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Size at Birth, Infant Growth, and Blood Pressure at 3 Years of Age

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Abstract

Objectives—Our aim was to determine the extent to which infant growth – in weight-for-length – from birth to 6 months is associated with systolic blood pressure (SBP) at 3 years, and to determine whether this association varies with birth size.

Study design—In 530 children from the prospective cohort Project Viva, we measured birth length and 6-month weight and length with research standard instruments and SBP at age 3 years with a Dinamap automated recorder. We derived weight-for-length z-scores (WFL-z) and analyzed data with mixed effect regression models.

Results—Mean (SD) WFL-z was 0.47(0.75) at birth and 0.70(0.96) at 6 months. Mean (SD) SBP at 3 years was 91.7(9.4) mmHg. After adjusting for confounding variables and birth WFL-z, child SBP was 1.0mmHg (95% CI 0.2, 1.8) higher for each z-score increment in 6-month WFL-z. SBP of children in the lowest birth WFL-z quartile and the highest 6-month WFL-z quartile was 5.5mmHg (95% CI 2.6, 8.4) higher than of children in the highest birth and lowest 6-month WFL-z quartiles.

Conclusions—More rapid increase in weight-for-length, a measure of adiposity, in the first 6 months of life is associated with higher early childhood systolic blood pressure, particularly in children who are thin at birth.

Keywords Not In Title

Hypertension; epidemiology

Numerous studies to date have demonstrated that lower birth weight is associated with higher blood pressure in children and adults, suggesting that poor fetal growth may be associated with the development of hypertension¹. There is also evidence that weight gain after birth is associated with higher blood pressure later in life^{1, 2}. Further, in some studies, the highest blood pressure is seen in those who were lightest at birth and heaviest later in childhood or adulthood^{3–9}, suggesting that rapid weight gain after birth is particularly detrimental to those

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with poor fetal growth. It is not clear, however, which period of weight gain during childhood is most important for determining blood pressure levels. Early infancy may be one important period, as it is a time of extremely rapid growth, particularly for those infants who experienced fetal growth restriction.

Several studies have examined the relationship between weight gain during childhood and later blood pressure, however few^{3, 10–12} have attempted to isolate the influence of early weight gain, and all but one of these studies are limited by their reliance on weight measures alone. Measures of size that include length or height in addition to weight reflect adiposity better than weight alone¹³, and thus may be more informative about future cardiovascular risk.

A better understanding of the nature and timing of pre- and post-natal influences on blood pressure is needed to guide public health strategies for the primary prevention of hypertension, and could further our understanding of the underlying biological relationship between infant weight gain and child blood pressure. The objectives of this study were: (1) to examine the associations of the change in weight-for-length in the first 6 months of life with systolic blood pressure at 3 years of age; and (2) to determine the extent to which the association between infant growth and systolic blood pressure varies with size at birth.

Methods

Study Design and Participants

We studied participants in Project Viva, a prospective, longitudinal cohort study designed to examine multiple pre- and perinatal factors in relation to outcomes of pregnancy and child health. Participants were recruited into Project Viva at their first prenatal visit at Harvard Vanguard Medical Associates, a large multi-specialty group practice in Eastern Massachusetts. Exclusion criteria included multiple gestation, inability to answer questions in English, plans to move from the area before delivery, and gestational age greater than 22 completed weeks at the initial prenatal clinical appointment. Additional details of recruitment and follow-up have been published elsewhere¹⁴.

Of the 2128 children born to Project Viva mothers, we included in the sample for this analysis the 530 children with complete measured exposure and outcome data at birth, six months, and 3 years of age. Human subjects committees of Harvard Pilgrim Health Care, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center approved the study protocols, and mothers of all participating children gave informed consent.

Measurements

We abstracted birth weight from the medical record. Project staff weighed children at age 6 months and 3 years with a digital scale (Seca Model 881, Seca Corporation, Hamburg, Germany), and measured length at birth and 6 months and height at 3 years using a Shorr measuring board (Shorr Productions, Olney, MD). Project staff followed a standardized protocol to measure child blood pressure at age 3 years with a Dinamap Pro100 (Critikon, Inc, Tampa, FL) automated oscillometric recorder, taking up to 5 measurements 1 minute apart in each child and recording the child's position and activity level, extremity used, cuff size, measurement sequence number, time of day, and ambient temperature. Project staff also used research standard instruments to measure the mother's blood pressure, weight, and height when the infant was 6 months and 3 years old.

We collected data regarding maternal demographic, social, economic, and health information through self-administered questionnaires and interviews at study visits during pregnancy, shortly after delivery, and when the infant was 6 months old. Definitions of covariates,

including gestational age and glucose tolerance status, have been described elsewhere¹⁴. We defined hypertensive disorders during pregnancy according to published standards¹⁵.

Analysis

Our main outcome of interest was systolic blood pressure at 3 years of age. We used systolic blood pressure in the analysis because it predicts later outcomes better than diastolic blood pressure¹⁶ and is measured more accurately with our automated instrument¹⁷. We included all blood pressure measurements for each child to minimize within-person variability¹⁸. We derived weight-for-length z-scores from the 2000 CDC growth charts^{19, 20}. Our main predictor was the weight-for-length z-score at 6 months of age, adjusted for the weight-for-length z-score at birth. We refer to this adjusted effect as the change in weight-for-length z-score from birth to 6 months because it is algebraically identical to the effect of the difference between the 6-month and birth weight-for-length z-scores, adjusted for the birth weight-for-length z-score. We chose our approach for ease of statistical modeling and interpretation.

To estimate the association of the change in weight-for-length z-score between birth and 6 months with systolic blood pressure, we used mixed effects regression models²¹ incorporating all available blood pressure measurements from each child as repeated outcome measurements. As compared with using the average of available measurements for each child, this method gives more weight to individuals with more measurements and less variability among the measurements than those with fewer measurements and/or more variability. We adjusted all models for blood pressure measurement conditions (cuff size, extremity used, child state and position, measurement sequence number).

To control for confounding, we considered covariates that could influence fetal growth, post-natal growth, or child blood pressure and adjusted for maternal and child covariates that changed the coefficient for weight-for-length z-score at 6 months by at least 10%. Adjustment for maternal age, maternal systolic blood pressure, parity, hypertensive disorders of pregnancy, gestational diabetes status, and infant feeding status did not change the estimates, so were not included in the final model. We then grouped weight-for-length z-score at birth and 6 months into quartiles and used our multivariable model to predict the mean systolic blood pressure at 3 years in each of the resulting categories, compared with the mean systolic blood pressure in the cell representing the combination of the highest birth weight-for-length quartile and lowest 6-month weight-for-length z-score quartile. We performed data analyses with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 2128 infants born to Project Viva mothers, we excluded 1069 who were missing newborn length, primarily because we did not attempt to measure infants born on a weekend (n=414) or infants admitted to the neonatal intensive care unit (n=78), or due to parents not consenting to the measurements (n=328). Of the remaining 1059 children, we were unable to obtain complete weight and length measurements in 346, primarily because the child did not attend the 6-month study visit. We excluded an additional 21 participants because either the birth or the 6-month weight-for-length z-score was biologically implausible (less than -4 or greater than 5). Of the remaining 692 participants, 634 were eligible for the 3-year follow-up visit and 601 had completed the 3-year follow-up visit at the time of this analysis. Of these, we were unable to measure blood pressure in 71. Thus, the sample for analysis was 530 children with complete measured exposure and outcome data at birth, six months, and 3 years of age.

Comparing characteristics of the original cohort of 2128 mother-infant pairs to the 530 included in this analysis, we found that mothers in this analysis tended to be better educated (75% vs. 65% had at least a college degree), were less likely to be from a racial or ethnic minority (22%

vs. 34%), and were less likely to have had preeclampsia (2.5% vs. 3.6%) or gestational diabetes (4.4% vs. 5.6%). Mothers in both groups had similar mean levels of weight gain during pregnancy (15.5 kg vs. 15.6 kg). Fewer infants in this analysis were born prior to 37 weeks gestation (3.8% vs. 7.2%), primarily because we were unable to obtain birth measurements on infants admitted to the neonatal intensive care unit. Mean birth weight among children included in this analysis was slightly higher (3.56 kg vs. 3.46 kg) than among children in the overall cohort, and mean birth weight for gestational age z-score²² was also higher (0.27 vs. 0.17) for children included in this analysis. At age 6 months, mean weight for length z-score was similar between the groups (0.70 vs. 0.71); and at age 3 years, mean systolic blood pressure was also similar (91.7 mmHg vs. 92.1 mmHg), and consistent with other studies of blood pressure at this age measured with a Dinamap^{23, 24}.

Table I describes the characteristics of the study participants according to quartile of infant weight-for-length z-score at age 6 months. No clear linear association is evident between quartile of infant weight-for-length at 6 months and systolic blood pressure at age 3 years, but they are unadjusted for size at birth or other covariates. Results of our multivariable models are shown in Table II. Adjusting for blood pressure measurement conditions and child age and sex, systolic blood pressure at age 3 years was 1.4 mmHg (95% CI -2.4, -0.4) lower for each unit increment increase in weight-for-length z-score at birth. For each unit increase in weight-for-length z-score at age 6 months, adjusted for weight-for-length z-score at birth (reflecting the change in weight-for-length z-score between birth and 6 months), systolic blood pressure was 1.1 mmHg (95% CI 0.3, 1.8) higher at age 3 years (Model 1). After further adjustment for child height at age 3 years and maternal income, education, race/ethnicity, and smoking status (Model 2), we found that this estimate was only slightly attenuated, to 1.0 mmHg (95% CI 0.2, 1.8) per z-score unit change in weight-for-length from birth to 6 months.

In a separate model we estimated systolic blood pressure within quartiles of weight-for-length z-score at birth and at age 6 months, adjusting for the same maternal and child covariates as in Model 2. For each of the 16 combinations of quartiles, we show the difference in estimated systolic blood pressure relative to the group representing the combination of the highest quartile of birth weight-for-length z-score and the lowest quartile of 6-month weight-for-length z-score (Figure). For example, estimated systolic blood pressure was 5.5 mmHg (95% CI 2.6, 8.4) higher in the lowest quartile of birth weight-for-length and the highest quartile of 6-month weight-for-length z-score, compared to the reference.

In a secondary analysis, we repeated the multivariable analyses with diastolic blood pressure as the outcome variable and found similar results, though the estimates were somewhat attenuated (data not shown).

Discussion

In this study, we found that systolic blood pressure at age 3 years was 1.0 mmHg higher for each unit increase in weight-for-length z-score between birth and 6 months. An increase in weight-for-length z-score over time indicates that a child's weight has increased out of proportion to his or her increase in length, and suggests that the child has experienced an increase in adiposity. As an example of a 1-unit difference in weight-for-length z-score, consider two 6-month old male infants who are of average length (67 cm). The infant with a weight-for-length z-score of 0 would weigh 7.7 kg, whereas the infant with a weight-for-length z-score of 1 would weigh 8.4 kg, a difference of 0.7 kg. Our estimates predict that, after adjusting for weight-for-length z-score at birth, the heavier of these two infants would have 1.0 mmHg higher systolic blood pressure at age 3 years. We also found the highest blood pressure in the children who were in the lowest quartile of weight-for-length at birth, but grew to be in the highest quartile at 6 months. That is, children who were thinnest at birth and had

the most rapid weight gain relative to length between birth and 6 months, experienced the highest blood pressure levels at age 3 years.

The results of our study contrast with the only prior study to have examined the relationship between infant growth, using a weight-for-length measure, and later blood pressure. Whereas we found that more rapid relative weight gain in the first 6 months of life was associated with higher blood pressure, Cheung et al¹¹ found, in a Hong Kong cohort born in 1967, that a one unit increase in ponderal index between birth and age 6 months was associated with a 1.4 mmHg *decrease* in systolic blood pressure at age 30 years. One possible explanation for our conflicting results is that our study populations reflect different ends of the spectrum of infant growth and nutrition. Children in the Hong Kong cohort, on average, had a decrease in ponderal index between birth and age 6 months, although children in our contemporary cohort, on average, had an increase in weight-for-length z-score from birth to 6 months of age. Although the authors of the Hong Kong study do not present specific data on infant nutrition, they report that living conditions were generally poor in Hong Kong at the time of the study. In contrast, it is reasonable to assume that infants in our study had adequate nutritional resources. Another study of infant growth and blood pressure in the Philippines found that larger gains in weight and length from birth to age 2 were associated with a lower odds of high blood pressure in Filipino adolescents⁷. However weight and length gains in that study were large only in relation to the overall study population but were likely not excessive, supported by the fact that fewer than 3% of adolescents in the study are overweight. Our results are likely more relevant to modern, developed countries, whereas the results of the Hong Kong and Filipino studies may be more applicable to children in the developing world.

Three prior studies have examined other measures of infant growth, primarily weight gain, with respect to later blood pressure. Our results are in agreement with those of Forsen et al¹⁰, who found in a rural Finnish cohort born in 1981 – 1982 that weight gain in the first year of life was positively associated with blood pressure at age 7 years. Similarly, in an older Finnish cohort born in 1966, rapid weight gain during the first year of life was associated with higher blood pressure at age 31 years¹². In contrast, there was no appreciable association between weight gain in the first year of life and blood pressure in a cohort of young adults born in the UK³, though this study examined weight gain over the entire first year, rather than a more narrow time period in the earliest months of life.

Consistent with our finding of an association between a more rapid increase in infant weight-for-length z-score and higher blood pressure later in childhood, animal and human studies have shown links between more rapid weight gain in infancy and other components of the metabolic syndrome, including increased fat mass²⁵ and obesity²⁶, insulin resistance²⁷, and impaired endothelial function²⁸, in addition to blood pressure.

Some authors have reported that *smaller* size during infancy is associated with insulin resistance and coronary heart disease, which themselves are related to blood pressure. In a Finnish cohort born between 1934 and 1944, adult men with coronary heart disease and adults with type 2 diabetes were thinner relative to the rest of the cohort at birth until early childhood, after which their BMI rose progressively, surpassing the average for the cohort by school-age^{29, 30}. However, there is an apparent upward trend in weight and/or BMI in the earliest months of life. Similarly, Bhargava et al³¹ found in a cohort of Indian young adults born in the early 1970's that those with the highest odds of developing insulin resistance were thinner from birth through age 2 years, and had a higher BMI at age 12, compared to the rest of the cohort. However, this study did not examine in detail weight gain in the first months after birth.

The relatively high socioeconomic status of our participants and the preferential loss to follow-up of participants in lower socioeconomic status and minority racial and ethnic groups could

limit the generalizability of our findings. A strength of our study is that we used weight-for-length measures which are more likely to represent adiposity than measures of just weight or length. Although we did not have birth length measurements for our entire cohort, our method for measuring length is more accurate than commonly used clinical measures such as the paper-and-pencil method, which tend to overestimate length in young children³². We also carefully measured child blood pressure and potentially confounding covariates, including maternal blood pressure.

Our results raise the possibility that strategies to moderate excess infant weight gain, particularly among infants who are thin at birth, may contribute to the primary prevention of hypertension. Any intervention to modify infant weight gain, however, must take into account the possible benefits of early growth, such as improved cognition³³, as well as the potential harms to cardiovascular and metabolic health.

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List of Abbreviations

BMI

Body mass index

CDC

Centers for Disease Control and Prevention

CI

Confidence interval

Figure.

Predicted difference in systolic blood pressure at age 3 years according to quartile of weight-for-length z-score at birth and age 6 months, adjusted for child age, sex, height, and blood pressure measurement conditions (child's state and position, extremity used, cuff size, measurement sequence) and maternal income, education, race, ethnicity, and smoking status. Range of weight-for-length z-score within quartiles at birth: Q1 (−2.2, −0.0), Q2 (−0.0, 0.5), Q3 (0.5, 1.0), Q4 (1.0, 2.8); and within quartiles at age 6 months: Q1 (−2.3, 0.0), Q2 (0.0, 0.7), Q3 (0.7, 1.4), Q4 (1.4, 3.3)

Table 1
Participant Characteristics According To Child Weight-For-Length Z-Score at 6 Months

	Quartile of weight-for-length z-score at 6 months (range)			
	1 (−2.25, 0.04)	2 (0.05, 0.70)	3 (0.70, 1.35)	4 (1.36, 3.33)
Mothers				
	Mean (SD)			
Pre-pregnancy BMI (kg/m ²)	23.1 (4.0)	24.2 (4.6)	24.7 (4.6)	25.5 (5.8)
Mean systolic blood pressure (mmHg) [*]	107.0 (10.1)	108.8 (9.8)	108.8 (10.5)	111.4 (12.3)
	Number (Percent)			
Smoked in 3 months before pregnancy	7 (5.5)	15 (11.5)	13 (9.9)	13 (10.1)
Race/Ethnicity				
White	99 (75.6)	99 (74.4)	110 (82.7)	104 (78.8)
Black	12 (9.2)	14 (10.5)	10 (7.5)	17 (12.9)
Hispanic	8 (6.1)	7 (5.3)	5 (3.8)	4 (3.0)
Asian, other, or >1 race/ethnicity	12 (9.2)	13 (9.8)	8 (6.0)	7 (5.3)
Education				
Less or equal to some college	24 (18.2)	41 (30.8)	33 (24.8)	32 (24.2)
College diploma	54 (40.9)	47 (35.3)	51 (38.4)	46 (34.9)
Graduate degree	54 (40.9)	45 (33.8)	49 (36.8)	54 (40.9)
Annual household income				
Less than \$40,000	11 (8.7)	16 (12.8)	11 (8.7)	18 (13.7)
\$40,000 – 70,000	25 (19.8)	31 (24.8)	35 (27.8)	26 (19.9)
More than \$70,000	90 (71.4)	78 (62.4)	80 (63.5)	87 (66.4)
Children				
<i>At birth</i>				
	Mean (SD)			
Gestational age (weeks)	39.8 (1.4)	39.8 (1.3)	39.9 (1.5)	39.6 (1.4)
Birth weight (kg)	3.56 (0.51)	3.48 (0.45)	3.56 (0.48)	3.66 (0.54)
Birth weight for gestational age z-score [†]	0.25 (0.96)	0.08 (0.84)	0.26 (0.90)	0.49 (1.0)
Birth weight-for-length z-score	0.30 (0.73)	0.37 (0.71)	0.50 (0.72)	0.72 (0.78)
<i>At age 6 months</i>				
	Mean (SD)			
Weight-for-length z-score	−0.53 (0.47)	0.39 (0.19)	1.05 (0.19)	1.90 (0.45)
<i>Feeding status</i>				
	Number (Percent)			
Formula only	10 (7.6)	11 (8.3)	11 (8.3)	13 (9.9)
Weaned	32 (24.2)	51 (38.4)	57 (42.9)	52 (39.4)
Mixed	52 (39.4)	38 (28.6)	28 (21.1)	32 (24.2)
Breast milk only	38 (28.8)	33 (24.8)	37 (27.8)	35 (26.5)
<i>At age 3 years</i>				
	Mean (SD)			
Weight-for-height z-score	−0.14 (0.93)	0.18 (0.83)	0.56 (0.78)	1.16 (0.87)
Mean systolic blood pressure (mmHg)	72.8 (8.4)	71.1 (8.0)	73.2 (8.9)	71.7 (8.6)

* Project staff measured mothers' blood pressure 6 months post-partum.

[†] Based on a United States national reference²².

Table 2

Associations of Change in Weight-For-Length From Birth to 6 Months With Child Systolic Blood Pressure (mmHg) at 3 Years of Age.

Model	β	95% CI	p-value
Model (1): WFL z-score at 6 months	1.1	0.3, 1.8	0.01
WFL z-score at birth	-1.4	-2.4, -0.4	0.01
Model (2): Model (1) + child height and maternal covariates			
WFL z-score at 6 months	1.0	0.2, 1.8	0.02
WFL z-score at birth	-1.4	-2.4, -0.3	0.01
Height at 3 years (cm)	0.4	0.2, 0.6	0.001

WFL is weight-for-length. 6 month WFL z-score adjusted for birth WFL z-score represents the z-score change in WFL from birth to 6 months. The regression estimate is the difference in child systolic blood pressure in mmHg for each z-score increment in WFL at the specified age, or for each centimeter (cm) increment in child height at 3 years. All models are adjusted for child age, sex, and blood pressure measurement conditions (child's state and position, extremity used, cuff size, and measurement sequence number). Model 2 is additionally adjusted for maternal income, education, race, ethnicity, and smoking status.