Growth of Very Low Birth Weight Infants to Age 20 Years

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ABSTRACT. *Objective.* **Intrauterine and neonatal growth failure of very low birth weight (VLBW; <1500 g) infants may influence adult growth attainment and have long-term implications for adult health. As part of a longitudinal study of VLBW infants, we sought to examine gender-specific changes in growth from birth to 20 years old and to identify the correlates of growth attainment at 20 years old.**

Design, Setting, Participants. **A cohort of 103 male and 92 female VLBW infants who had a mean birth weight of 1189 g and mean gestational age of 29.8 weeks, were born from 1977 through 1979 and treated at Rainbow Babies and Children's Hospital in Cleveland, Ohio, and were free of neurosensory impairment were followed prospectively from birth and compared with a population-based sample of 101 male and 107 female normal birth weight (NBW) controls selected at 8 years old. Maternal sociodemographic status and infant birth and neonatal data did not differ significantly between male and female VLBW subjects. However, male VLBW subjects had significantly higher rates of rehospitalization during infancy than female VLBW (39% vs 21%). At 20 years, their rates of chronic illness were similar (18% vs 24%).**

Main Outcome Measures. **Weight and height *z* scores were computed at birth, 40 weeks, 8 and 20 months, and 8 and 20 years among the VLBW subjects, and at 8 and 20 years among the NBW controls. Body mass index (BMI) *z* scores were computed at 8 and 20 years. Among the VLBW subjects, gender-specific longitudinal growth measures were examined at birth, at the expected term date (40 weeks corrected age), and at 8 and 20 months, and 8 and 20 years of age. In addition, we compared the weight, height, and BMI of the VLBW and NBW controls at 8 and 20 years. Predictors of 20-year growth were examined via multivariate analyses.**

Results. **Among the VLBW males, mean weight for age *z* scores at birth, 40 weeks, and 8 years were −0.7, −1.8, and −0.5; and height for age *z* scores were −1.2, −2.6, and −0.5, respectively. For VLBW females, mean weight for age *z* scores were −1.1, −2.0, and −0.2 and height for age *z* scores were −1.2, −2.4, and −0.2, respectively. At 8 years of age, VLBW males had a significantly lower mean weight, height, and BMI than NBW controls, whereas VLBW females differed significantly from their NBW controls in mean weight and BMI but not in height. Catch-up growth in weight, height, and BMI occurred between 8 and 20 years among VLBW females but not among VLBW males who remained significantly smaller than their controls at 20 years old. At 20 years mean weight of VLBW males was 69 kg versus 80 kg for controls (*z* score −0.4 vs +0.5); mean height was 174 cm versus 177 cm (*z* score −0.4 vs +0.03) and mean BMI was 23 versus 26, respectively. For VLBW females, mean weight was 65 kg versus 68 kg for controls (*z* score +0.3 vs +0.5), mean height was 162 versus 163 cm (*z* score −0.3 vs −0.1) and mean BMI was 25 versus 25, respectively. Rates of obesity (BMI >30) for VLBW males were 7% compared with 15% for controls and for VLBW females 15% compared with 18% for controls. Age of menarche was 12.4 years for VLBW females and 12.3 years for controls.**

Nineteen (18%) male and 20 (22%) female VLBW subjects were born small for gestational age (SGA; weight less than −2 standard deviation for gestational age). At 20 years, significantly more SGA than appropriate for gestational age VLBW males remained subnormal (less than −2 standard deviation) in weight (32% vs 6%) and height (21% vs 4%), whereas rates of subnormal growth did not differ significantly between SGA and appropriate for gestational age females (weight 5% vs 1%, height 0% vs 7%).

Predictor variables included in the multivariate analyses of 20-year growth attainment were maternal education and height, race, birth weight *z* score (a measure of intrauterine growth failure), neonatal hospital stay (a measure of neonatal illness), and chronic illness at 20 years.

Twenty-year weight was predicted by black race and chronic illness among females. Twenty-year height was predicted by maternal height and birth weight *z* score among both males and females and by duration of neonatal hospital stay among males only. In a separate model, when we examined the effect of being SGA at birth instead of the effect of birth weight *z* score, SGA birth was predictive of 20-year height among males but not among females.

Conclusions. **VLBW females catch up in growth by 20 years of age whereas VLBW males remain significantly shorter and lighter than controls. Since catch-up growth may be associated with metabolic and cardiovascular risk later in life, these findings may have implications for the future adult health of VLBW survivors.** ***Pediatrics*** **2003;112:e30–e38. URL: http://www.pediatrics.org/cgi/content/full/112/1/e30;** ***growth, adult, very low birth weight.***

ABBREVIATIONS. VLBW, very low birth weight; NBW, normal birth weight; BMI, body mass index; SGA, small for gestational age; AGA, appropriate for gestational age; SD, standard deviation; CDC, Centers for Disease Control and Prevention.

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Disturbances of intrauterine and postnatal growth during critical periods of human development may have long-term implications for adult health. It has been hypothesized that adaptations the fetus or young infant makes when undernourished induce alterations in metabolism, hormonal output, and distribution of cardiac output, which result in central obesity, diabetes, and cardiovascular disease in middle age.[1] There is also evidence that subjects who demonstrate catch-up growth are at greatest risk for these sequelae.[2–5] Studies of the long-term growth of very low birth weight (VLBW) infants (those weighing <1500 g), the majority of whom experience intrauterine and/or neonatal growth failure may thus yield important information in this regard.[6–9] Recent reports of the adolescent growth attainment of VLBW infants indicate that catch-up occurs during childhood; however, they continue to lag behind in growth when compared with normal birth weight (NBW) controls.[10–15] The only report of the adult growth attainment of VLBW infants is a report of 19-year-old male conscripts to the Swedish army that found that those born with VLBW were shorter and lighter than the rest of the population.[16] There have been no reports of adult growth attainment of VLBW women.

As part of a longitudinal study of the outcomes of VLBW infants we sought to examine gender-specific changes in growth from birth to 20 years and to identify the correlates of growth attainment at 20 years old.[17–19]

METHODS

VLBW Group

A cohort of 490 VLBW infants was admitted to Rainbow Babies and Children's Hospital in Cleveland, Ohio, between 1977 and 1979, of whom 312 children (64%) survived. Seventy subjects were lost to follow-up and 242 (78%) subjects were followed to 20 years of age.[20] Forty-seven subjects were excluded from the present 20-year study of growth; 25 had neurosensory impairments, 1 had Liddles syndrome, 12 women were pregnant, and 9 had missing growth measurements. The population thus included 195 VLBW subjects who had weight and height measures at 20 years old. They constituted 68% of the birth cohort who did not have neurosensory impairments. They had a mean birth weight of 1189 g and mean gestational age of 29.8 weeks; 105 were black and 90 white; 103 were male and 92 female. Length was measured at birth in 72 of the males and 59 of the females. Height was measured in 159 of their mothers.

A description of maternal sociodemographic status, infant data, and rates of rehospitalization of the VLBW cohort is presented in Table 1. Males and females did not differ in maternal sociodemographic status or in infant birth data, but the males had significantly higher rates of rehospitalization before 8 months. At 20 years, 18% of the males and 24% of the females reported chronic conditions ($P = .29$). These included medical or psychiatric illness lasting 12 months or more.[20]

The 20-year-old participants 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 females (47% vs 61%), attributable to the exclusion of those pregnant at the time of study. The female participants had a significantly shorter neonatal hospital stay than the female nonparticipants ($P < .05$). Female participants who had birth length measures had a significantly higher birth weight and gestational age than those without birth length measures ($P < .05$). Fewer of the mothers who had height measured compared with those who did not have height measured ($n = 36$) had less than high school education (13% vs 36%, $P < .01$), although they did not differ in marital status, race, or in their children's birth data.

NBW Control Group

The original control group included 366 NBW children born in 1977, 1978, and 1979, who were selected at age 8 years by means of a population sampling procedure.[21] Two hundred thirty-three (64%) were followed to 20 years old, of whom 25 were excluded from the growth study; 1 had neurosensory impairment, 9 women were pregnant, and 15 had missing growth measures. The control population thus included 208 participants. They constituted 57% of those recruited at 8 years of age. Height was measured in 180 of their mothers.

The 208 controls had a mean birth weight of 3277 g. They were born at term gestation (>37 weeks); however, specific information on their gestational age was not available: 110 were black and 98 white; 101 were male and 107 female. They did not differ in birth

TABLE 1. Maternal Demographic Status and Infant Birth and Neonatal Data for Male and Female VLBW 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%)
Preclampsia	15 (15%)	7 (8%)
Birth and neonatal data		
Birth weight (mean g ± SD)	1192 ± 213	1187 ± 215
Gestational age (mean wk ± SD)	29.6 ± 2.2	30.0 ± 2.3
SGA‡	19 (18%)	20 (22%)
Multiple birth	18 (18%)	20 (22%)
Born at perinatal center	56 (54%)	37 (41%)
Respiratory distress syndrome	79 (77%)	64 (70%)
Endotracheal ventilation	20 (19%)	11 (12%)
Sepsis	14 (14%)	10 (11%)
Neonatal hospital stay (median, range)	58 (12–365)	55 (7–456)
Rehospitalization		
Before 8 mo§	40 (39%)¶	19 (21%)¶
Between 8 and 20 mo§	13 (13%)	10 (11%)

* The maternal status at the child's eighth year.
‡ Less than −2 SD.[26]
§ Age corrected for preterm birth.
¶ $P < .01$.

weight or gender from the 156 nonparticipants, but 10% of the participants' mothers had less than high school education compared with 26% of the nonparticipants' mothers; 64% versus 42% were married and 53% versus 75% were black ($P < .001$ for all comparisons). The mothers who had height measured did not differ in race, education, or marital status from those not measured.

Comparison of VLBW to Control Group

Fewer mothers of the VLBW participants than mothers of the controls had graduated from high school (17% vs 10%, respectively, $P < .05$). They did not differ in marital status (59% vs 64% married) or race (54% vs 53% black). Age of menarche was 12.4 years for the VLBW and 12.3 years for the NBW participants ($P = .55$).

Follow-up Protocol

The methods of neonatal care have been previously described.[9,22] Weight and length were measured at birth and longitudinally at the expected term date of delivery (40 weeks after the last menstrual period), and then at 8 months, 20 months, and 8 years of age corrected for preterm birth, and at 20 years postnatal age. Participants were weighed unclothed at all time periods before 20 years. At 20 years, they 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 females and 1.0 kg from that of males.[23,24] At birth, length was measured with a tape measure in the isolette or crib. At 40 weeks and at 8 and 20 months, length was measured supine using a Harpenden Infantometer. At 8 and 20 years, standing height was measured with a Harpenden Stadiometer after removing shoes and stockings.[25]

At birth and at the corrected term date, weight and length z scores (ie, standard deviation [SD] scores) were computed from the intrauterine growth standards of Usher.[26] We used these norms, which include mainly white infants and are not sex-specific because available intrauterine growth data in the United States do not include length or head circumference[27–29]. At 8 and 20 months and 8 and 20 years, weight and height z scores were computed from the revised Centers for Disease Control and Prevention (CDC) growth data, which are sex-specific.[30] We used z scores because they provide a more sensitive assessment of growth than percentile cut-offs.[25,31] Because clinicians are interested in classifying children categorically, participants were also categorized as having subnormal weight or height if the measure fell below −2 SD for age.[30] We used the 20-year norms for the 12 subjects (7 male, 5 female) who were 21 years and older. 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 years.[30] The study was approved by the Institutional Review Board of University Hospitals of Cleveland and written informed consent obtained from all participants.

Documentation of Correlates of Growth

Variables examined for their relationship to growth included maternal marital status, level of education, race, height, and preeclampsia. Infant data considered included birth weight, gestational age, the birth weight z score used as a measure of intrauterine growth, multiple birth, 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.[32,33] Rehospitalization was used as a measure of morbidity during infancy. Additional variables included age at menarche and chronic illness at 20 years, which had lasted 12 months or more. We used the mother's educational status at the time the child was 8 years old as a proxy for social class, because it was considered to span childhood and be more relevant to child growth and development than their 20-year educational status.[20] Results pertaining to head circumference measures and their correlates will be the subject of a separate report.

Data Analysis

The analyses were conducted separately for male and female participants. Within the VLBW cohort, we first examined weight, length, and BMI and their respective z scores at each time of study. We also compared the VLBW and NBW controls, using 2 sample t tests at 8 years and 20 years of age with regard to weight, height, BMI, and their respective z scores. This comparison was made because our Cleveland population differs sociodemographically from the national population used for the CDC norms.[30] The results of the comparisons were adjusted for maternal level of education and race via multiple linear regression.

We initially performed univariate linear regression analyses to examine the effects of the potential correlates of the weight, height/length, and BMI z scores at 20 years. Multivariate linear regression analyses were then performed with maternal level of education and race entered together with the main factors found to be significant in the univariate analyses. In separate models, we examined the effects of being small for gestational age (SGA; less than −2 SD birth weight for gestation), the effect of multiple birth, and among females, the effect of age of menarche. Logistic regression was also used to examine correlates of subnormal (less than −2 SD) weight and height at 20 years old.

RESULTS

Growth From Birth to 20 Years

Weight

The mean weight z scores at birth for VLBW males and females were −0.73 and −1.12, respectively. These decreased to −1.79 and −2.0 by 40 weeks because of neonatal growth failure and then in-

TABLE 2. VLBW Participants: Weight and Height Measures From Birth to 20 Months Corrected Age

	Weight				Height			
	N	Mean ± SD (kg)	z Score ± SD*	Less Than −2 SD*	N	Mean ± SD (cm)	z Score ± SD*	Less Than −2 SD*
Males†								
Birth	103	1.2 ± 0.2	−0.73 ± 1.34	19 (18%)	72	38 ± 3	−1.18 ± 2.16	19 (26%)
40 wk (term)	101	2.6 ± 0.7	−1.79 ± 1.44	58 (57%)	85	46 ± 3	−2.56 ± 1.71	51 (60%)
8 mo	99	7.8 ± 1.3	−1.70 ± 1.48	38 (38%)	96	69 ± 4	−0.94 ± 1.53	22 (23%)
20 mo	100	11.0 ± 1.7	−1.16 ± 1.43	24 (24%)	100	83 ± 5	−0.55 ± 1.26	13 (13%)
Females§								
Birth	92	1.2 ± 0.2	−1.12 ± 1.09	20 (22%)	59	39 ± 3	−1.22 ± 1.65	17 (29%)
40 wk (term)	90	2.5 ± 0.5	−2.00 ± 1.02	45 (50%)	75	46 ± 3	−2.38 ± 1.38	45 (60%)
8 mo	91	7.6 ± 1.2	−1.09 ± 1.35	19 (21%)	91	68 ± 4	−0.51 ± 1.18	9 (10%)
20 mo	90	10.8 ± 1.5	−0.82 ± 1.37	16 (18%)	89	83 ± 5	−0.16 ± 1.37	9 (10%)

* Usher's norms used at birth and 40 weeks[26] and CDC norms[30] at 8 months and 20 months corrected age.

† For males, mean corrected ages for growth measures were 40.3 weeks at the term assessment, 8.6 months at the 8-month assessment, and 21.1 months at the 20-month assessment.

§ For females, mean corrected ages for growth measures were 39.9 weeks at the term assessment, 8.5 months at the 8-month assessment, and 20.5 months at the 20-month assessment.

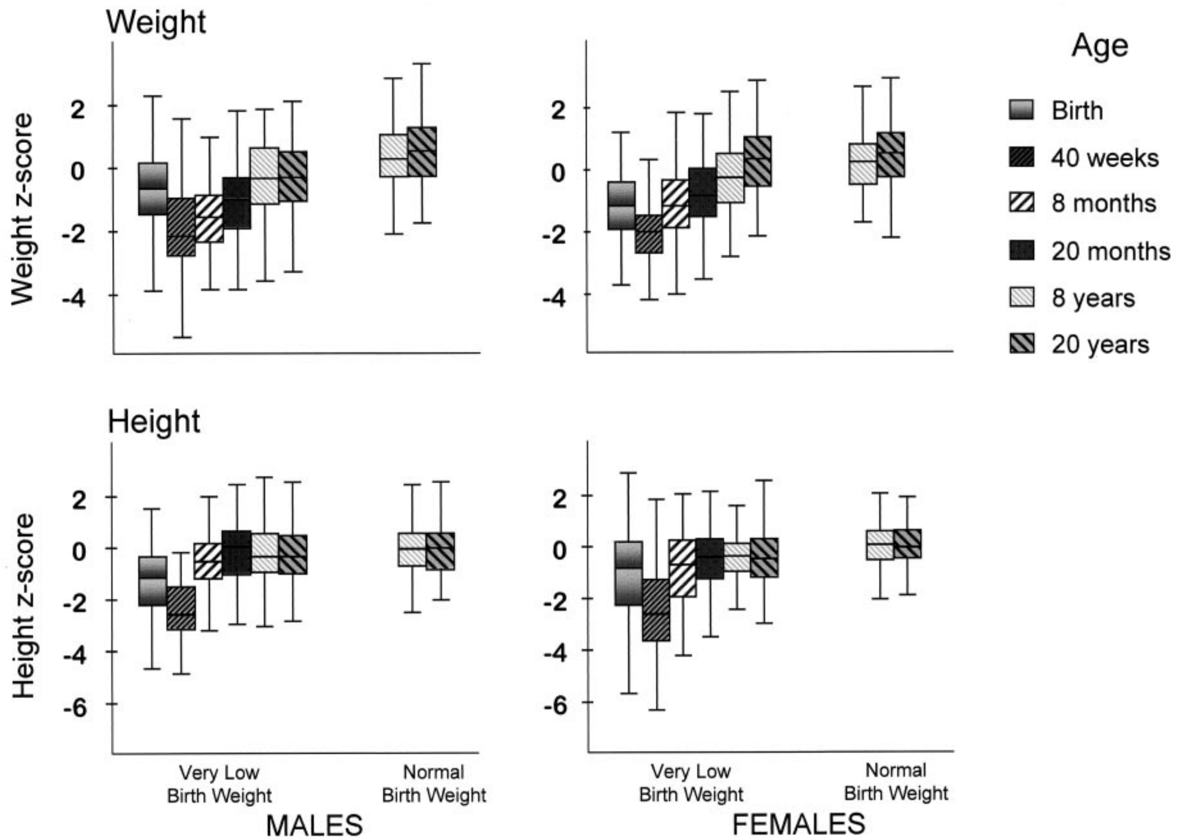

Fig 1. Weight and height *z* scores at each age, contrasted between males and females. Box plots show median (solid line in box), the interquartile range (top and bottom of the box), and the range of the data.

creased to −0.35 and +0.26, respectively, by 20 years (Tables 2 and 4 and Fig 1). The decrease in weight *z* score from birth to 40 weeks was similar among males and females (Table 3). However, between 40 weeks and 8 months, and between 8 years and 20 years, VLBW females demonstrated a significantly greater increase in weight *z* score than males. In contrast, among the NBW controls, the increases in weight *z* score between 8 years and 20 years were similar for males and females.

Compared with their NBW controls, VLBW males and females had significantly lower mean weight *z* scores at 8 years of age. These differences persisted among the males at 20 years, whereas among the females they were no longer significant. At 20 years, VLBW males weighed a mean of 11 kg less than their NBW controls, whereas the females weighed only 2 kg less than their controls (Table 4).

Height

The mean length *z* scores at birth for VLBW males and females were −1.18 and −1.22, respectively. These decreased to −2.56 and −2.38 by 40 weeks and increased to −0.44 and −0.26 by 20 years (Tables 2, 4, and Fig 1).

The decrease in length *z* scores from birth to 40 weeks and the later increases in height *z* scores between the various time periods of the study did not differ significantly between males and females (Table 3).

Compared with their NBW controls, VLBW males had significantly lower mean height *z* scores at both

TABLE 3. Distance Growth of Weight and Height Expressed as Changes in *z* Scores Between Time Periods of Study

Changes in *z* Scores	Weight			Height		
	Males	Females	*P*	Males	Females	*P*
VLBW*						
Birth to 40 wk	−1.05	−0.88	0.36	−1.32	−1.13	0.60
40 wk to 8 mo	0.20	0.93	<0.001	1.78	1.97	0.44
8 mo to 20 mo	0.53	0.27	0.06	0.39	0.32	0.66
20 mo to 8 y	0.66	0.58	0.63	0.09	−.06	0.29
8 y to 20 y	0.13	0.49	0.002	0.03	−0.09	0.24
NBW						
8 y to 20 y	0.20	0.25	0.67	0.01	−0.08	0.39

* Age corrected for preterm birth until 8 years of age.

TABLE 4. Comparison of Weight, Height, and BMI Between VLBW and NBW Participants at 8 and 20 Years

	Males			Females		
	VLBW (N = 103)	NBW (N = 101)	Mean Difference or Odds Ratio†§ (95% CI)	VLBW (N = 92)	NBW (N = 107)	Mean Difference or Odds Ratio†§ (95% CI)
8 y††						
Weight¶						
Mean (kg ± SD)	26.9 ± 5.1	31.1 ± 6.3	−4.3 (−5.9, −2.7)***	28.0 ± 6.3	31.7 ± 8.1	−3.6 (−5.7, −1.5)**
z score ± SD	−0.46 ± 1.31	0.34 ± .96	−0.78 (−1.10, −0.46)***	−0.23 ± 1.14	0.20 ± 1.10	−0.39 (−0.71, −0.07)*
Less than −2 SD	11 (11%)	1 (1%)	10.6 (1.3, 85.3)*	3 (4%)	2 (2%)	2.0 (0.3, 13.2)
Height¶						
Mean (cm ± SD)	129.2 ± 6.4	133.1 ± 5.9	−3.9 (−5.6, −2.1)***	130.2 ± 7.6	133.2 ± 7.0	−2.9 (−5.0, −0.8)**
z score ± SD	−0.45 ± 1.04	0.02 ± 0.91	−0.46 (−0.74, −0.18)**	−0.20 ± 1.16	0.03 ± 1.04	−0.21 (−0.52, 0.10)
Less than −2 SD	8 (8%)	3 (3%)	2.6 (0.7, 10.3)	5 (6%)	2 (2%)	2.7 (0.5, 15.0)
BMI						
Mean (kg/m² ± SD)	16.0 ± 2.2	17.4 ± 2.6	−1.5 (−2.1, −0.8)***	16.3 ± 2.3	17.7 ± 3.1	−1.3 (−2.1, −0.5)**
z score ± SD	−0.35 ± 1.21	0.38 ± 0.94	−0.72 (−1.03, −0.42)***	−0.16 ± 1.05	0.29 ± 1.03	−0.41 (−0.72, −0.11)**
20 y§§						
Weight						
Mean (kg ± SD)	69.2 ± 13.9	79.9 ± 16.7	−10.5 (−14.8, −6.2)***	64.9 ± 16.8	67.6 ± 18.3	−2.0 (−6.9, 2.8)
z score ± SD	−0.35 ± 1.25	0.53 ± 1.06	−0.86 (−1.19, −0.54)***	0.26 ± 1.17	0.45 ± 1.16	−0.14 (−0.47, 0.18)
Less than −2 SD	11 (11%)	0	−‡ (2.23, ∞)	2 (2%)	3 (3%)	0.8 (0.1, 5.1)
Height						
Mean (cm ± SD)	173.7 ± 7.9	177.0 ± 6.8	−3.1 (−5.2, −1.1)**	161.7 ± 7.3	163.0 ± 7.0	−1.2 (−3.2, 0.9)
z score ± SD	−0.44 ± 1.10	0.03 ± 0.95	−0.44 (−0.72, −0.15)**	−0.26 ± 1.13	−0.06 ± 1.08	−0.18 (−0.50, 0.14)
Less than −2 SD	7 (7%)	3 (3%)	2.3 (0.6, 9.3)	5 (5%)	1 (1%)	4.0 (0.4,36.4)
BMI						
Mean (kg/m² ± SD)	22.9 ± 4.2	25.5 ± 4.9	−2.6 (−3.8, −1.3)***	24.7 ± 5.2	25.4 ± 6.2	−0.5 (−2.1, 1.0)
z score ± SD	−0.33 ± 1.24	0.42 ± 1.09	−0.75 (−1.08, −0.43)***	0.42 ± 0.93	0.45 ± 1.24	0.03 (−0.27, 0.34)

CI indicates confidence interval.
* $P < .05$.
** $P < .01$.
*** $P < .001$.
† Adjusted for maternal education and race.
§ Odds ratio pertains to rates of subnormal (less than −2 SD) weight and height.[30]
‡ Infinite odds ratio.
¶ 99 male and 87 female VLBW and all the NBW subjects had weight and height measurements at age 8 years.
†† For males, mean age at the 8-year assessment was 8.7 years for VLBW and 8.9 years for NBW subjects. For females, mean age at the 8-year assessment was 8.6 years for VLBW and 9.0 years for NBW subjects.
§§ For males, mean age at the 20-year assessment was 20.2 years for VLBW and 20.1 years for NBW subjects. For females, mean age at the 20-year assessment was 20.1 years for VLBW and 20.1 years for NBW subjects.

8 and 20 years, whereas the females did not differ significantly from their controls at either 8 or 20 years.

The mothers of the VLBW males tended to be shorter than mothers of controls (mean height 161.6 vs 163.5 with z scores of −0.26 and 0.02, respectively, P = .06). The mean height of mothers of the VLBW females was similar to that of their control mothers (162.3 vs 163.1 cm with z scores of −0.16 and −0.04, respectively, P = .48). There was a significant relationship between the maternal height z score and that of her young adult child; r = 0.50 and 0.32 for VLBW males and females and their mothers, respectively, and r = 0.44 and 0.57 for the NBW controls and their mothers, respectively (all $P < .05$).

BMI

Compared with their NBW controls, the VLBW males had a significantly lower BMI at both 8 years and 20 years, whereas the VLBW females differed from their controls at 8 years but not at 20 years (Table 4). This was because of the significantly greater female increase in BMI z score between 8 and 20 years (0.58 vs 0.02, $P < .001$). At 20 years, 6% of the VLBW males were underweight (BMI <18.5) compared with 2% of their controls; 18% versus 29% were overweight (BMI 25–29.9) and 7% versus 15%, respectively, were obese (BMI ≥30; χ^2 for trend, P = .02).[25] In contrast, at 20 years 2% of the VLBW females were underweight compared with 7% of the controls; 21% vs 23% were overweight, and 15% vs 18%, respectively, were obese (χ^2 for trend, P = .36).

Growth Outcomes of SGA Infants

Nineteen (18%) male and 20 (22%) female VLBW participants had a subnormal (less than −2 SD) birth weight for gestational age and were considered SGA.[26] The rates of subnormal growth attainment for the SGA and appropriate for gestational age (AGA) subjects at the various time points of study are presented in Fig 2. At 20 years, significantly more SGA than AGA males remained subnormal (less than −2 SD) in weight (32% vs 6%, P = .005) and in height (21% vs 4%, P = .02), whereas SGA females did not differ significantly from their AGA counterparts in rates of subnormal weight (5% vs 1%, P = .39) or subnormal height (0% vs 7%, P = .58).

Correlates of 20-Year Weight, Height, and BMI z Scores

Predictor variables included in the multivariate analyses of 20-year growth attainment were maternal education, race, maternal height, birth weight z score, the neonatal hospital stay, and chronic illness. Among females, black race and chronic illness were

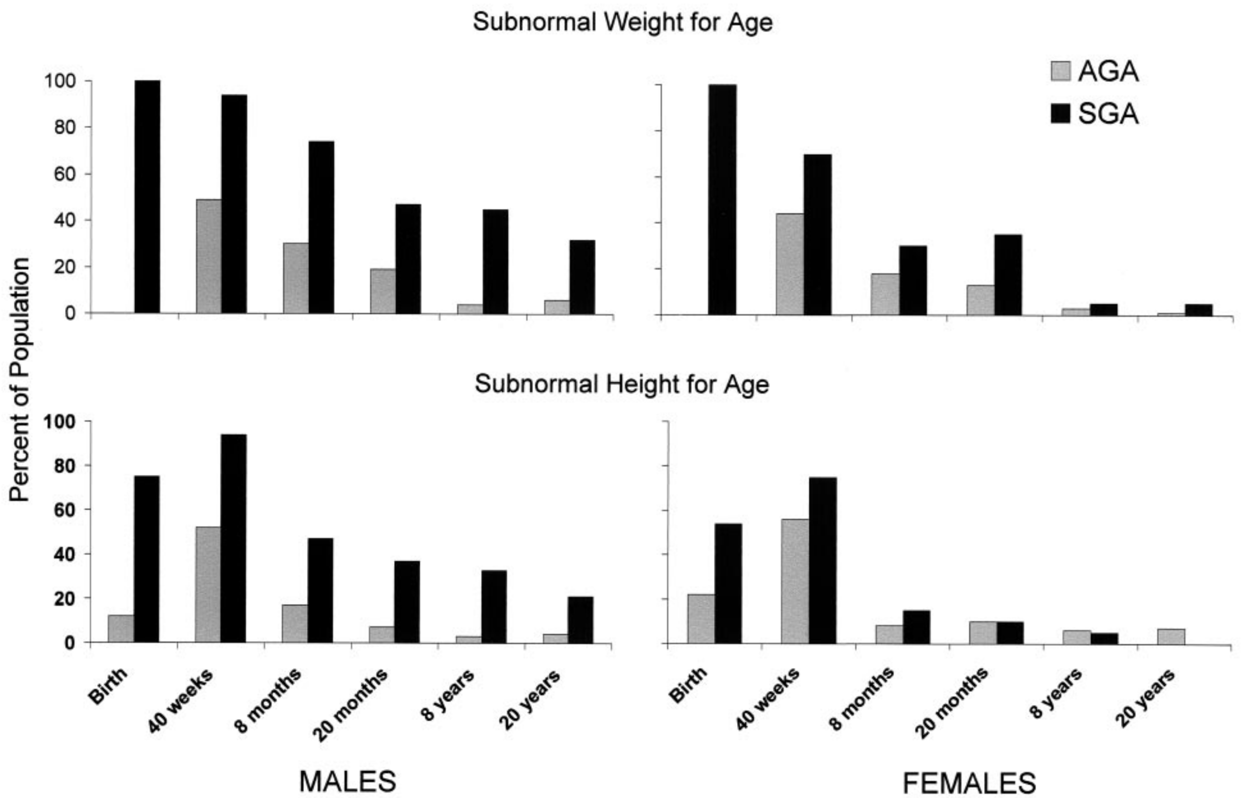

Fig 2. Percentage of VLBW infants born AGA or SGA (less than −2 SD[26]) with subnormal (less than −2 SD[30]) weight or height for age at birth, 40 weeks, 8 months, 20 months, and 8 years corrected age and at 20 years postnatal age.

significantly related to the weight *z* score, whereas among males no individual factor was significant (Table 5). Among both males and females, maternal height and birth weight *z* score were significantly related to the 20-year height *z* score, whereas length of hospital stay was significant for males only. This model explained 40% of the variance in 20-year height attainment among males and 16% of the variance among females. When correlates of BMI were examined, maternal education was significantly related to the 20-year BMI *z* score among males, whereas black race and the presence of chronic illness were related to the 20-year BMI *z* score among females (Table 5).

When we used separate models to examine the effect of being SGA at birth instead of the effect of the birth weight *z* score, the findings were similar, with the exception that among males maternal education also predicted 20-year height and being SGA was not predictive of 20-year height among females. In a separate model when the effect of age of menarche was examined in females, age of menarche predicted 20-year BMI but not 20-year weight and height.

Compared with the singleton births, the 38 participants who were of multiple birth (35 twins and 3 triplets) had a significantly lower birth weight *z*-score (−1.47 vs −0.78, $P = .002$) and higher rates of subnormal intrauterine growth, ie, more were SGA at birth (40% vs 15%, $P < .001$). In a model that examined the correlates of 20-year growth for singleton births only, the results were similar to those when multiple births were included, with the exception that among singleton males the birth weight *z* score was not related to the 20-year height *z* score, and among singleton females, maternal height was related to the 20-year weight *z* score. Exclusion of multiple births from the model thus resulted in a diminished effect of the birth weight *z* score on height attainment among males.

DISCUSSION

This is the first report of the gender-specific trajectory of the growth of VLBW infants born during the initial years of neonatal intensive care and followed to young adulthood. The outcomes described in this report pertain to VLBW infants born in the 1970s. Since that time, progressive advances in neonatal intensive care have increased survival. However, the rates of intrauterine growth failure and of the neonatal complications of prematurity have not changed. Furthermore, neonatal growth failure continues to be a major problem, especially among the smallest and sickest infants.[8,34] Our findings thus have relevance to current survivors.

The results reveal that male and female VLBW infants had similar rates of intrauterine and neonatal growth failure. However, the females demonstrated greater catch-up in growth than their male counterparts such that by 20 years old they did not differ significantly in weight, height, or BMI when compared with their NBW peers. In contrast, the VLBW males remained shorter and weighed less than their NBW controls. The negative effect of neonatal illness on 20-year height attainment was greater among males, whereas the positive effects of black race and chronic illness on 20-year weight and BMI were

TABLE 5. Multivariate Analysis of Correlates of Weight, Height, and BMI *z* Scores at 20 Years of VLBW Males and Females

Independent Variables	Weight		Height		BMI	
	β Coefficient‖	95% CI	β Coefficient‖	95% CI	β Coefficient‖	95% CI
Males						
Education†						
<High school	−0.57	−1.16, 0.03	0.005	−0.43, 0.44	−0.68	−1.33, −0.04*
High school	−0.32	−1.29, 0.66	−0.60	−1.31, 0.11	0.001	−1.05, 1.06
Race (black)§	0.35	−0.21, 0.92	0.13	−0.28, 0.54	0.38	−0.23, 1.00
Maternal height (cm)	0.03	−0.01, 0.08	0.07	0.04, 0.10***	−0.005	−0.05, 0.04
Birth weight *z* score	0.10	−0.09, 0.30	0.18	0.04, 0.32*	0.01	−0.20, 0.22
Neonatal stay‡	−0.07	−0.72, 0.57	−0.62	−1.09, −0.15*	0.21	−0.49, 0.92
Chronic illness§§	−0.43	−1.20, 0.33	0.08	−0.48, 0.64	−0.56	−1.39, 0.27
R^2	0.13		0.40		0.10	
Females						
Education†						
<High school	−0.10	−0.71, 0.52	−0.09	−0.66, 0.48	−0.07	−0.55, 0.42
High school	0.17	−0.66, 1.00	−0.27	−1.03, 0.50	0.21	−0.44, 0.87
Race (black)§	0.63	0.12, 1.14*	0.24	−0.23, 0.71	0.54	0.14, 0.95**
Maternal height (cm)	0.03	−0.01, 0.07	0.04	0.01, 0.08*	0.01	−0.02, 0.04
Birth weight *z* score	0.12	−0.11, 0.34	0.21	0.004, 0.42*	0.001	−0.18, 0.18
Neonatal stay‡	0.07	−0.36, 0.49	−0.09	−0.48, 0.31	0.16	−0.18, 0.49
Chronic illness§§	0.85	0.22, 1.49**	−0.07	−0.65, 0.52	0.78	0.27, 1.28**
R^2	0.23		0.16		0.26	

CI indicates confidence interval.
* $P < .05$.
** $P < .01$.
*** $P < .001$.
‖ Refers to the unstandardized coefficient of the independent variable in the linear regression model with weight *z* score as the dependent variable and containing maternal education, race and height, birth weight *z* score, neonatal hospital stay and chronic illness.
† Maternal status at child's eighth year. Reference group consists of mothers with more than high school education.
§ Maternal race used, coded as 1 black, 0 white.
‡ Natural log of the length of the neonatal hospital stay (in days).
§§ At 20 years. Includes medical or psychiatric illness lasting 12 months or more.

greater among females. The effects of maternal height on their children's height and of intrauterine growth failure were similar for males and females. We included multiple births in the study because they constitute a fairly large proportion of VLBW births. Their high rates of intrauterine growth failure explain the diminished effect of the birth weight *z* score on growth when only singletons were included in the multiple regression analyses of growth.

The strengths of this longitudinal study include its gender specificity, its large size, and the use of *z* scores, which are comparable across ages and provide a more sensitive assessment of deviations of growth than the use of percentiles or cut-offs of subnormal growth.[25,31] Consideration of possible weaknesses include the lack of the fathers' height, of parents' weight, of information concerning neonatal and childhood nutritional intake, and of the timing of puberty among males. We may have underestimated final height for some males who can grow after 20 years old, although the vast majority attain final height by 18 years old.[35–37] Similar to other studies, length measures at birth were missing for about a third of the VLBW subjects, mainly because of the difficulty in stretching immature and sick infants.[11,38] This difficulty may also explain the lower mean birth-length *z* scores when compared with the corresponding mean birth weight *z* scores. The female participants had a significantly shorter neonatal hospital stay and thus less neonatal morbidity than nonparticipants, which might have contributed to their better growth attainment. Because males have higher birth weights than females,[27,28] our use of the Usher growth norms, which are not gender-specific, may have led to an overestimation of the birth weight *z* scores among males and a corresponding underestimation among females, thus influencing the results of the multiple regression analyses. However, additional analyses using sex-specific birth weight norms of both Alexander and Kramer[27,28] revealed the effects of the birth weight *z* score on growth to be similar to those using Usher's norms, reassuring the validity of our results (data not shown).

We and others have previously identified significant correlates of growth and catch-up among VLBW infants including the negative effects of intrauterine growth failure during childhood and into adolescence;[9,10–12,15,17,33,38–41] of neonatal complications during infancy and early childhood;[8,9,17,33,39] and of parental height during childhood and adolescence.[12,13,15,38,41,42] Thus, it is not surprising that these effects persist into adulthood.

Similar to our findings of poor catch-up growth among VLBW males, inferior rates of catch-up growth have been reported for male term-born SGA children at 4 years and among males with birth weights of <1000 g at 14 years.[12,43] Saigal[12] similarly reported that females with birth weights of <1000 g had a greater increase in BMI than males between age 8 and 14 years. The sex differences in growth are probably multifactorial. The greater susceptibility of VLBW males to neonatal complications is well described.[44] In our population, males had higher rates of respiratory distress syndrome and a longer neonatal hospital stay than females, but the differences were not significant. Their higher rates of rehospitalization and inferior growth between 40 weeks and 8 months are indicative of poor health resulting from neonatal sequelae. Genetic potential may also have played a role since mothers of the male VLBW subjects tended to be shorter than mothers of their controls.

The ability to catch-up in weight among females might be partly related to their lesser neonatal and early childhood morbidity. We and others have noted a similar age of menarche, a correlate of growth, for the VLBW females and their NBW controls.[10–12,41,45] The relationship of black race to 20-year weight and BMI attainment among the VLBW females in our cohort is in agreement with the reported association between black race, female sex, and obesity.[46,47] The positive relationship between chronic illness and 20-year weight and BMI among our VLBW females is also in agreement with the reported relationship between asthma and BMI in women.[48,49] We found little evidence in our population of a relationship between social class, as measured by maternal education and childhood growth. The literature in this regard among both normal and VLBW populations has been inconsistent.[24,46,50,51]

On the surface, it appears that the male VLBW subjects might be at a disadvantage in that they remain shorter than their NBW controls. However, we are more concerned about the future health of the VLBW females who as a group caught up in weight more than in height, 21% of whom were overweight and 15% obese at 20 years of age. There is growing evidence that children who grow rapidly during childhood are more likely to be obese as adults and at risk for metabolic disturbances such as insulin resistance and noninsulin-dependent diabetes mellitus, and for hypertension and cardiovascular disease.[2–4,52,53] This risk also pertains to catch-up growth among term born children following intrauterine growth restriction and/or growth failure during infancy.

CONCLUSIONS

VLBW females catch up in growth by 20 years, whereas males remain significantly shorter and thinner than controls. Neonatal intensive care has resulted in an increase in the numbers of preterm and SGA infants who will survive to adulthood. Thus, it will be important to continue to follow this cohort into mature adulthood to fully understand the long-term metabolic and cardiovascular implications of the preferential catch-up growth of VLBW females.

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