Original Paper

Big Mother or Small Baby: Which Predicts Hypertension?

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According to the Barker hypothesis, intrauterine growth restriction and premature delivery adversely affect cardiovascular health in adult life. The association of childhood hypertension as a cardiovascular risk factor and birth weight has been understudied. In a prospective cohort study, the authors evaluated the effect of birth weight, gestational age, maternal prepregnancy body mass index (BMI), and child BMI z score at the time of enrollment on the systolic and diastolic blood pressure (BP) z score in 3024 (1373 women) consecutive outpatient clinic patients aged 2.05 to 18.58 years. The latest National Health and Nutrition Examination Survey (NHANES III) was used to calculate the age-dependent z scores. The median z scores of BMI (+0.48, range −6.96–6.64), systolic BP (+0.41, range −4.50–6.73), and diastolic BP (+0.34, range −3.15–+6.73) were all significantly greater than the NHANES III reference population. Systolic BP z score did not correlate with birth weight or gestational age, but did correlate with maternal prepregnancy BMI (r=.090, P<.0001) and BMI z score (r=.209, P<.0001). Diastolic BP z score positively correlated with birth weight (0.037, P=.044), gestational age (r=.052, P=.005), BMI z score(r=.106, P<.0001), and maternal prepregnancy BMI (r=.062, P=.0007). In contrast to what would be expected from the Barker hypothesis, the authors found no negative correlation between BP z score and birth weight or gestational age. This study suggests that a high BMI, a big mom, and a high birth weight are more important risk factors for hypertension during childhood than low birth weight or gestational age. J Clin Hypertens (Greenwich). *2011;13:35–41.* ©*2010 Wiley Periodicals, Inc.*

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According to the Barker hypothesis, disturbed intrauterine growth has a negative influence on the development of the cardiovascular system and favors the occurrence of hypertension in adult life.[1–3] This "fetal origins" hypothesis, first proposed by Barker and colleagues and elaborated by several groups during the past 15 years, was later termed the Developmental Origins of Adult Health and Disease (DOHaD).[4,5] Since its original formulation, the evidence for developmental origins or "prenatal programming" of common adult disease has been expanded from hypertension and cardiovascular disease to chronic kidney disease,[6] asthma,[7] osteoporosis,[8] mental illness[9] and even cancer.[10] Most of these studies do not characterize disturbed intrauterine growth

by small-for-date babies, but rather by the presence of low birth weight. While there are numerous studies that established the inverse relationship between low birth weight and blood pressure (BP) in adults, few pediatric studies exist.[11]

Hypertension is the single most important risk factor for cardiovascular events in adulthood.[12] Epidemiologic and clinical data also support a strong link between obesity and hypertension.[13] Unfortunately, children in Canada rank among the most obese children in the world. Windsor, Ontario, and London, Ontario, rank as the 4th and 5th most obese cities in Canada, respectively.[14] They reflect a large proportion of the catchment area of Children's Hospital, London Health Sciences Centre. We undertook a cross-sectional study of children attending our institution and compared the BP (expressed as age-independent *z* scores) with body mass index (BMI) (expressed as age-independent BMI *z* score), birth weight, gestational age, and maternal prepregnancy BMI. The objective of this study was to establish the determinants of BP *z* score in childhood. To prove that the Barker hypothesis applies to children, a negative correlation between BP *z* score and birth weight and gestational age was to be expected. If a high BMI, a high birth weight, or maternal obesity were more important, a positive correlation between BP *z* score and these determinants was to be expected.

PATIENTS AND METHODS

The investigation was a prospective cohort study using the convenience sample of patients attending Children's Hospital, London Health Science Centre. After obtaining approval from the institutional ethics review board (#13746E), 3024 patients attending the center (1373 females, 45.4%), aged 2.05 to 18.58 years, were recruited into the study from the emergency department and large outpatient clinics including orthopedic surgery, cardiology, gastroenterology, nephrology, endocrinology, neurology, neurosurgery, respirology, and others. All clinics were invited to participate; however, some small clinics elected against participation because of understaffing. Between 60% (orthopedic surgery clinic) and 93% of patients or parents (emergency department) agreed to participate in the study. Patients younger than 2 were not considered for this study because of the lack of reference intervals to calculate BMI *z* scores. Eligible participants were all patients who gave informed consent. Patient enrollment commenced during a 9-month period and 37.5% of possible patients aged 2 to 18 were enrolled. We were unable to enroll all patients since the emergency department recruitment only occurred between noon and 8 PM every day. Excluded were patients for whom no consent was obtained or who attended the clinics outside of recruitment hours. After obtaining written informed consent, a questionnaire was filled out by the parents to determine birth weight, duration of pregnancy, and maternal prepregnancy height and weight. Random BP measurements using a standardized protocol were taken at the clinic visits using automated oscillometric BP machines (patient seated, calm, second of two measurements performed 5 minutes apart with either Welch Allyn Spot Vital Signs LXi (Welch Allyn, Skaneateles Falls, NY) or Dinamap Pro 100, Pro 300, and Dinamap XL Vital Signs Monitor (Criticon, Tampa, FL). Anthropometric measurements (height, measured by stadiometers [Infant stadiometer from Perspection Enterprises, Portage, MI; otherwise Seca 242 mechanical personal measuring rod, Hanover, MD]; weight measured using a high-precision industrial scale at both institutions [Scale-Tronix scales 6002 for wheelchair patients, 4802 for infants and 5002 otherwise; Scale-Tronix, Wheaton, IL]) were obtained as clinical routine. BMI was calculated from the ratio of weight (kg) and the square of the height (cm). Age-independent BMI *z* scores were calculated using the methodology provided by the Centers for Disease Control and Prevention (CDC) Web site with age- and sex-matched controls taken from the National Center for Health Statistics (United States). We used the most recent National Health and Nutrition Examination Survey (NHANES) III database (1999–2002) for all patients (National Center for Health Statistics 2000 CDC Growth Charts: United States [accessed July 29, 2006, at http://www.cdc.gov/growthcharts/]). We also calculated height and weight *z* scores as well as BP *z* scores using the published Box-Cox transformations.

For a subset of 658 patients born in London, we linked data to an existing maternal fetal database to test agreement between the reported and measured prepregnancy weight, height, and birth weight.

To study the effect of prepregnancy BMI and birth weight, we classified the data according to the following birth weight groups: birth weight <1500 g (significant prematurity); 1500 g to 2500 g (low birth weight); 2500 g to 4000 g (normal birth weight); 4000 g to 4500 g (mildly elevated birth weight); and >4500 g (significantly elevated birth weight). Similarly, we divided the prepregnancy BMI into the following groups: <18.5 kg/m^2 (underweight);

18.5 kg/m^2 to 25 kg/m^2 (normal weight); 25 kg/m^2 to 30 kg/m^2 (overweight); and >30 kg/m^2 (obese). To study the effect of age after birth, we also divided the patients into two age groups of younger than or older than 8 years, as the effect of prematurity on cardiovascular risk factors has been described beyond 8 years of life.

Statistical analysis was performed with the GRAPHPAD PRISM version 4.02 for Windows (GraphPad Software, San Diego, CA). Contiguous data were analyzed for normal distribution with the Shapiro-Wilk normality test. Mean and standard deviation were reported for normally distributed data; otherwise, median and quartiles were given. Simple descriptive tests were employed, using appropriate parametric tests for normally distributed data and nonparametric tests otherwise. Comparison between groups was performed using standard *t* test for normally distributed parameters and the Wilcoxon signed rank test otherwise. Associations between variables (eg, date of presentation and BMI *z* score) were assessed with standard regression analysis. Multivariate regression analysis was also performed to control for BMI *z* score when analyzing the relationship between BP *z* score and birth weight. Agreement between variables was assessed using Bland & Altman analysis. A *P* value of <.05 was considered statistically significant. For the current study, we only included the 3024 complete data sets of children older than 2 years, therefore no adjustments were needed for missing values.

RESULTS

Between April 2007 and January 2008, 3024 patients were included into the study (1373 female, 45.4%). Patients were from the emergency department (2046), the nephrology clinic (296), the cardiology clinic (253), the neurology clinic (179), the endocrinology clinic (86), and other clinics (164).

We tested for agreement between the reported and measured parameters after linking with an existing perinatal database in 658 cases. Spearman rank correlation between reported and actual prepregnancy BMI data revealed a strong positive correlation (r=.907, P<.0001). Bland & Altman analysis revealed a bias of 2.69%±9.37% for prepregnancy BMI, with a median underestimation of 0.875% of the reported prepregnancy BMI (P<.0001). For the birth weight, Spearman rank correlation was 0.942 (P<.0001), and Bland & Altman analysis revealed a bias of 15±201 g or 0.65%±6.6%.

Median BP was 108/66 mm Hg. Patient characteristics and appropriate *z* scores for all measurements are summarized in Table I.

Interestingly, we found no significant correlation between systolic BP *z* score and birth weight (r=−.006, P=.729, Spearman rank correlation), nor was there a correlation with gestational age (r=.30, P=.098, Spearman rank correlation). Systolic BP *z* score correlated with diastolic BP *z* score (r=.556, P<.0001, Spearman rank correlation), BMI *z* score (r=.209, P<.0001, Spearman rank correlation), and maternal prepregnancy BMI (r=.090, P<.0001, Spearman rank correlation).

With regards to the diastolic BP *z* score, we found a weak but significant positive correlation with birth weight (r=.037, P=.044) and a weak positive correlation with gestational age (r=.052, P=.005, Spearman rank correlation). Better correlations were found with BMI *z* score (r=.106,

Table I. Patient Characteristics

Parameter	10th Percentile	25th Percentile	Median	75th Percentile	90th Percentile	Significantly Non-Zero? (Wilcoxon Signed Rank Test)
Age, y	3.19	5.143	9.43	13.52	15.85	NA
Weight, kg	14.95	19.6	32.4	53.9	68	NA
Height, cm	96	110	136	160	171	NA
BMI *z* score	−0.99	−0.29	0.48	1.19	1.85	P<.0001
Height *z* score	−1.15	−0.34	0.5	1.33	2.2	P<.0001
Weight *z* score	−0.92	−0.22	0.51	1.2	1.92	P<.0001
Systolic BP *z* score	−0.97	−0.3	0.41	1.23	2.02	P<.0001
Diastolic BP *z* score	−0.8	−0.25	0.34	0.92	1.44	P<.0001
Maternal BMI, kg/m^2	19.02	20.61	22.69	25.83	30.08	NA
Birth weight, g	2528	3011	3408	3806	4119	NA

Abbreviations: BMI, body mass index; NA, not applicable. Age-independent *z* scores were compared with the American reference population (zero=normal). Values are expressed as median and range

$P<.0001$, Spearman rank correlation) and maternal prepregnancy BMI ($r=.062$, $P=.0007$, Spearman rank correlation).

BMI z score had a positive correlation with birth weight ($r=.123$, $P<.0001$, Spearman rank correlation) and maternal prepregnancy BMI ($r=.202$, $P<.0001$, Spearman rank correlation) and a weak yet significant positive correlation with gestational age ($r=.060$, $P=.001$). Maternal BMI correlated weakly and significantly with birth weight (Spearman $r=.079$, $P<.0001$).

We also performed a multivariate analysis with systolic and diastolic BP z scores taken as dependent variables and the birth weight, controlling for BMI z score. There was a significant positive correlation between birth weight and BP z scores (Pillai's Trace 0.008; Wilks Lambda, 0.008; Hotteling's trace, 0.008; Roy's Largest Root method, 0.012). For the between-subjects effect, we found a significant correlation between birth weight and systolic BP z score (0.026) as well as with diastolic BP z score (0.018). Due to the lack of a nonparametric test, we used a general linear model (y=A+B * BMI z score+C * birth weight), where A, B, and C are constants. We further considered two age groups: 8 years and younger (n=1282) and older than 8 years (n=1742). Similar multivariate analysis was applied for the two age groups. Results found for the younger group of patients indicated the presence of a significant positive correlation between birth weight and BP z scores (Pillai's Trace, 0.000; Wilks Lambda, 0.000; Hotteling's trace, 0.000. Roy's Largest Root method, 0.000). For the between-subjects effect, the analysis demonstrated a significant correlation between birth weight and systolic BP z score (0.001) as well as with diastolic BP z score (0.000). For the older group of patients, there was no significant correlation between birth weight and BP z scores (Pillai's Trace, 0.064; Wilks Lambda, 0.065; Hotteling's trace, 0.066; Roy's Largest Root method, 0.057). We did not find a significant correlation between birth weight and systolic BP (0.238) or diastolic BP (0.185). According to the Barker hypothesis, BP should have correlated negatively with the birth weight.

To address the potential for a developmental lag for the development of hypertension secondary to low birth weight, we compared two age groups: younger than 8 years and older than 8 years. The reason for choosing the cut-off of 8 years of age stems from studies in prematurely born children in whom hypertension typically developed beyond the 8th year of life. There was a significant difference in the systolic BP z score between both groups (adolescents median, 0.289; children younger than 8 years, median=0.560; $P<.0001$, Mann-Whitney test) as well as the diastolic BP z scores (adolescent median, 0.201; children younger than 8 years +0.510; $P<.0001$, Mann-Whitney test). Conversely, there was a significant difference between the maternal prepregnancy BMI (median for adolescents, 22.35 kg/m^2; children younger than 8 years, 23.33 kg/m^2; $P<.0001$, Mann-Whitney test). However, there was no correlation between birth weight and systolic BP z score in both groups (younger than 8 years: $r=.008$, $P=.776$; older than 8 years: $r=-.013$, $P=.590$, Spearman rank correlation)), whereas the diastolic BP z score correlated weakly but positively in the younger group only ($r=.079$, $P=.005$, Spearman rank correlation).

Finally, we tested BP z scores in relationship to various groups of birth weight and prepregnancy BMI as outlined in the methods, using the nonparametric Kruskal-Wallis analysis of variance test and found significant differences in the BP z scores among the birth weight groups (Table II). Interestingly, when repeating the analysis of systolic BP for the subgroup of patients older than 8 years, there was no significant difference in medians of these groups ($P=.1570$). The same applied for the diastolic BP in the older group ($P=.2139$). By contrast, there was a significant positive relationship between the prepregnancy BMI and the systolic and diastolic BP (Table III). This suggests that offsprings of big moms are a greater risk factor for childhood hypertension than small babies.

DISCUSSION

According to the Barker hypothesis, disturbed intrauterine growth and low birth weight have a negative influence on the development of the cardiovascular system and favors the occurrence of hypertension in adult life. This hypothesis was not tested in children. The current study attempts to fill this gap.

Numerous large studies have recently confirmed the relationship between low birth weight and raised BP, as recently elegantly reviewed by Dötsch.[15] The mechanism for the development of hypertension due to low birth weight has not been well defined, but may include both renal[16] and extrarenal mechanisms. Renal mechanisms may include the reduction of nephron number, which is encountered in patients and animals with low birth weight.[17] According to the so-called Brenner hypothesis, this may lead to increased arterial BP.[18,19] Another important renal mechanism is the renin-angiotensin-aldosterone system, which appears to be more active on a number of levels in persons with low birth weight.[20]

Table II. Comparison Between Birth Weight Groups

Variable	<1500 g (N=89)	1500–2500 g (N=188)	2500–4000 g (N=2296)	4000–4500 g (N=368)	>4500 g (N=82)
Systolic BP *z* score	0.113 (−0.79, 0.66)[a]	0.266 (−0.47, 1.27)	0.431 (−0.27, 1.26)	0.407 (−0.40, 1.18)	0.287 (−0.20, 1.15)
Diastolic BP *z* score	−0.219 (−0.84, 0.39)	0.277 (−0.29, 0.86)	0.361 (−0.24, 0.93)	0.328 (−0.27, 1.04)	0.482 (−0.04, 0.85)

Abbreviation: BMI, body mass index. [a](25%, 75%). Analysis of variance (ANOVA) Kruskal–Wallis *P* value for systolic blood pressure (BP) *z* score =.0092 for diastolic blood pressure (BP) *z* score <.0001.

Interestingly, we did not find any relationship between low birth weight and an elevated BP *z* score. This was even true when analyzing older patients separately.

It could be argued that the entire process of hyperfiltration as a consequence of reduced nephron dosing responsible for the development of hypertension might take longer than the childhood to occur. Clearly, young adults born with a very low birth weight have higher BP.[21] The time effect, especially when aggravated by excessive weight gain, is well recognized.[22] To test this hypothesis, we chose a cutoff of 8 years because it has previously been shown that low birth weight already affects BP at age 8.[23] Surprisingly, we found absolutely no negative correlation between birth weight and BP *z* score even in the older patients analyzed separately, thereby questioning the applicability of the Barker hypothesis to adolescents. It is important to point out that in utero growth restriction due to famine was responsible for the increased rate of hypertension and cardiovascular morbidity,[1,2] but we currently rarely see famine but rather feast.

Today, we witness an unprecedented obesity epidemic.[5] Even within our study, we were able to demonstrate increased obesity within a single decade: both BMI *z* scores for children older than 8 and their mother's prepregnancy BMIs were significantly lower than the younger children. It is possible that being leaner confounded the effect of low birth weight; however, in the multivariate models, there was a positive correlation between birth weight and BMI *z* score. Matched with the results presented in Table III, this would suggest an adverse effect of high birth weight on future BP. It is impossible to derive from the data whether this is due to prenatal programming or the environment in which the child grows up.

In a study of 739 children from Brazil, children with both a low and a high birth weight had higher BP when using covariance analysis.[24] It was concluded that weight gain during childhood adds to the risk. It appears that both famine and feast during pregnancy are unfavorable for BP. In other words, both small babies/tiny moms and big babies/big moms are both a risk factor. In contrast to these findings, the data from the current study suggest that a high prepregnancy BMI and a high birth weight are the most important factors for higher BP in childhood. The socioeconomical environment in Canada and Brazil differ.

Our data raise the question of whether childhood hypertension could be the result of feast in pregnancy. Prevention of hypertension might have

Table III. Comparison Between Prepregnancy BMI Groups				
Variable	BMI <18.5 (n=188)	BMI 18.5–25 (n=1916)	BMI >25–30 (n=600)	BMI >30 (n=320)
Systolic BP *z* score	0.219 (−0.45, 1.15)[a]	0.352 (−0.36, 1.12)	0.645 (−0.09, 1.44)	0.563 (−0.24, 1.44)
Diastolic BP *z* score	0.238 (−0.30, 0.92)	0.302 (−0.31, 0.89)	0.436 (−0.10, 0.10)	0.408 (−0.17, 1.02)

Abbreviation: BMI, body mass index. [a](25%, 75%). Analysis of variance (ANOVA) Kruskal–Wallis *P* value for systolic blood pressure (BP) *z* score <.0001 and for diastolic BP *z* score=.0005.

to start before pregnancy.[25] Prepregnancy BMI, insulin resistance during pregnancy, and weight gain after birth are all potentially modifiable and may well be the target to improve the overall cardiovascular risk factors later in life.

Limitations and Strengths

About one third of patients were seen in the clinics for chronic diseases. Certainly in the nephrology clinic, a patient selection toward hypertension may have occurred. Furthermore, the inclusion of hospital children could induce a potential bias from the detrimental effect of chronic disease on the growth parameters.[26–29] However, few datasets contain prepregnancy, pregnancy, and childhood information. Without all such time points, life course effects will remain only partially understood.[30] This study is unique in that it enlists the necessary information and is verified from an existing perinatal database. Despite expected growth retardation, height as well as BMI *z* scores in our study group were higher than their American counterparts. Particularly, the emergency department and orthopaedic clinic patients, who reflect a more normal patient cohort, were particularly taller than the NHANES III study group. A large study sample also enhances the validity of our observations. A mixed patient representation from different clinics minimizes a potential selection bias. Nonetheless, the sample taken from patients attending our hospital represents a bias with a predominantly white patient clientele from a predominantly blue-collar background. Unfortunately, we did not collect ethnicity, socioeconomic background, or other descriptors of our patient cohort.

CONCLUSIONS

Our study suggests that the potentially modifiable factor of BMI forms the single most important determinant for BP *z* score. In less than a decade, the problem of high BMI *z* score is increasing, and focusing on effective prevention and intervention is a priority. It appears that a high pregnancy BMI contributes to elevated BP. Targeting a healthy prepregnancy BMI also has to become a priority. The effect of the unmodifiable risk factor of low birth weight is of lesser importance. Our study suggests that big moms may be a more significant risk factor for childhood hypertension than small babies.

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