prehypertensive

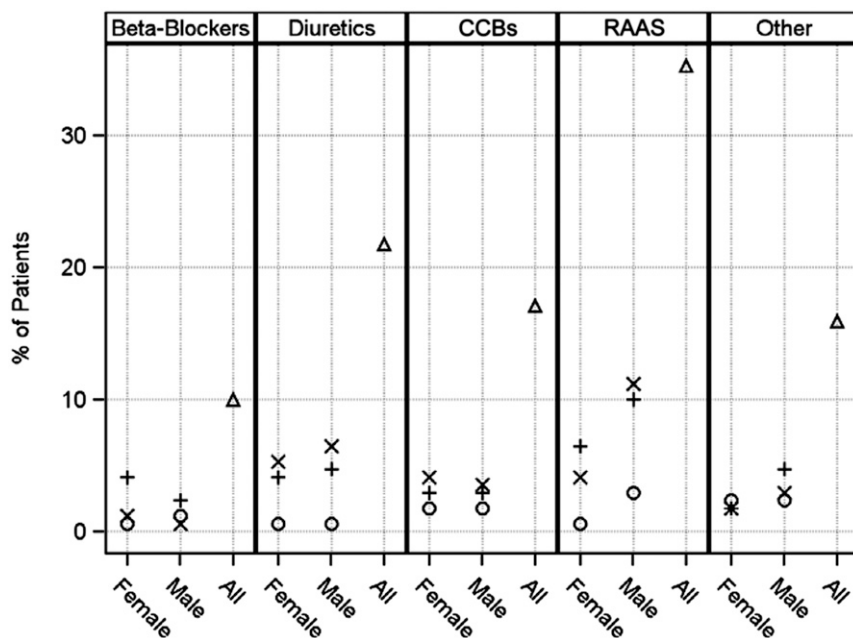


FIGURE 2 Overall and sex and age distribution of antihypertensive medication initially prescribed in study population with diagnosed hypertension within 12 months. *N* = 170 drugs among 158 patients ages 3–9 years (○○○○), 10–14 years (+), and 15–18 years (x), and over all ages and sexes (Δ).CCB, calcium channel blocker.

and hypertensive BP threshold values are higher in boys than girls and higher BPs are more likely to be recognized or the fact that hypertension is known to occur earlier in men than in women and has higher morbidity and mortality at younger ages.³⁰ Tall children are more likely to have higher BP, which similarly may lead to increased diagnosis.

Because of the large number of children in our cohort and because we followed patients over time, we were able to assess the initiation of antihypertension medication treatment. Because of the low rates of disease, large samples are essential to study factors associated with diagnosis and treatment. Unlike hypertension guidelines for adults that recommend the initiation of particular antihypertensive medications for specific clinical indications, pediatric hypertension guidelines generally do not specify any antihypertensive medication initiation hierarchy.^{14,31}

Current guidelines state that children with stage 2 hypertension or

symptomatic stage 1 hypertension should be started on antihypertensive medication at the time of diagnosis, and children with asymptomatic stage 1 hypertension should be started on antihypertensive medication if their hypertension persists after 3 to 6 months without pharmacological intervention.¹⁴ Therefore, all children with hypertension should be prescribed antihypertensive medications at diagnosis or at least within 6 months of diagnosis with persistently abnormal BP. In this study, children were given 12 months in which to initiate medication. Patients with stage 2 hypertension were more likely to be prescribed antihypertensive medications than those with stage 1, although the 2% absolute increase in prescribing was small. The finding that only 1 in 20 children with diagnosed, persistent hypertension for ≥ 1 year were prescribed antihypertensive medication indicates poor compliance with current pediatric hypertension guidelines recommending pharmacological treatment if no

improvement occurs at least within 3 to 6 months.¹⁴

RAAS blockers were the most common antihypertensive medications prescribed. This finding was surprising because these agents are teratogenic and were prescribed in a substantial number of adolescent girls. Diuretics, recommended for first-line treatment in adults,³² were the second most commonly initiated drug class, consistent with their low side effect profile. Calcium channel blockers were the third most commonly prescribed drug class, analogous to their secondary or tertiary recommended use in adults.³² β -blockers were the fourth most commonly prescribed drug class, consistent with their relative contraindication in overweight and obese children, where exercise would be an additional treatment management strategy. In addition, 16% of the children were prescribed “other” antihypertensives, including peripheral α -antagonists, vasodilators, and α -agonists.

This study demonstrates both the limitations and the power of pooling EHR data from multiple, disparate health care systems and clinicians using different EHRs to create “big data” for research. Particularly in pediatrics, EHRs, as demonstrated here, show great potential to investigate questions in uncommon conditions or conditions with infrequent treatment. More than 1.2 million original patients were needed initially to address the ultimate question of which antihypertensive medications were commonly prescribed in less than 175 patients. However, pooling EHR data across systems with different EHRs is challenging because of a lack of data standards and data collection inconsistencies.^{17,33,34} For example, race or ethnicity and insurance information existed for only $\sim 70\%$ of our final eligible population, and several sites did not collect or preserve data on these important

factors. Although race or ethnicity and insurance were not included in our analysis, imputation methods that use direct patient identifiers (name and address) are available for critical race and ethnicity analyses.³⁵ We lacked name and address in the limited data set used. As EHR incentives to promote data collection and adoption continue to expand, these limitations should decrease.^{33,36,37} The usefulness of pooled EHR data for research, especially in smaller subpopulations, should increase with broader EHR use, growing ease of EHR data extraction, and the modest additional cost to support EHR-based observational research.

This study had several limitations. It relied on entered ICD-9 codes as the gold standard for the positive identification by a provider of a child or adolescent with abnormal BPs. However, given that manual chart review of a subset of EHR records showed <10% with only text notations of an abnormal BP, this limitation is unlikely to have substantially influenced our overall findings. Also, we relied on standard clinical (nonresearch), in-office BP measurements recorded in the EHR and included all reasons (preventive care and nonpreventive care) for visits to primary care pediatric providers. These limitations have the potential to inappropriately identify hypertension (eg, abnormal BPs due to inaccurate measures, pain, or white-coat hypertension). However, the overall prevalence of pediatric hypertension in this study (3.3%) is consistent with other studies specifically designed to measure the prevalence of chronic hypertension.¹⁻⁵ We relied on the August 2004 definitions of hypertension and prehypertension, although some visits and BPs occurred before then. However, only 11% of BPs in the hypertension or prehypertension range, and 8.4% of all available BPs, were from before August 2004. And if a pediatric provider identified a post-August 2004 abnormal BP, the normal

process should have been to evaluate or reevaluate pre-August 2004 BPs in the EHR against post-August 2004 criteria. Therefore, we do not expect pre-August 2004 visits or BPs to have had any significant impact on our findings.

Additionally, we relied on EHRs to identify prescribing of antihypertensive medications. All sites were using computerized physician order entry in their EHRs for the years included for analysis. Our results might be biased toward the underdiagnosis of hypertension and its undertreatment if children treated by specialists did not have their medications abstracted in the EHR or did not share the same EHRs as the pediatric primary care clinicians. However, the standard of care is that pediatric primary care clinicians should maintain a complete diagnosis and medication record of all diagnoses and medications that a patient takes, not just the ones they are actively managing. The fact that at least some of the EHRs in our sites provided decision support for identification and management of pediatric prehypertension or hypertension during the study period means that this study may actually overreport the diagnosis of hypertension or prehypertension compared with primary care pediatric provider sites without advanced EHRs. Of the >1.2 million patients seen at the primary care pediatric provider sites in the CER² network, >50% of patients were excluded because they did not have ≥ 3 visits during the study period. We lack data on the diagnosis and medication treatment of pediatric hypertension in these patients. Missing data on race or ethnicity and insurance precluded formal imputation and reliable analysis of these secondary factors. Finally, BP measurements followed routine clinical procedures, as opposed to more rigorous measurement methods. It is impossible to know how well standard clinical procedures were followed, what percentage of the BPs

obtained from EHRs were repeated, or the method used to obtain the BP (automated or manual). However, the EHR BPs obtained were the ones in the legal medical record. In addition, the fact that the overall prevalence of hypertension is in the range identified through more rigorous methods is reassuring.

CONCLUSIONS

Hypertension and prehypertension, well-defined, prevalent, and generally asymptomatic conditions in children and adolescents, are often undiagnosed and untreated with medications. Because appropriate diagnosis and guideline-based medication management are important for effective treatment, intervention is needed to help pediatric primary care clinicians recognize and treat hypertension and prehypertension. The description of antihypertensive medication treatment could not have been accomplished without the large initial cohort, demonstrating the power of pooling EHR data across practice sites.

ACKNOWLEDGMENTS

CER² Consortium authors include Robert W. Grundmeier, MD, and Jenny Steffes. We acknowledge and thank Laura Shone, PhD and Banita McCarn for their help with this research.

ABBREVIATIONS

BP: blood pressure
CER²: Comparative Effectiveness Research Through Collaborative Electronic Reporting
CI: confidence interval
EHR: electronic health record
ICD-9: *International Classification of Diseases, Ninth Revision*
IRB: Institutional Review Board
RAAS: renin-angiotensin-aldosterone system

Dr Kaelber conceptualized and designed the study, assisted in obtaining data, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Liu helped design the study, carried out data analyses, helped draft the initial manuscript, and reviewed and revised the manuscript; Drs Ross and Localio helped design the study, helped carry out data analyses, and reviewed and revised the manuscript; Ms Leon helped design the study, assisted in obtaining data, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Pace helped design the study, assisted in obtaining data, and reviewed and revised the manuscript; Dr Wasserman helped conceptualize and design the study, assisted in obtaining data, and reviewed and revised the manuscript; Dr Fiks helped conceptualize and design the study, assisted in obtaining data, drafted the initial manuscript, and reviewed and revised the manuscript; the Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER²) Consortium reviewed the study design and coordinated and supervised data collection at each CER² site; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-2195

Accepted for publication Sep 22, 2016

Address correspondence to David C. Kaelber, MD, PhD, MPH, 3158 Kingsley Rd, Shaker Heights, OH 44122. E-mail: david.kaelber@case.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Health Resources and Services Administration of the US Department of Health and Human Services under grants R40MC24943, "Primary Care Drug Therapeutics CER in a Pediatric EHR Network"; UB5MC20286, "Pediatric Primary Care EHR Network for CER"; and UA6MC15585, "National Research Network to Improve Child Health Care." Funding was also provided by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development under the Best Pharmaceuticals for Children Act. This information or content and conclusions are those of the authors and should not be construed as the official position or policy of, nor should any endorsements be inferred by, the Health Resources and Services Administration, the US Department of Health and Human Services, the National Institute of Child Health and Human Development, or the US government. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2016-2857.

REFERENCES

1. Moore WE, Stephens A, Wilson T, Wilson W, Eichner JE. Body mass index and blood pressure screening in a rural public school system: the Healthy Kids Project. *Prev Chronic Dis.* 2006;3(4):A114
2. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics.* 2004;113(3 pt 1):475–482
3. Ford ES, Mokdad AH, Ajani UA. Trends in risk factors for cardiovascular disease among children and adolescents in the United States. *Pediatrics.* 2004;114(6):1534–1544
4. Koebnick C, Black MH, Wu J, et al. The prevalence of primary pediatric prehypertension and hypertension in a real-world managed care system. *J Clin Hypertens (Greenwich).* 2013;15(11):784–792
5. Lo JC, Sinaiko A, Chandra M, et al. Prehypertension and hypertension in community-based pediatric practice. *Pediatrics.* 2013;131(2). Available at: www.pediatrics.org/cgi/content/full/131/2/e415
6. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med.* 1998;338(23):1650–1656
7. Arnett DK, Glasser SP, McVeigh G, et al. Blood pressure and arterial compliance in young adults: the Minnesota Children's Blood Pressure Study. *Am J Hypertens.* 2001;14(3):200–205
8. Burke GL, Arcilla RA, Culpepper WS, Webber LS, Chiang YK, Berenson GS. Blood pressure and echocardiographic measures in children: the Bogalusa Heart Study. *Circulation.* 1987;75(1):106–114
9. Johnson MC, Bergersen LJ, Beck A, Dick G, Cole BR. Diastolic function and tachycardia in hypertensive children. *Am J Hypertens.* 1999;12(10 pt 1):1009–1014
10. Knoflach M, Kiechl S, Kind M, et al. Cardiovascular risk factors and atherosclerosis in young males: ARMY study (Atherosclerosis Risk-Factors in Male Youngsters). *Circulation.* 2003;108(9):1064–1069
11. Hanevold C, Waller J, Daniels S, Portman R, Sorof J; International Pediatric Hypertension Association. The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. *Pediatrics.* 2004;113(2):328–333
12. Theodore RF, Broadbent J, Nagin D, et al. Childhood to early-midlife systolic blood pressure trajectories: early-life predictors, effect modifiers, and adult cardiovascular outcomes. *Hypertension.* 2015;66(6):1108–1115
13. US Preventive Services Task Force. Final Update Summary: Blood Pressure in Children and Adolescents (Hypertension): Screening. 2013. Available at: <https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/blood-pressure-in-children-and-adolescents-hypertension-screening>. Accessed October 20, 2016
14. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 suppl 4th report):555–576
15. Leiba A, Twig G, Levine H, et al. Hypertension in late adolescence

- and cardiovascular mortality in midlife: a cohort study of 2.3 million 16- to 19-year-old examinees. *Pediatr Nephrol*. 2016;31(3):485–492
16. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA*. 2007;298(8):874–879
 17. Fiks AG, Grundmeier RW, Steffes J, et al; Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER2) Consortium. Comparative effectiveness research through a collaborative electronic reporting consortium. *Pediatrics*. 2015;136(1). Available at: www.pediatrics.org/cgi/content/full/136/1/e215
 18. Observational Medical Outcomes Partnership. Common Data Model. July 2012. Available at: <http://omop.org/CDM>. Accessed November 12, 2015
 19. Daymont C, Fiks AG, Grundmeier RW. An automated method for cleaning growth measures in large datasets. Poster presentation at the 2014 Pediatric Academic Societies Annual Meeting; May 3-6, 2014; Vancouver, BC
 20. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11*. 2002; (246):1–190
 21. Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. *Int J Epidemiol*. 2014;43(3):962–970
 22. Begg MD, Parides MK. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Stat Med*. 2003;22(16):2591–2602
 23. Berlin JA, Kimmel SE, Ten Have TR, Sammel MD. An empirical comparison of several clustered data approaches under confounding due to cluster effects in the analysis of complications of coronary angioplasty. *Biometrics*. 1999;55(2):470–476
 24. Neuhaus JM, Kalbfleisch JD. Between- and within-cluster covariate effects in the analysis of clustered data. *Biometrics*. 1998;54(2):638–645
 25. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP; 2015
 26. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations (with discussion). *J R Stat Soc B*. 2009;71(2):319–392
 27. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013
 28. Dufendach KR, Eichenberger JA, McPheeters ML, et al. *Core Functionality in Pediatric Electronic Health Records*. Rockville, MD: Agency for Healthcare Research and Quality; 2015
 29. Bar-Shain DS, Palcisco K, Greco PJ, Kaelber DC. Using advanced electronic clinical decision support to improve the quality and recognition of abnormal blood pressure values in children. Pediatric Academic Societies Meeting; May 4-7, 2013; Washington, DC
 30. Doumas M, Papademetriou V, Faselis C, Kokkinos P. Gender differences in hypertension: myths and reality. *Curr Hypertens Rep*. 2013;15(4):321–330
 31. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560–2572
 32. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520
 33. Blumenthal D, Tavenner M. The “meaningful use” regulation for electronic health records. *N Engl J Med*. 2010;363(6):501–504
 34. Sutherland SM, Kaelber DC, Downing NL, Goel W, Longhurst CA. Electronic health record-enabled research in children: using the electronic health record for clinical discovery. *Pediatr Clin North Am*. 2016;63(2):251–268
 35. Grundmeier RW, Song L, Ramos MJ, et al. Imputing missing race/ethnicity in pediatric electronic health records: reducing bias with use of US census location and surname data. *Health Serv Res*. 2015;50(4):946–960
 36. Adler-Milstein J, DesRoches CM, Furukawa MF, et al. More than half of US hospitals have at least a basic EHR, but stage 2 criteria remain challenging for most. *Health Aff (Millwood)*. 2014;33(9):1664–1671
 37. DesRoches C. Progress and challenges in electronic health record adoption: findings from a national survey of physicians. *Ann Intern Med*. 2015;162(5):396

Diagnosis and Medication Treatment of Pediatric Hypertension: A Retrospective Cohort Study

David C. Kaelber, Weiwei Liu, Michelle Ross, A. Russell Localio, Janeen B. Leon, Wilson D. Pace, Richard C. Wasserman, Alexander G. Fiks and for the Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER 2) Consortium

Pediatrics 2016;138;

DOI: 10.1542/peds.2016-2195 originally published online November 22, 2016;

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/138/6/e20162195
References	This article cites 30 articles, 8 of which you can access for free at: http://pediatrics.aappublications.org/content/138/6/e20162195#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Health Information Technology http://www.aappublications.org/cgi/collection/health_information_technology_sub Electronic Health Records http://www.aappublications.org/cgi/collection/electronic_health_records_sub Pulmonology http://www.aappublications.org/cgi/collection/pulmonology_sub Hypertension http://www.aappublications.org/cgi/collection/hypertension_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS[®]

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Diagnosis and Medication Treatment of Pediatric Hypertension: A Retrospective Cohort Study

David C. Kaelber, Weiwei Liu, Michelle Ross, A. Russell Localio, Janeen B. Leon, Wilson D. Pace, Richard C. Wasserman, Alexander G. Fiks and for the Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER 2) Consortium

Pediatrics 2016;138;

DOI: 10.1542/peds.2016-2195 originally published online November 22, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/138/6/e20162195>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN[®]

