

# Childhood Risk Factors and Pregnancy-Induced Hypertension: The Bogalusa Heart Study

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## BACKGROUND

Pregnancy-induced hypertension (PIH) causes increased risk of maternal, fetal, and neonatal morbidity and mortality. Identification of risk factors for PIH in early life is central to the development of prevention strategies.

## METHODS

A cohort of 703 women aged 25.5–51.3 years from the Bogalusa Heart Study were included. PIH were defined as self-reported hypertension during pregnancy and a blood pressure level <140/90 mm Hg without antihypertensive medication ( $n = 131$ ) at the subsequent examinations. Body mass index (BMI), systolic and diastolic blood pressure, high- and low-density lipoprotein cholesterol, and triglycerides measured during childhood (4–17 years) were considered. General linear models were used to examine differences in childhood between those who did and those who did not develop PIH. Logistic regression models were used to estimate odds ratios for PIH associated with childhood risk factors.

## RESULTS

Compared to women who did not develop PIH, those who developed PIH had higher BMI (20.2 vs. 19.2 kg/m<sup>2</sup>,  $P = 0.0002$ ) and systolic blood pressure (104.1 vs. 103.3 mm Hg,  $P = 0.008$ ) in childhood. After adjustment for other variables, childhood BMI was the only risk factor associated with PIH, with each standard deviation increase in childhood BMI being associated with an odds ratio of 1.35 (95% confidence interval: 1.08–1.68) for PIH. The odds of PIH increased significantly as childhood BMI increased from the bottom quartile to the top quartile ( $P$  for trend = 0.006).

## CONCLUSIONS

Elevated childhood BMI is a significant risk factor for PIH in adulthood, which underscores the importance of body weight control in childhood for prevention of PIH.

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## INTRODUCTION

Pregnancy-induced hypertension (PIH) refers to a condition in which high blood pressure ( $\geq 140/90$  mm Hg) develops during pregnancy but blood pressure returns to the nonhypertensive range following delivery.<sup>1,2</sup> PIH affects 3–10% of all pregnancies, and leads to increased risk of maternal, fetal, and neonatal morbidity and mortality.<sup>2,3</sup> Women with PIH are at increased risk for developing a wide range of chronic conditions, including cardiovascular disease, later in life.<sup>4–7</sup> Identification of risk factors for PIH is an essential first step in efforts to reduce the burden of illness due to PIH.

Previous studies have shown that adult cardiovascular risk factors, such as obesity, elevated blood pressure, insulin resistance, and triglyceridemia, before pregnancy are associated with the risk of PIH.<sup>2,3,8–11</sup> However, it is not known whether measurements during childhood can predict the risk of subsequent PIH. Such information would be very helpful in understanding the pathogenesis of PIH and efforts to prevent its occurrence.

We used data from the Bogalusa Heart Study (BHS), a long-term, community-based study of natural history of atherosclerosis beginning in childhood,<sup>12</sup> to examine childhood risk factors for adult PIH.

## METHODS

### Study population

The BHS, established in 1973 by Dr Gerald Berenson, is based on a series of long-term studies in a semi-rural community (65% white and 35% black) in Bogalusa, LA to explore the natural history of cardiovascular disease from childhood.<sup>12</sup> Between 1973 and 2010, 9 BHS cross-sectional surveys were conducted in children and adolescents aged 4–17 years, and 10 BHS surveys were conducted in adults aged 18–51 years who had participated in earlier BHS surveys as children. We identified 703 women who had been examined at least once during their childhood (aged 4–17 years), had PIH information based on their response

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to a standardized questionnaire, and were nonhypertensive (blood pressure < 140/90 mm Hg and not taking any anti-hypertensive medications) during their subsequent BHS examinations as adults (aged 25.5–51.3 years). The average follow-up time between their first and last BHS examinations was 28.3 (range: 16.2–36.6) years.

All of the adults in this study provided written informed consent at each examination, and consent of a parent/guardian was obtained for those under 20 years of age. Study protocols were approved by the Institutional Review Board of the Tulane University Health Sciences Center, New Orleans, LA.

### Examinations

All of the BHS surveys followed an almost identical protocol for measurement of risk factors for both children (4–17 years old) and adults (>18 years old).<sup>12</sup> Participants were instructed to fast for 12 hours prior to each visit. Height and weight were measured twice to within 0.1 cm and within 0.1 kg, respectively, and the mean values of these measurements were used to estimate body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters). Replicate sitting blood pressure measurements were obtained on the right arm of each participant using the correct size cuff following at least 5 minutes of quiet rest. Systolic and diastolic blood pressure levels were recorded as the first, fourth (in children), and fifth (in adults) Korotkoff phases using a mercury sphygmomanometer. Blood pressure levels were reported as the mean of six replicate readings taken by two randomly assigned trained staff members.

### Definition of PIH

PIH, the outcome measure, was defined as self-reported hypertension during pregnancy, based on a “Yes” response to the question “Did you have hypertension in any of your previous pregnancies?” in a standardized questionnaire, and an average blood pressure <140/90 mm Hg without treatment for hypertension at the participant’s last available BHS examination (after pregnancy). The requirement of returning to a nonhypertensive level of blood pressure after pregnancy was designed to avoid inclusion of participants with hypertension prior to pregnancy. Those whose blood pressure returned to the nonhypertensive blood pressure range after pregnancy would have been unlikely to be hypertensive before pregnancy. We recognize that the requirement might have led to exclusion of women with PIH who later developed chronic hypertension as PIH women have a much increased risk of developing chronic hypertension.<sup>13</sup> In total, 131 (18.6%) of the 703 women studied met the criteria for PIH. For participants who had been examined more than once, we used data in the last survey; the overall agreement for the responses at different occasions was 95.2%.

### Laboratory analysis

Between 1973 and 1986 serum cholesterol and triglyceride levels were measured using a Technicon AutoAnalyzer II (Technicon Instrument Corp, Tarrytown, NY) according

to the Laboratory Manual of the Lipid Research Clinics Program.<sup>14</sup> Between 1986 and 1996 an Abbott VP instrument (Abbott Laboratories, North Chicago, IL) that employed an enzymatic procedure was used to measure these variables.<sup>15,16</sup> From 1996 to the present the measurements have been made using a Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum high-density lipoprotein cholesterol levels were determined using a combination of heparin–calcium precipitation and agar–agarose gel electrophoresis procedure.<sup>17</sup> Both the chemical and enzymatic measurements met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention (CDC).

### Statistical methods

Risk factor measurements during childhood, including BMI, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and systolic and diastolic blood pressure (SBP and DBP), were used as exposures, and PIH as the outcome. For participants with multiple examinations during childhood, we used the average value of their exposure measurements during childhood to increase statistical power. To compare differences in childhood variables between women with and without PIH, general linear models were used with adjustment for race and (average) childhood age. We used general linear models to examine the differences in risk factor variables after pregnancy, adjusting for race and age. We used logistic regression models to examine the association between PIH and childhood risk factor variables that had been standardized to age- and race-specific *z*-scores and adjusted for race. We also calculated BMI *z*-scores during childhood and overweight was defined as BMI *z*-score above the 85th percentile according to CDC growth charts (<http://www.cdc.gov/growthcharts/>). We performed sensitivity analysis to examine the associations of PIH with risk factor variables measured before (*N* = 490) or after (*N* = 665) the age of 12 years. We also examined the interactions between childhood risk factors and race on PIH risk in logistic regression models. All data analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

### RESULTS

Mean age ( $\pm$ SD, standard deviation) at the participant’s last examination was  $38.0 \pm 4.9$  years, and the average age during childhood was  $12.5 \pm 2.2$  years. In the entire cohort (*n* = 703), black participants tended to have a higher blood pressure as adults and a better lipid profile in childhood compared to their white counterparts (Table 1).

Following adjustment for childhood age and race, BMI (*P* = 0.0002) and SBP (*P* = 0.008) were higher during childhood in those who developed compared to their counterparts who did not develop PIH (Table 2), but there were no differences between the other variables measured in childhood. After further adjustment for childhood BMI, childhood SBP was no longer significantly associated with PIH (*P* = 0.12). In logistic regression analysis, the odds ratio of one BMI standard deviation increase in childhood for PIH

**Table 1.** Characteristics of the cohort (*n* = 703) by race

Variable	Whites ( <i>n</i> = 481)	Blacks ( <i>n</i> = 222)	<i>P</i> <sup>a</sup>
Childhood <sup>b</sup>			
Age (years)	12.6±2.3	12.5±2.0	0.74
BMI (kg/m <sup>2</sup> )	19.1±3.3	20.1±4.1	<0.001
Systolic BP (mm Hg)	103.5±7.7	103.5±7.5	0.86
Diastolic BP (mm Hg)	65.2±6.6	64.6±6.3	0.27
HDL cholesterol (mg/dl)	59.3±15.2	63.5±13.4	<0.001
LDL cholesterol (mg/dl)	90.7±21.7	93.2±22.5	0.16
Triglycerides (mg/dl)	76.6±28.2	62.5±17.1	<0.001
Adulthood <sup>c</sup>			
Age (years)	38.4±4.7	37.0±5.2	<0.001
BMI (kg/m <sup>2</sup> )	28.5±7.1	31.8±8.6	<0.001
Systolic BP (mm Hg)	110.2±11.0	118.4±15.8	<0.001
Diastolic BP (mm Hg)	69.8±8.6	73.4±10.6	<0.001

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

<sup>a</sup>*P* values were adjusted for age and race where appropriate.

<sup>b</sup>Mean values of multiple measurements during childhood are presented.

<sup>c</sup>Measured after pregnancy when the questionnaire was administered.

was 1.35 (95% confidence interval: 1.08–1.68). When the lowest quartile of BMI during childhood was employed as a reference, having a BMI in the second, third, and highest quartile during childhood was associated with an odds ratio of 1.57, 2.08, and 2.30 for PIH, respectively (*P* for trend = 0.006) (Figure 1). When age- and race-specific BMI z-scores were replaced with z-scores calculated according to CDC growth charts, the results essentially remained the same (odds ratio: 1.31; 95% confidence interval: 1.05–1.63; *P* = 0.016).

In sensitivity analysis, odds ratio was 1.16 (95% confidence interval: 0.92–1.48; *P* = 0.21) for BMI before 12 years of age and 1.51 (95% confidence interval: 1.21–1.90; *P* = 0.0003) for BMI between 12 and 17 years of age. We did not find significant interaction effects between childhood risk factors and race on PIH risk (*P* > 0.20 for all risk factor variables considered).

## DISCUSSION

In this community-based cohort, we showed that women who experienced PIH in adult life had higher BMI and SBP during childhood than women who did not. However, the observed association between PIH and childhood SBP was largely driven by childhood BMI because after adjustment for childhood BMI, childhood SBP was no longer associated with PIH. One BMI standard deviation increase during childhood was associated with a 35% (95% confidence interval: 8–68%) higher odds of developing PIH. The association between childhood BMI and subsequent PIH was continuous across the entire range of BMI. Noteworthy is that girls who later developed PIH had one unit higher BMI than girls who did not, a difference equivalent

**Table 2.** Characteristics of the study sample by PIH status

Variable	PIH		<i>P</i> <sup>a</sup>
	No ( <i>n</i> = 572)	Yes ( <i>n</i> = 131)	
Childhood <sup>b</sup>			
Age (years)	12.6±0.1	12.1±0.2	0.007
BMI (kg/m <sup>2</sup> )	19.2±0.1	20.2±0.4	0.0002
Overweight (%)	14.5	24.4	0.006
Systolic BP (mm Hg)	103.3±0.3	104.1±0.7	0.008
Diastolic BP (mm Hg)	65.0±0.3	64.8±0.5	0.19
HDL Cholesterol (mg/dl)	61.0±0.6	59.2±1.1	0.27
LDL Cholesterol (mg/dl)	91.0±0.9	93.5±1.8	0.51
Triglycerides (mg/dl)	71.8±1.1	73.9±2.5	0.25
Adulthood <sup>c</sup>			
Age (years)	38.1±0.2	37.7±0.5	0.48
BMI (kg/m <sup>2</sup> )	28.8±0.3	32.5±0.7	<0.0001
Systolic BP (mm Hg)	112.3±0.6	115.0±0.9	0.03
Diastolic BP (mm Hg)	70.2±0.4	74.0±0.7	<0.0001

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PIH, pregnancy-induced hypertension. Childhood overweight was defined as BMI greater than the 85th percentile according to Centers for Disease Control and Prevention growth charts. Mean ± SE (standard error) is shown.

<sup>a</sup>*P* values were adjusted for age and race where appropriate.

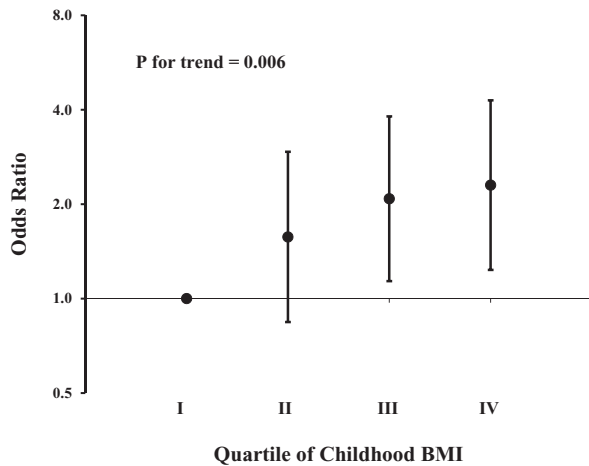
<sup>b</sup>Mean values of multiple measurements during childhood are presented.

<sup>c</sup>Measured after pregnancy when the questionnaire was administered.

to about 5.5 pounds in body weight with average height at age 12 years. Such a difference is clinically significant. Our findings highlight, for the first time to our knowledge, the importance of increased body weight during childhood as a risk factor for the development of PIH in later life.

The underlying mechanisms for the association between childhood BMI and PIH are unclear. It is known that childhood obesity is predictive of adult obesity,<sup>18–22</sup> a known risk factor for PIH<sup>10,23–25</sup>; overweight and obesity before pregnancy are also associated with excessive gestational weight gain, another risk factor for PIH.<sup>26</sup> However, we did not have data on adult risk factor variables before pregnancy, which precluded us from exploring the possibility of adult BMI mediating the association between childhood BMI and PIH. Speculatively, the influence of childhood BMI is likely to be mediated, at least in part, by adult BMI before pregnancy, which should be examined in future studies. Other pathways for the link between childhood BMI and PIH may include obesity-associated elevated blood pressure,<sup>27–30</sup> insulin resistance,<sup>31</sup> inflammation,<sup>32–35</sup> and renal and endothelial dysfunction.<sup>36</sup>

Interestingly, the observed association for BMI measured after puberty was relatively stronger than that before puberty. This is consistent with available evidence that obesity in adolescence is a risk factor for poor pregnancy outcomes.<sup>37</sup> Obesity during adolescence may exacerbate insulin sensitivity decrease and lead to sustained insulin



**Figure 1.** Odds ratios (ORs) for pregnancy-induced hypertension by quartile of childhood body mass index using the lowest quartile as the reference (OR = 1). *P* value was adjusted for race, systolic blood pressure, and levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides, in childhood. Error bars show 95% confidence interval.

resistance and other cardiometabolic risk factors in adult life.<sup>37</sup> Lifestyle intervention during adolescence reduces excessive weight gain<sup>38</sup> and may ultimately lead to reduced risk of pregnancy-related health outcomes.

Although childhood blood pressure was not significantly associated with subsequent PIH after adjustment for childhood BMI ( $P = 0.12$ ), we cannot rule out an independent association between childhood blood pressure and PIH due to the relatively small size of our study sample. The association between childhood blood pressure and PIH should be examined in larger studies or in a meta-analysis.

Our observation that childhood BMI was associated with the development of PIH has important implications for prevention and control of PIH, a condition that has serious health consequences. Taken together with other adverse health outcomes of childhood obesity, it is clear that prevention and interventions to manage childhood obesity have multifaceted benefits later in adult life, including, but not limited to, reduced risk of obesity, type 2 diabetes, cardiovascular disease, and now PIH, as indicated by recent data showing that resolution of metabolic syndrome in adult life can substantially mitigate the adverse effects of childhood risk factors on cardiometabolic risk.<sup>39</sup>

Our study has several strengths. We have consistently and rigorously followed strict quality control protocols in the collection of the BHS observations used in our analysis. The health profile of our participants at baseline and longitudinal nature of the analysis make reverse causation an unlikely explanation for the findings. In addition, those who reported having history of hypertension during pregnancy were unlikely to have had sustained chronic hypertension before their pregnancy because their blood pressure levels at the most recent BHS examination were below 140/90 mm Hg based on an average of carefully measured blood pressures obtained by trained nurses.

Several limitations of the study need to be considered. First, PIH in our study was based on a self-report, which might have led to some bias in PIH ascertainment. However, such bias would have led to underestimation of the true association between childhood BMI and PIH because PIH tends to be over reported<sup>14</sup> and thus women with self-reported PIH in the current study likely included some without PIH. Second, we did not have information on proteinuria during pregnancy so we cannot separate gestational hypertension from preeclampsia, a severe and yet much less frequent form of PIH. However, PIH is thought to be part of the same continuum and shares many risk factors with preeclampsia.<sup>40,41</sup> Increased body weight in childhood may also be a risk factor for preeclampsia. Nevertheless, future studies should specifically examine childhood risk factors for preeclampsia. Third, we did not have information on parity and age at pregnancy, as a result of which we were not able to differentiate the impact of childhood BMI on PIHs at different pregnancies and different ages. The potential confounding effects by age at pregnancy and parity, if present, might be limited because age at pregnancy tends to increase with increasing parity<sup>42</sup> and thus age at pregnancy and parity might have opposing effects on PIH risk in the current study. Fourth, we could not examine the influences of central obesity (waist circumference) and glucose and insulin and other potential confounding factors like serum uric acid and renal function during childhood because data on these variables were not available. Thus, we cannot rule out the possibility of residual confounding by unmeasured factors. Finally, the sample size of our study was relatively small and replication studies are needed to confirm the findings from the current study.

In conclusion, increased childhood BMI is associated with elevated risk of PIH. As a result, the current obesity epidemic in children will likely increase the burden of adverse pregnancy-related health conditions. Prevention and control of childhood obesity will have enormous benefits in reducing risk of numerous chronic conditions, PIH included. Promotion of a healthy lifestyle, including increased physical activity and a healthy diet, is of paramount importance.

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## DISCLOSURE

The authors declared no conflict of interest.

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