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Blood Pressure Among Very Low Birth Weight (<1.5 kg) Young Adults

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ABSTRACT

Our objective was to compare the blood pressure of 20-y-old very low birth weight (VLBW; <1.5 kg) individuals with that of normal birth weight (NBW) control individuals. The population included 195 VLBW (92 female and 103 male) and 208 NBW (107 female and 101 male) individuals who were born between 1977 and 1979. Independent effects of birth weight status (VLBW *versus* NBW) and within the VLBW cohort of intrauterine growth (birth weight *z* score) were examined *via* multiple regression analyses. VLBW individuals had a higher mean systolic blood pressure (SBP) than NBW control individuals (114 ± 11 *versus* 112 ± 13 mm Hg). SBP for VLBW female infants was 110 ± 9 *versus* NBW 107 ± 12 and for VLBW male individuals was 118 ± 11 *versus* NBW 117 ± 11 mm Hg. After adjustment for gender, race, and maternal education, the difference in SBP between VLBW and NBW individuals was 1.9 mm Hg but was 3.5 mm after also adjustment for later size (20-y weight and height *z* scores), which reflects catch-up growth. For female individuals, the difference in SBP between VLBW and NBW individuals was significant both unadjusted and adjusted for later size, whereas for male individuals, the difference was significant only after adjustment for later size. Intrauterine growth did not have a significant effect on SBP within the VLBW group, even after adjustment for later size. VLBW individuals, specifically female individuals, have a higher SBP than NBW control individuals. This is not explained by intrauterine growth failure. **(*Pediatr Res* 58: 677–684, 2005)**

Abbreviations

BMI, body mass index
BP, blood pressure
DBP, diastolic blood pressure
NBW, normal birth weight
SBP, systolic blood pressure
SGA, small for gestational age
VLBW, very low birth weight

Reports of the outcomes of very low birth weight (VLBW) infants have until recently pertained mainly to neurodevelopmental sequelae (1–3). However, as the survivors of neonatal intensive care reach adulthood, there is increasing interest in sequelae that may present later in life (4,5). This interest is heightened by growing evidence that intrauterine and/or early childhood experiences may have long-term implications for adult health. Biologic markers that are considered to be predictors of long-term adult health outcomes include catch-up growth (6), blood pressure (BP) (7–9), and metabolic abnormalities (10).

As part of a longitudinal study of the outcomes of VLBW (<1.5 kg) individuals, we recently reported on young adult health and educational outcomes, behavior, and growth attainment compared with normal birth weight (NBW) control individuals (4,6,11). The objective of the present study was to examine gender-specific BP and to identify perinatal, childhood, and young adult correlates of BP at age 20 y. We hypothesized that the VLBW group would have higher BP at age 20 y compared with the NBW control individuals. Because of our previous finding of greater catch-up growth among VLBW female individuals than among VLBW male individuals (6) and the reported association between catch-up growth and adult cardiovascular risk (12,13), we hypothesized that the difference in BP between the VLBW and NBW control individuals would be greater in the female individuals. We further hypothesized that within the VLBW group, BP at age 20 y would be associated with intrauterine growth failure.

METHODS

VLBW population. A total of 490 VLBW infants were admitted to Rainbow Babies and Children's Hospital in Cleveland, Ohio, between 1977 and 1979, 312 (64%) of whom survived. A total of 242 (78%) individuals were followed to 20 y of age, 47 of whom were excluded: 25 had neurosensory impairments, one had Liddles syndrome, 12 women were pregnant, and nine

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had missing BP measurements. The population thus included 195 VLBW individuals who had BP and growth measured at age 20 y. BP and height were also measured in 159 (82%) of their mothers. The VLBW cohort constituted 68% (195 of 287) of the birth cohort who did not have neurosensory impairments. They did not differ significantly from the birth cohort of nonparticipant survivors in maternal sociodemographic status or in infant birth or neonatal descriptors with the exception that there were fewer female individuals (47 *versus* 61%; $p < 0.05$) as a result of the exclusion of those who were pregnant at the time of study. Fewer of the mothers who had BP measured compared with those who did not had less than a high school education (17 *versus* 36%; $p < 0.01$), but they did not differ in marital status, race, or their children's birth data. Preeclampsia was present in 10% of mothers who had BP measured *versus* 16% of those who did not ($p = 0.384$).

Control population. The control group was selected at age 8 y by means of a population sampling procedure. The original plan was to randomly select 8-y-old NBW children from 50 randomly selected schools that were assigned to six strata on the basis of racial composition and median family income of the schools' catchment area. However, because of busing of school children in the city of Cleveland, the stratification scheme was used only for children who were enrolled in suburban and Catholic schools. For children who attended public school in the city of Cleveland, a random sample was selected. A total of 643 children were selected, 124 (19%) of whom refused to participate and 156 (24%) of whom were either born outside the area or preterm. The original control population thus included 363 NBW individuals who were born in 1977, 1978, and 1979 (3). A total of 233 (64%) were followed to 20 y, 25 of whom were excluded: one had a neurosensory impairment, nine women were pregnant, and 15 had missing BP measures. The control population thus included 208 participants. They constituted 57% of eligible individuals who were recruited at 8 y of age and did not have a neurosensory impairment. BP and height were also measured in 180 (87%) of their mothers.

The 208 control individuals did not differ from the nonparticipating control individuals in birth weight or gender but differed significantly in maternal sociodemographic descriptors: fewer of their mothers had less than a high school education (10 *versus* 26%), fewer were black (53 *versus* 75%), and more were married (64 *versus* 42%; $p < 0.001$ for all comparisons). The mothers who had BP and height measured did not differ in race, education, or marital status from those who were not measured.

Follow-up protocol. The methods of neonatal care have been previously described (14,15). The children were followed prospectively, and growth was measured at birth and then longitudinally at the expected term date of delivery (40 wk after the last menstrual period) and then at 8 mo, 20 mo, and 8 y of age corrected for preterm birth and at 20 y postnatal age.

At 20 y of age, BP was measured according to standard procedure recommended by the American Heart Association (16). The research assistants were trained and certified in BP measurement techniques. The individual was seated in a comfortable position with the right arm fully exposed and resting on a supportive surface at heart level. A standard mercury gravity sphygmomanometer was used and an appropriately sized cuff was selected. After inflation of the cuff, the first Korotkoff sound in phase I, which is heard on deflation of the cuff, corresponded to systolic BP (SBP), and the cessation of the fifth sound corresponded to diastolic BP (DBP). Two measurements were made 1–2 min apart and averaged. Standing height was measured with a Harpenden Stadiometer after removal of shoes and stockings (17). The individuals were weighed lightly clothed on an electronic portable scale. To correct for the weight of clothing, similar to others, we subtracted 0.5 kg from the measured weight of female individuals and 1.0 kg from that of male individuals (18,19). A similar proportion of VLBW and NBW study subjects were seen by each of the three research assistants who participated in the study.

Weight and length/height *z* scores (*i.e.* SD) were computed from the intrauterine growth standards of Usher and McLean (20) at birth and at the corrected term date and from the revised Centers for Disease Control and Prevention growth data thereafter (21). Body mass index (BMI) was calculated as the relation of body weight to height squared (wt/ht^2, kg/m^2), and *z* scores were computed at 8 and 20 y (21). The study was approved by the Institutional Review Board of University Hospitals of Cleveland, and informed consent was obtained from all participants.

Documentation of correlates of BP. Variables that were examined for their relationship to young adult BP included maternal marital status, level of education, race, a history of preeclampsia, and current maternal BP and height. We used the mother's educational status at the time the child was 8 y old as a proxy for social class because it was considered to span childhood and be more relevant to child growth and development than 20-y status. Infant data that were considered included birth weight, gestational age, the birth weight *z* score used as a measure of intrauterine growth, small for gestational age (SGA) status [birth weight <-2 SD for gestational age (20)], multiple birth, type of delivery, and the duration of the neonatal hospital stay. We used the duration of neonatal hospital stay as the measure of severity of neonatal illness because it represents an index of immaturity and severity of respiratory distress syndrome such as oxygen and ventilator dependence (22,23). Indices of postnatal growth included distance growth between the time periods of study and weight, height, and BMI *z* scores at each time period. Additional variables that were considered included age at menarche and chronic illness at 20 y.

Data analysis. The analyses were carried out for the total population and separately for male and female participants. Variables of interest were compared between the VLBW and NBW participants using the two-sample *t* test for continuous measures and χ^2 for categorical measures.

We initially performed univariate linear regression analyses to examine the effects of the potential correlates of SBP and DBP at age 20 y. Multiple regression analyses then were performed *via* two models. In model 1, we included VLBW and NBW individuals to examine the independent effect of birth weight status on BP. The specific effect of intrauterine growth on BP could not be examined in model 1 as the birth weight and gestational age of the NBW control individuals was obtained by maternal report at age 8 y and was not believed to be reliable. The effect of birth weight status (VLBW *versus* NBW) thus was examined in this model, with VLBW status representing the overall impact of being born VLBW rather than of intrauterine growth *per se*. In model 2, we included only VLBW individuals to examine the independent effect of intrauterine growth (birth weight for gestational age *z* score) on BP. We used the regression models suggested by Lucas *et al.* (24). for these analyses. They included *1*) an early model that included early size, which we defined as birth weight status in model 1 and birth weight *z* score in model 2; *2*) a later model that included later size, which we defined as the 20-y weight and height *z* scores; *3*) a combined model that included early and later size; and *4*) an interaction model that considered the interaction between early and later size. Adjustment for later size is equivalent to adjustment for change in size between birth and 20 y, *i.e.* postnatal catch-up growth (24). In both models, we adjusted for maternal education, race, and gender where appropriate. In separate models, we also examined the singleton births separately and the effect of being born SGA (birth weight <-2 SD for gestational age) and of growth attainment at the expected date of delivery (*i.e.* the 40 wk weight *z* score).

RESULTS

Comparison of VLBW and NBW individuals. The 195 VLBW individuals had a mean birth weight of 1189 g and mean gestational age of 29.8 wk; male and female VLBW individuals did not differ in maternal sociodemographic status or in infant birth or perinatal data (Table 1). The 208 control individuals had

Table 1. *Maternal Demographic Status and Infant Birth Data for Very Low Birth Weight Male and Female Participants**

	Males (n = 103)	Females (n = 92)
Maternal Factors		
Married†	59 (57%)	56 (61%)
Education†		
< High School	16 (16%)	17 (19%)
High School	54 (52%)	55 (60%)
> High School	33 (32%)	20 (22%)
Black Race	60 (58%)	45 (49%)
Preeclampsia	15 (15%)	7 (8%)
Birth and Perinatal Data		
Birth Weight (mean g ± SD)	1192 ± 213	1187 ± 215
Gestational Age (mean wks ± SD)	29.6 ± 2.2	30.0 ± 2.3
Birth weight z-score (mean ± SD)	−0.73 ± 1.34	−1.12 ± 1.09
Birth length z-score (mean ± SD)	−1.18 ± 2.16	−1.22 ± 1.65
Small for Gestational Age‡	19 (18%)	20 (22%)
Delivery by Cesarean Section	30 (29%)	32 (35%)
Multiple Birth	18 (18%)	20 (22%)
Respiratory Distress Syndrome	79 (77%)	64 (70%)
Endotracheal Ventilation	20 (19%)	11 (12%)
Length of Hospital Stay (median, range)	58 (12–365)	55 (7–456)

† The maternal status at the child's eighth year.

‡ < -2SD for gestational age (18).

* None of the characteristics are different between male and females (all p values >0.05).

a mean birth weight of 3277 g. They were born at term gestation (≥37 wk), but specific information on their gestational age was not available. The VLBW and NBW individuals did not differ in race or gender (54% VLBW *versus* 53% NBW were black, and 46% *versus* 47% were white; 53% VLBW *versus* 49% NBW were male, and 47% VLBW *versus* 51% NBW were female). More of the mothers of VLBW participants than mothers of the control individuals had less than a high school education (17 *versus* 10%, respectively; $p < 0.05$). They did not differ in marital status (married 59 *versus* 64%) or race (54 *versus* 53% black).

The total VLBW population, including male and female individuals, had a significantly higher SBP than the NBW control individuals (114.2 ± 11 *versus* 111.9 ± 13; $p < 0.05$). DBP did not differ significantly between groups (73.1 ± 9 *versus* 72.6 ± 9).

VLBW male individuals did not differ from their NBW control individuals in SBP or DBP. They had a significantly lower 20-y weight, height, and BMI than the NBW control individuals, as previously reported (6). VLBW female individuals had a significantly higher SBP than the NBW control individuals (110 *versus* 107 mm Hg; $p = 0.03$) but did not differ in DBP or in 20-y weight, height, or BMI (see Table 2).

There were no significant differences between the VLBW and NBW groups in the rates of hypertension, *i.e.* levels of SBP of 140 and above, of DBP of 90 and above, or of prehypertension (systolic BP 120–139) (25). However, significantly more VLBW female individuals had a DBP between 80 and 89 compared with the NBW control individuals (Table 3). The results were similar when the first or second SBP or DBP measurements rather then the mean of the two measurements were considered.

Univariate correlates of SBP and DBP. Among VLBW male individuals, significant correlates ($p < 0.05$) of SBP included cesarean section delivery, birth length z score, change in length/height z score between birth and 20 y, and 20-y weight and BMI z scores. Significant correlates of DBP included the maternal DBP, 8- and 20-y weight and BMI z scores, and change in weight z score between birth and 20 y (Tables 4 and 5).

Among VLBW female individuals, significant correlates of SBP included the maternal DBP, cesarean section delivery, the 20-mo length z score, 8- and 20-y weight and height z scores, and change in weight z score between birth and 20 y. Significant correlates of DBP included maternal DBP, the birth weight z score, 20-y weight z score, and change in weight z score between birth and 20 y. The correlation between black race and DBP bordered on significance ($p = 0.05$).

Within the VLBW group, there were no significant differences in SBP or DBP between single or multiple births or between children who were born appropriate for gestational age or SGA.

Multivariate Analyses

Model 1: effect of VLBW on BP. This model examined the independent effect of birth weight status (VLBW *versus* NBW) on BP after adjustment for maternal education and race and gender, where applicable. Examination of the total population revealed that the difference in SBP between the VLBW and NBW individuals bordered on significance ($p = 0.08$) but became highly significant (difference = 3.5 mm Hg; confidence interval 1.4–5.6; $p = 0.001$) after also adjusting for later

Table 2. *Comparison of Very Low Birth Weight and Normal Birth Weight Young Adult and Maternal Blood Pressure and Growth*

	Males			Females		
	Very Low Birth Weight (n = 103)	Normal Birth Weight (n = 101)	P Value	Very Low Birth Weight (n = 92)	Normal Birth Weight (n = 107)	P Value
Young Adult						
Age (years)	20.2 ± 0.5	20.1 ± 0.4	.01	20.1 ± 0.4	20.1 ± 0.4	.62
Blood Pressure (mm Hg)						
Systolic	117.5 ± 10.6	116.9 ± 11.0	.66	110.4 ± 9.1	107.2 ± 12.1	.03
Diastolic	73.7 ± 8.6	73.1 ± 8.6	.65	72.5 ± 8.5	72.1 ± 8.9	.78
Chronic Illness	18 (18%)	16 (16%)	.45	22 (24%)	14 (13%)	.04
Asthma	8 (8%)	6 (6%)	.41	7 (8%)	2 (2%)	.05
Growth Measures						
Weight (kg)	69.2 ± 13.9	79.9 ± 16.7	.000	64.9 ± 16.8	67.6 ± 18.3	.28
Weight z-score*	−0.35 ± 1.25	0.53 ± 1.06	.000	0.26 ± 1.17	0.45 ± 1.16	.25
Height (cm)	173.7 ± 7.9	177.0 ± 6.8	.001	161.7 ± 7.3	163.0 ± 7.0	.20
Height z-score*	−0.44 ± 1.10	0.03 ± 0.95	.001	−0.26 ± 1.13	−0.06 ± 1.08	.20
BMI (kg/m^2)	22.9 ± 4.2	25.5 ± 4.9	.000	24.7 ± 5.2	25.4 ± 6.2	.37
BMI z-score*	−0.33 ± 1.24	0.42 ± 1.09	.000	0.42 ± 0.93	0.45 ± 1.24	.88
Maternal Data†	(n = 79)	(n = 85)		(n = 79)	(n = 94)	
Age	44.5 ± 5.1	46.6 ± 5.3	.01	44.5 ± 5.2	45.1 ± 4.7	.39
Blood Pressure						
Systolic	123.1 ± 13.6	124.1 ± 18.4	.71	124.0 ± 13.8	120.1 ± 13.5	.07
Diastolic	81.2 ± 9.1	80.8 ± 13.5	.81	81.0 ± 10.2	79.5 ± 9.4	.30
Height						
Height (cm)	161.6 ± 6.4	163.4 ± 5.9	.06	162.2 ± 7.1	163.1 ± 6.9	.48
Height z-score*	−0.26 ± 0.98	0.01 ± 0.91	.06	−0.17 ± 1.09	−0.04 ± 1.07	.43

* Using CDC weight norms (21).

† For mothers with blood pressure measurements at 20 years.

Table 3. *Comparison of Blood Pressure Levels Between Very Low Birth Weight and Normal Birth Weight Participants*

Blood Pressure	Males		Females	
	Very Low Birth Weight (n = 103)	Normal Birth Weight (n = 101)	Very Low Birth Weight (n = 92)	Normal Birth Weight (n = 107)
Systolic				
<120	54 (52%)	60 (59%)	80 (87%)	93 (87%)
120–139	48 (47%)	39 (39%)	11 (12%)	12 (11%)
140+	1 (1%)	2 (2%)	1 (1%)	2 (2%)
Diastolic				
<79	79 (77%)	77 (76%)	71 (77%)	92 (86%)
80–89	21 (20%)	21 (21%)	19 (21%)	9 (8%)*
90+	3 (3%)	3 (3%)	2 (2%)	6 (6%)

* p < .05.

Table 4. *Univariate Correlates (Pearson) of Systolic and Diastolic Blood Pressure Among Very Low Birth Weight Males and Females*

	Males (n = 103) Blood Pressure		Females (n = 92) Blood Pressure	
	Systolic	Diastolic	Systolic	Diastolic
Maternal Factors				
Married†	−0.08	−0.04	0.01	0.18
Education < High School†	0.15	0.15	−0.07	0.11
Black Race	−0.15	−0.15	0.08	0.21§
Height z-score	0.06	−0.03	0.07	−0.07
Systolic Blood Pressure	0.19	0.11	0.22	0.18
Diastolic Blood Pressure	0.20	0.24*	0.25*	0.38**
Preeclampsia	−0.10	−0.07	0.08	0.15
Birth Data and Health				
Birth Weight	0.02	−0.02	0.04	0.001
Gestational Age	−0.11	−0.03	0.08	0.15
Birth weight z-score	0.13	0.06	−0.09	−0.23*
Birth length z-score	0.24*	−0.01	0.02	−0.04
Small for Gestational Age‡	−0.09	−0.06	0.03	0.14
Delivery by Cesarean Section	−0.22*	−0.05	0.25*	0.04
Multiple Birth	−0.02	−0.09	0.02	0.02
Length of Hospital Stay‖	−0.04	0.09	−0.06	−0.05
Age at Menarche	N/A	N/A	0.05	0.05
Chronic Illness at 20 years	−0.04	−0.16	0.07	0.12

* p < .05; ** p < .01; *** p < .001.
§ p = 0.05.
† The maternal status at the child's eighth year.
‡ < −2SD for gestational age (18).
‖ Spearman correlation.

Table 5. *Univariate Correlates (Pearson) of Growth and Systolic and Diastolic Blood Pressure Among Very Low Birth Weight Males and Females*

	Males (n = 103) Blood Pressure		Females (n = 92) Blood Pressure	
	Systolic	Diastolic	Systolic	Diastolic
Indices of Postnatal Growth				
40 week weight z-score	0.13	0.14	0.01	−0.02
40 week length z-score	0.16	0.07	0.01	−0.01
8 month weight z-score	0.02	0.09	0.08	0.05
8 month length z-score	−0.03	−0.02	0.13	−0.06
20 months weight z-score	0.04	0.09	0.17	0.09
20 months length z-score	0.05	0.08	0.26*	0.12
8 year weight z-score	0.17	0.29**	0.22*	0.08
8 year length z-score	0.05	0.15	0.22*	0.13
8 year BMI z-score	0.17	0.26**	0.14	0.01
20 year weight z-score	0.34¶	0.35¶	0.26*	0.23*
20 year length z-score	0.04	0.05	0.23*	0.16
20 year BMI z-score	0.36¶	0.35¶	0.17	0.19
Distance Growth†				
Weight				
Birth to 20 years	0.15	0.22*	0.25*	0.33**
40 weeks to 20 years	0.14	0.18	0.21	0.21
Length/Height				
Birth to 20 years	−0.25*	0.04	0.22	0.22
40 weeks to 20 years	−0.16	−0.05	0.17	0.12

* p < .05; ** p < .01; ¶ p < .001.
† Change in z-score.

size, *i.e.* 20-y weight and height (Table 6). Tests for birth weight–gender interactions with SBP and DBP in this model were not significant. However, because of clinical implications, we also examined gender-specific differences in BP. These revealed that among male individuals, there was a significant difference in SBP only after adjustment for later size (mean difference 3.2 mm Hg), whereas among the female individuals, the difference was significant both unadjusted and adjusted for later size (3.4 and 3.8, respectively). DBP did not differ between the VLBW and NBW individuals. Examination of the full Lucas model also revealed that 20-y weight but not height had a significant effect on both SBP and DBP both unadjusted and adjusted for birth weight status. There was no significant interaction between 20-y weight or height and birth weight status (data not shown). Examination of the singleton births revealed results similar to those described above.

Model 2: effect of intrauterine growth on BP within the VLBW cohort. This model examined the independent effect of intrauterine growth (defined by the birth weight *z* score) on BP within the VLBW cohort adjusting for maternal education, race, and gender where applicable (see Table 7). Examination of the total population revealed that the birth weight *z* score had no effect on SBP or DBP unadjusted or adjusted for later size. The tests for interaction indicated that the effects were different for male and female individuals when SBP was considered ($p = 0.06$ unadjusted and $p = 0.01$ adjusted for 20-y weight and height) but not for DBP. However, despite the significant interaction, the effect of the birth weight *z* score on SBP was not significant when the male and female individuals were examined separately (Table 7). Among female individuals the β coefficient of the birth weight *z* score was significant both unadjusted and adjusted for current size, indicating that the higher the birth weight *z* score (*i.e.* the better the intrauterine growth), the lower the DBP. Birth weight *z* score had no effect on DBP among male individuals. Complete results of the Lucas model also revealed that 20-y weight but not

Table 6. *Effect of Birth Weight Status (VLBW vs NBW) on Systolic and Diastolic Blood Pressure*

Blood Pressure	Males (n = 204) Difference between VLBW and NBW (95% CI)†	P Value	Females (n = 199) Difference between VLBW and NBW (95% CI)†	P Value	Total Population (n = 403) Difference between VLBW and NBW (95% CI)‡	P Value
Systolic						
Before adjusting for later size§	0.8 (−2.2, 3.8)	0.58	3.4 (0.3, 6.5)	0.03	1.9 (−0.2, 4.1)	0.08
After adjusting for later size§	3.2 (0.1, 6.2)	0.04	3.8 (0.8, 6.8)	0.01	3.5 (1.4, 5.6)	0.001
Diastolic						
Before adjusting for later size§	0.6 (−1.8, 3.0)	0.64	0.5 (−2.0, 3.0)	0.69	0.4 (−1.4, 2.1)	0.67
After adjusting for later size§	2.4 (−0.1, 4.8)	0.06	0.8 (−1.7, 3.2)	0.5	1.4 (−0.25, 3.1)	0.09

† Mean blood pressure difference adjusted for maternal education and race.
‡ Mean blood pressure difference adjusted for education, race, and gender.
§ Later size = 20 year weight and height z-score.

Table 7. *Effect of Growth in Utero (Birth Weight Z-Score) on Systolic and Diastolic Blood Pressure Among VLBW Subjects*

	Males (n = 103)			Females (n = 92)			Total Population (n = 195)		
	β Coeff. of Birth Weight Z-score†	95% CI	P Value	β Coeff. of Birth Weight Z-score†	95% CI	P Value	β Coeff. of Birth Weight Z-score‡	95% CI	P Value
Systolic BP									
Before adjusting for later size§	1.1	−0.5, 2.6	0.18	−0.7	−2.5, 1.1	0.42	0.4	−0.8, 1.5	0.53
After adjusting for later size§	0.9	−0.6, 2.4	0.23	−1.0	−2.8, 0.8	0.26	0.1	−1.0, 1.2	0.83
Diastolic BP									
Before adjusting for later size§	0.4	−0.9, 1.6	0.58	−1.6	−3.2, −0.02	0.047	−0.4	−1.4, 0.6	0.40
After adjusting for later size§	0.2	−1.0, 1.4	0.76	−1.9	−3.5, −0.2	0.03	−1.6, 0.3	−1.6, 0.3	0.19

† Adjusted for maternal education and race.
‡ Adjusted for maternal education, race and gender.

height had a significant effect on SBP and DBP with and without adjustment for the birth weight *z* score. There was no significant interaction between 20-y weight or height and birth weight *z* score (data not shown).

The results were similar when the analyses were performed for singleton births only. Intrauterine growth measured categorically as SGA status (*i.e.* birth weight <−2 SD) had no significant effect on SBP or DBP in male or female individuals. Growth at 40 wk, the expected term date of delivery, similarly had no effect on SBP or DBP (data not shown). The results in models 1 and 2 did not change after inclusion of maternal BP in the analyses.

DISCUSSION

As the initial VLBW survivors of neonatal intensive care have reached young adulthood, there is increasing interest in the predictors of possible chronic sequelae later in life. We examined the effects of VLBW on BP in a cohort of 20-y-old VLBW individuals who were born between 1977 and 1979. Results revealed that VLBW individuals had a higher SBP than the NBW control individuals. These differences bordered on significance after adjustment for maternal race and education and gender and were significant after adjustment for later body size (*i.e.* 20-y weight and height). Among female individuals, the increase in BP was evident after adjustment for maternal education and race and both with and without adjustment for later size. Among male individuals, however, the effect of VLBW on BP was significant only after adjustment for later size. Birth weight status (*i.e.* VLBW *versus* NBW) had no effect on DBP in male or female individuals. Intrauterine growth within the VLBW cohort did not have an effect on SBP in male or female individuals when considered continuously as the birth weight *z* score or categorically as birth weight <−2 SD. However, among female individuals, intrauterine growth had a significant effect on DBP when measured continuously as the birth weight *z* score both adjusted and unadjusted for current size. Growth before 40 wk conceptual age, the equivalent to intrauterine growth among term-born infants, had no effect on SBP or DBP in male or female individuals.

This is the largest study of the effects of VLBW status on BP to date. Its strengths include that we considered gender-specific differences and confounding factors such as maternal BP and catch-up growth. Possible weaknesses include that we did not measure nocturnal or ambulatory BP, and thus an effect of heightened anxiety during measure of the BP in female VLBW individuals cannot be excluded (26). We also have no information on the fathers' BP, maternal smoking during pregnancy (27), or on early nutrition, including breastfeeding (28). Because male individuals have higher birth weights than female individuals, our use of the Usher and McLean growth norms (20), which are not gender specific, may have led to an overestimation of the birth weight *z* score among VLBW male individuals and a corresponding underestimation among VLBW female individuals who have lower birth weights than male individuals. However, additional analyses using the gender-specific birth weight norms of Alexander *et al.* (29) and Kramer *et al.* (30) revealed results similar to those obtained using the norms of Usher and McLean (20). Because we had no information on the specific gestational age of the NBW population, we could not calculate their birth weight *z* score and thus could not examine the effect of their *in utero* growth on BP. We thus examined the effect of birth weight status *per se* (VLBW *versus* NBW) on BP, in which birth weight status represents the overall experience of being born of low birth weight, including the postnatal period. The follow-up rate of VLBW individuals was 78% compared with only 64% of NBW individuals, which might bias the results. The VLBW and NBW groups were similar in terms of maternal sociodemographic characteristics at 8 y of age, when the NBW group was recruited. From 8 to 20 y of age, both groups had greater losses to follow-up among children whose mothers had less education, but more of the losses occurred in the NBW group than in the VLBW group. This resulted in a discrepancy in maternal education between the VLBW and NBW groups at age 20 y. To control for this bias, we adjusted for maternal education in all the analyses.

Reviews of the relationship between birth weight and BP among predominantly term-born populations have revealed that SBP increases with decreasing birth weight, the effect size being 2–3 mm Hg/kg birth weight (31,32). This association between birth weight and BP has been used as evidence to support the "fetal origins hypothesis" of the effects of the early environment on adult cardiovascular and other chronic disease (33). However, the results of the majority of studies on the relationship between birth weight and BP have been based on analyses that adjusted for current weight. This takes into account the change in body size between birth and the time of study, *i.e.* catch-up growth. Adjustment for current body size increases the strength of the association between birth weight and later BP and is considered to give misleading results (24,34–37). Huxley *et al.* (37) on reexamination of all of the available data recently concluded that studies that report a strong inverse association between birth weight and BP may reflect the impact of random error, selective emphasis of certain results, inappropriate adjustment for current body size, and lack of adjustment for other confounding factors such as sociodemographic status and maternal BP (36,37). Schluchter (38) undertook a meta-analysis and similarly concluded that publication bias and heterogeneity of studies may have influenced the reported results.

Similar to our results, other studies of preterm births, the majority being VLBW, have reported a significantly higher mean SBP among preterm survivors compared with term-born NBW control individuals (7,8,39–41). The mean difference in SBP is ~3 mm Hg. This difference has been documented during adolescence (8,39) and young adulthood (7,40,41). Those who specifically examined the association between intrauterine growth and SBP did not find a significant relationship when intrauterine growth was measured as birth weight z score (7,42), birth weight ratio (39,43), or categorically as SGA (40). Similarly, no association has been found between the child's birth weight z score at the time of neonatal discharge, *i.e.* effect of intrauterine and neonatal growth (42,44).

Doyle *et al.* (7), whose cohort is most comparable to ours in year of birth, birth weight, and age of study, followed 145 VLBW and 38 NBW individuals to at least 18 y of age and performed both sphygmomanometer and ambulatory BP measurements. He found that VLBW individuals had a significantly higher mean SBP and DBP than the NBW control individuals and in addition that significantly more of the VLBW individuals had an ambulatory SBP above the 95th percentile. Similar to our findings, he did not find a significant relationship between BP and the birth weight z score or an effect of multiple birth. He earlier reported a significantly higher SBP at age 14 y among individuals who received antenatal steroids to accelerate pulmonary maturity (45). Dessens *et al.* (9), however, reported lower SBP for 20-y-old preterm survivors who received antenatal steroids. VLBW individuals in our cohort did not receive ante- or postnatal steroids.

Correlates of BP in normative populations include gender, race, a family history of hypertension, and other genetic and environmental effects (27,46). Perinatal correlates include maternal anemia (47), pregnancy-induced hypertension, and maternal diet (48–50). Correlates during childhood and adolescence include sodium intake during infancy (51), type of early nutrition (52–55), somatic growth (56,57), obesity, and sexual maturity (46).

It has been postulated that the increase in SBP among preterm survivors may be explained by postnatal experiences associated with prematurity. These include neonatal illness and/or therapy, nutrition, and possibly stress (7,40). There is very little information on these relationships. Singhal *et al.* (42) reported a significantly lower BP among 13-y-old adolescents who were born preterm and received breast milk compared with term or preterm adolescents who received formula, but protein and calorie intake had no effect on the children's BP. In this longitudinal study, breast milk had no effect on SBP when the children were 8 y old (44). The results of Singhal *et al.* need replication because only one quarter of the subjects were followed to age 13 y (44). Calculation of the neonatal sodium intake in this population had no effect on BP when the children were 18 mo of age (58).

Morley *et al.* (59) reported that SBP in 7- to 9-y-old preterm children who were born to smoking compared with nonsmoking mothers was significantly lower among those who were born before 33 wk gestation and significantly higher among those who were born at or after 33 wk gestation. Similar to our results, they did not find a significant relationship between pregnancy-induced hypertension and the children's BP. The nephron number hypothesis of the relationship between poor renal growth and the risk for developing later hypertension also needs to be considered in our cohort (60). Nephrogenesis occurs predominantly between 32 and 36 wk gestation and is completed 4–6 wk before term gestation (61,62). Poor neonatal growth, which is prevalent among VLBW infants during the extrauterine preterm period, may have had detrimental effects on nephrogenesis (15). Kistner *et al.* (41) reported a significantly higher BP in a small group of 15 young adult women who were born at <32 wk gestation but did not find differences in GFR, renal plasma flow, or urinary albumin excretion when they compared them with 18 term-born SGA and 17 NBW control subjects. This suggests that hyperfiltration in individuals with a lower nephron number maintains a normal filtration rate that may predispose to long-term renal consequences (63). Kistner *et al.* also reported abnormal retinal vascularization in the preterm group of women as evidenced by significantly longer retinal arterioles and a reduced number of vascular branching points (64). They and others suggested that this abnormal retinal vascularization, which is independent of retinopathy of prematurity, may indicate a general effect of prematurity on the vascular system (64,65). Elastin synthesis, reported to be limited primarily to the fetal and perinatal period between 20 and 40 wk gestation, may possibly also be affected (66).

The greater effect of birth weight on BP in female individuals that we have found has previously been noted by others (67). Murray *et al.* (68) also reported a negative relationship between birth weight and pulse wave velocity, a measure of arterial compliance in young adult women but not in men. We previously reported that catch-up growth occurred by age 20 y among the VLBW women but not among the men (6). This may partly explain the gender-specific effect of birth weight status (VLBW *versus* NBW) on SBP and the effect of growth *in utero* (*i.e.* birth weight z score) on DBP among our VLBW female individuals. The positive relationship between the velocity of weight gain during childhood and adolescence and BP is well recognized in normative populations (46,56,57,69,70). Catch-up growth in children of lower birth weight (71), in children who were born SGA (72), or after postnatal failure to thrive (73) is similarly associated with higher BP levels.

We conclude that VLBW young adult women have a significantly higher SBP than NBW control subjects. This together with their greater catch-up in growth during childhood and adolescence puts them at greater risk for future cardiovascular sequelae. It has been shown that the higher the BP in a nonhypertensive population, the greater the risk for development of hypertension in later life (74,75). The mean difference in SBP of 3 mm Hg in population BP, although minor, may be of significance for the development of later life hypertension, coronary heart disease, and resultant death as a result of cardiovascular disease (76). Anticipatory guidance and periodic monitoring of BP of VLBW survivors, especially among women, thus is advisable.

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