Growth of Extremely Preterm Survivors From Birth to 18 Years of Age Compared With Term Controls

WHAT’S KNOWN ON THIS SUBJECT: Children born at very low birth weights have significant catch-up weight gain but differences in height remain. Their BMI, however, tends not to be higher than expected. Data are lacking regarding representative cohorts, defined by gestation and compared with contemporaneous controls.

WHAT THIS STUDY ADDS: In a geographic cohort of extremely preterm participants followed until age 18, compared with term controls, weight differences diminish over time, and height differences persist. BMI at age 18 is similar. Height at age 2 is a better predictor of final height than midparental height.

abstract

OBJECTIVES: To determine changes in height, weight, and BMI of extremely preterm (EPT; gestational age <28 completed weeks) survivors from birth to 18 years of age, compared with term controls.

METHODS: Birth, discharge, and follow-up at ages 2, 5, 8, and 18 years of consecutive EPT survivors and contemporaneous term controls born in 1991–1992 in Victoria, Australia. Weight, height, and BMI were converted to z scores and compared between groups. Height z scores at age 2 and midparental height z scores were examined as predictors of height z score at age 18 years.

RESULTS: Follow-up rates were >90% until 18 years, when 166 (74%) of 225 EPT subjects and 153 (60%) of 253 controls were assessed. EPT subjects had lower weight z scores than controls at birth, with a much greater difference at discharge, which reduced progressively until age 18 years. EPT children were shorter than controls at all ages, and this difference did not alter greatly over time. BMI z scores were higher in EPT children at younger ages, but by age 18 were similar between groups. Height at age 2 was a better predictor of height at age 18 in EPT participants, compared with midparental height.

CONCLUSIONS: EPT survivors were substantially lighter than term controls from birth to late adolescence, although the gap in weight steadily decreased over time from a peak at the time of discharge. The height disadvantage in EPT children compared with controls remained constant over time and BMI scores were similar at age 18 years. Pediatrics 2013;131:1–7
Over the past 2 decades, there has been a steady increase in survival rates for children born extremely preterm (EPT; gestational age at birth <28 completed weeks). These children are at high risk of adverse long-term medical and developmental outcomes. Saigal et al reported that adults who were born extremely low birth weight have catch-up weight gain during childhood and adolescence, although height disadvantages persist compared with term controls. A 2008 review of growth in preterm children by Euser et al reported similar findings. A limitation of this review is that many studies used birth weight as the selection criterion. The use of birth weight, rather than gestational age, as a selection criterion can introduce bias, as more mature growth-restricted infants (who may be at higher risk of future growth disorders) are included with infants who are more premature, but appropriate weight for gestation. As with other outcomes of prematurity, such as neurodevelopment, it is preferable to examine growth according to gestational age, rather than birth weight.

Height and weight have been investigated in studies that used gestational age as the inclusion criterion, however. A Dutch national cohort born in 1983 at <32 weeks of gestation was followed-up at 19 years of age, with a response rate of 62%. These young adults had mean heights and weights approximating 0.5 of a SD lower than Dutch reference weights and heights. There was no control group, and limited information about growth trajectories, as previous measurements had been obtained only at 3 months and 1 year of age. More recent studies have used gestational age as the selection criterion, but have reported growth outcomes only until early childhood. Others have examined growth outcomes into young-adulthood, but have continued to use birth weight as their main inclusion criterion.

Body composition and metabolic risk are of interest in EPT children, given Barker's fetal origins of adult disease hypothesis. Low birth weight and growth restriction have been shown to be a risk factor for adverse adult cardiovascular outcomes. During childhood, preterm children tend to have reduced fat mass compared with their peers, but have catch-up weight gain during adolescence, although their final BMI is not greater than the reference range in most studies. There are conflicting results with respect to the proportion of overweight adults born preterm, with some studies reporting higher-than-expected rates and some lower-than-expected rates.

Midparental height has traditionally been used to predict adult height in the general population. Concerns have been raised, however, that this method may not be accurate for children with very short stature. For very low birth weight children, Trebar et al have shown that growth during the second year of life is an important predictor of height at age 6, using a prediction model that also included midparental height (MPH), birth weight, and height at age 1 year. To date, MPH has not been compared with early childhood growth as a predictor of final height in EPT children.

In this study, our primary aim was to examine the growth outcomes of a geographic cohort of EPT infants followed into late adolescence, and compare their outcomes with matched term controls, recruited at birth. We hypothesized that weight disadvantages that are present early in life would disappear over time, although height disadvantages would persist. Our secondary aims were to examine changes in BMI over time and also to examine potential predictors of height at age 18 years. We were particularly interested in whether MPH or growth in early childhood was a better predictor for adolescent height in EPT children, and whether this differed in EPT and term children.

METHODS

Study participants represent all consecutive EPT survivors born during 1991–1992 in the state of Victoria, Australia. Victoria comprises approximately one-fourth of the population of Australia and has 3 level-III perinatal centers (obstetric referral centers with a NICU, and 1 level-III NICU in a children’s hospital, all of which participated in the study, enabling recruitment of a geographic cohort. Controls comprised randomly selected term births, matched for the mother’s health insurance status, language spoken primarily in her country of birth (English or other), and the child’s gender. Perinatal data were collected, as previously described.

Height and weight were measured according to standard guidelines. Growth data were collected at birth, at discharge from hospital, and at ages 2, 5, 8, and 18 years (corrected for gestation).

The Ethics Committees at the Royal Women’s Hospital, Mercy Hospital for Women, and Monash Medical Centre (Melbourne, Australia) approved these follow-up studies. Written informed consent was obtained from parents at all ages, and the subjects themselves at the 18-year follow-up. Early follow-up was considered routine clinical care for children born EPT, but written informed consent was obtained from the EPT subjects and their families when they were teenagers.

Data were analyzed by using SPSS version 19 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). The participants who were seen at age 18 years
were compared with those who were not seen, with respect to perinatal variables, height and weight z scores at age 8, maternal education (as a proxy for social risk), and MPH z score (if known). Dichotomous variables were compared between the 2 groups using \( \chi^2 \) and continuous variables were compared by using t tests, assuming unequal variances if Levene’s test for equality of variances was statistically significant. BMI was calculated by using the formula (BMI = weight [kg]/height [m]²). Height, weight, and BMI measurements were converted into z scores (standard scores) by using the 1990 British Growth Reference data.²¹

Mean height, weight, and BMI z scores were compared between EPT and control participants at each time point using t tests, and mean differences and 95% confidence intervals (CIs) calculated, assuming unequal variances as above. Paired t tests were used to compare mean MPH z scores with mean age 18 height z scores for both groups. Regression analyses were used to explore possible predictors of height at 18 years. Initially the relationship between height z scores at 18 years and the main predictors of interest, MPH z scores and age 2 height z scores were presented graphically. \( R^2 \) was used as a measure of the variability in height at 18 years explained by each of these factors. In subsequent analyses, the potential predictors included prenatal variables (MPH, antenatal corticosteroids), neonatal variables (gestational age, birth weight z score, postnatal corticosteroids, bronchopulmonary dysplasia (oxygen requirement at 36 weeks corrected gestational age), cystic periventricular leukomalacia), and postnatal variables (height z score at age 2 years), with models fitted separately for both EPT and term control groups. These variables were entered in the order stated previously, to reflect the distal to proximal temporal relationship they have with the outcome measure. A final regression analysis was conducted including both EPT and control subjects: height z scores at age 2 years, MPH z scores, EPT or term group status, and interaction terms for group with both height z score at 2 years and MPH z scores were examined to determine if there was a differential relationship for these variables between the 2 groups. Again, \( R^2 \) was used as a measure of the variability in height at 18 years explained in the previously mentioned models.

**RESULTS**

The follow-up rates for growth measurements for the 225 EPT participants at ages 2, 5, 8, and 18 years were 96% (\( n = 215 \)), 93% (\( n = 210 \)), 92% (\( n = 207 \)), and 74% (\( n = 166 \)), respectively. The equivalent follow-up rates for the 253 controls at ages 2, 5, 8, and 18 years were 90% (\( n = 228 \)), 86% (\( n = 217 \)), 84% (\( n = 213 \)), and 60% (\( n = 152 \)), respectively. Table 1 compares adolescents with and without growth data at age 18 on several perinatal and demographic characteristics, and height and weight z scores at age 8. The EPT adolescents without growth data were more likely to have cystic periventricular leukomalacia and to have parents who were shorter, compared with those with growth data. The controls without growth data were more likely to be male and less likely to have mothers who had completed 11 years of schooling, compared with controls with growth data. The EPT subjects had weight z scores that were significantly lower than controls at birth, but the difference was small (Table 2). A larger difference was apparent at discharge after the primary hospitalization, which reduced progressively over time, until by age 18 years the difference between the groups was similar to the difference at birth. EPT children were shorter than controls at all ages from 2 to 18 years, and, in contrast to the change in weight over the same time, the difference between the groups in height z scores did not alter greatly over time (Table 2). Of the EPT participants, 15 (9%) had a height z score < –2 SD and 48 (29%) had a height z score < –1 SD at age 18 years. Of the term participants, however, only 1 child (0.7%) had a height z score < –2 SD, and 10 (6.6%) had a height z score < –1 SD at age 18 years. BMI z scores were lower in the EPT subjects at ages 2, 5, and 8 years, but the BMI z scores at age 18 were similar between the 2 groups. If the analyses were restricted to only those with growth data at 18 years, no statistical conclusions were altered (data not shown). Imputing missing values of height and weight by substituting height and weight at age 8 years (or at age 5 years if also missing at age 8 years) resulted in additional data for 44 EPT subjects and 59 controls, but resulted in no changes to any statistical conclusions at 18 years (eg, mean difference in height z score between groups was −0.76 with imputation, compared with −0.73 without imputation). The EPT subjects’ height z score at 18 years was slightly lower than their MPH z score but this did not reach statistical significance (mean difference, −0.17, 95% CI −0.37–0.02, \( P = .08 \)), whereas the height z score of the controls was significantly higher than their MPH z score (mean difference, 0.41, 95% CI 0.26–0.57, \( P < .001 \)). There were strong positive associations between height z score at 18 years and both height z score at 2 years (Fig 1) and MPH z score (Fig 2) for both EPT and control subjects. Within EPT subjects, height z score at 2 years explained a larger amount of the variability in final height (\( R^2 = 0.50 \)) compared with MPH z score (\( R^2 = 0.18 \)).
For EPT subjects, with all potential predictor variables entered into a single regression model for height z score at 18 years, there was evidence that MPZh score (0.27 [95% CI 0.09–0.45, P = .003]) increase in z score at 18 years for each unit increase in MPZh score) and height z score at age 2 years (0.67 [95% CI 0.52–0.82, P < .001]) increase in z score at 18 years for each unit increase in z score at 2 years) were both predictive of height z score at 18 years, total model $R^2 = 0.57$. MPH contributed 0.18 and height z score at age 2 contributed a further 0.30 to the $R^2$. Antenatal corticosteroids, gestational age, birth weight z scores, postnatal corticosteroids, bronchopulmonary dysplasia, and cystic periventricular leukomalacia were not significant predictors.

For the term subjects, with all potential predictor variables entered into a single regression model for height z score at 18 years, there was evidence that MPH z score (0.45 [95% CI 0.29–0.62, P < .001]) increase in z score at 18 years for each unit increase in MPZh score) and height z score at age 2 (0.47 [95% CI 0.31–0.62, P < .001]) increase in z score at 18 years for each unit increase in z score at 2 years) were both predictive of height z score at 18 years, a total model $R^2 = 0.57$. MPH contributed 0.39 and age 2 height a further 0.17 to the $R^2$. Gestational age, and birth weight z scores were not significant predictors, and antenatal corticosteroids, postnatal corticosteroids, bronchopulmonary dysplasia, and cystic periventricular leukomalacia were not included, as they were not relevant to the term subjects.
In the final analysis that included all participants as well as the interaction terms examining differential group effects, there was evidence that MPH z score at age 2 (0.28 [95% CI 0.12–0.44, \( P = .001 \)) increase in z score at 18 years for each unit increase in MPH z score), and height z score at 2 years (0.65 [95% CI 0.53–0.77, \( P < .001 \)) increase in z score at 18 years for each unit increase in height z score at 2 years) were predictive of outcome, with a main effect of group (controls 0.36 [95% CI 0.16–0.57] higher than EPT subjects). Neither of the interaction terms was significant, although there was a trend toward a weaker association between height z score at 2 years and 18 years (interaction coefficient –0.18 [95% CI –0.39–0.03; \( P = .09 \)), and a stronger association between MPH z score and height at 18 years (interaction coefficient 0.18 [95% CI –0.05–0.42; \( P = .13 \)), in controls compared with EPT subjects.

**DISCUSSION**

On average, EPT subjects were lighter and shorter than their term peers throughout childhood and into late adolescence. Differences in weight z scores between groups were largest at the time of initial discharge, and gradually reduced over time. Height differences between groups persisted over time with no evidence of catch-up between 2 and 18 years of age. Because EPT subjects showed more rapid weight gain over time, compared with their height, than did the controls, by 18 years of age the BMI scores were not different, on average, between the 2 groups. The other major finding is that height z scores were strongly related to both height z scores at 2 years of age and MPH z scores in both EPT and term controls, as would be expected. The interesting and novel finding, however, is that the relationship between height z score at 18 years with height z score...
at 2 years was stronger in EPT subjects than in controls, and stronger than genetic influences acquired from their parents as measured using the MPH z score.

The growth results are consistent with previous studies examining growth in cohorts selected using gestational age as the primary inclusion criterion, although differing selection of control groups and ages at follow-up make direct comparisons difficult. The EPI-Cure study group assessed all children born in the UK and Ireland at <26 weeks of gestation at age 6, compared with classroom controls, and reported that the EPT children were 1.2 SD lighter than the term-born controls, and 0.97 SD shorter than the controls, compared against local published standards.7 Mean weight and height were ~1.0 SD lower than the population mean for children at <26 weeks and ~0.7 SD lower for children at 26 to 28 weeks. Similar to our study findings, they noted more catch-up weight gain compared with height gain from 2 years of age.7

It could be considered reassuring that there was little difference in mean BMI between the EPT and term cohorts at age 18; however, to reach this point, the EPT cohort had more rapid weight gain during childhood, which may place them at higher metabolic risk. This increased risk has been described by Eriksson et al,13 who reported that children born in the 1920s and 1930s in Helsinki, who had a lower BMI in early childhood but whose BMIs rose rapidly to the average or above average range in later childhood, had a greater risk of death due to coronary disease in adulthood. As individuals born preterm have a higher risk of “metabolic programming” toward adverse metabolic outcomes, compared with term controls,15 it is important that metabolic outcomes are examined carefully in the growing number of young adults who were born preterm. We do not have any metabolic data on our subjects.

In EPT young adults, the finding that height at age 2 was a stronger predictor of height at age 18 years than MPH is interesting. As expected, MPH was a good predictor of height at age 18 in the term-born controls. In the EPT adolescents, however, height at age 2 explained more of the variability in height at age 18, compared with MPH. These results suggest that medical risk factors during the early years may be more important predictors of adult height than genetic predisposition in EPT individuals. Medical risk factors are more common in preterm children, compared with term children, and may impair growth in infancy and early childhood. These include, but are not limited to, poor nutrition, respiratory illnesses, and increased hospitalization.4 Trebar et al18 have demonstrated that a prediction model including early growth parameters and MPH can be used to predict growth at age 6 in very low birth weight children. The results from the current study show that the common clinically used prediction tool of MPH should be used with caution in EPT children, but that if growth is satisfactory in early childhood, families can be reassured that their EPT child is likely to follow expected growth trajectories over time.

The strengths of the current study include longitudinal follow-up, at multiple time points, of a large geographic cohort of EPT participants and matched term controls, who were recruited at birth. Limitations include the lower follow-up rate at age 18 years, which is consistent with other follow-up studies that have recruited participants during young adulthood.4 Length data were also incomplete at birth and discharge, so that comparisons could not be made with height at later ages.

CONCLUSIONS

EPT children remain at a height disadvantage compared with term controls at 18 years of age, although the weight disadvantage reduces steadily over time. More research into growth differences in preterm children at later gestational ages is needed, as is research into the metabolic consequences of these altered growth trajectories.

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