Extreme Preterm Infant Rates of Overweight and Obesity at School Age in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes Cohort

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Objective To identify rates of overweight (body mass index [BMI] ≥85th percentile) and obesity (BMI ≥95th percentile) at 6-7 years of age and associated risk factors among extremely preterm infants born at <28 weeks of gestation.

Study design Anthropometrics, blood pressure, and active and sedentary activity levels were prospectively assessed. Three groups were compared, those with a BMI ≥85th percentile (overweight or obese for age, height, and sex) and ≥95th percentile (obese) vs <85th percentile. Multiple regression analyses estimated the relative risks of BMI ≥85th percentile and ≥95th percentile associated with perinatal and early childhood factors.

Results Of 388 children, 22% had a BMI of ≥85th percentile and 10% were obese. Children with obesity and overweight compared with normal weight children had higher body fat (subscapular skinfold and triceps skinfold >85th percentile), central fat (waist circumference >90th percentile), spent more time in sedentary activity (20.5 vs 18.2 vs 16.7 hours/week), and had either systolic and/or diastolic hypertension (24% vs 26% vs 14%), respectively. Postdischarge weight gain velocities from 36 weeks postmenstrual age to 18 months, and 18 months to 6-7 years were independently associated with a BMI of ≥85th percentile, whereas weight gain velocity from 18 months to 6-7 years was associated with obesity.

Conclusions One in 5 former extremely preterm infants is overweight or obese and has central obesity at early school age. Postdischarge weight gain velocities were associated with overweight and obesity. These findings suggest the obesity epidemic is spreading to the most extremely preterm infants. *(J Pediatr 2018;■■:■■-■■).*

Trial registration ClinicalTrials.gov NCT00063063 and NCT0000.

The current epidemic of obesity and associated cardiovascular morbidities in the US is a significant public health problem,[1-7] but there have been few longitudinal investigations of very preterm infants to evaluate whether they are at risk for long-term effects of overweight and obesity.[7-11] Most studies of older preterm infants reported that they are shorter and weigh less than term control infants.[8,11-18] However, there has been limited evaluation of rates of overweight and obesity among extremely preterm (EPT) children at early school age born in the postsurfactant era.

Findings of elevated body mass index (BMI) in childhood are of concern because obesity is associated with abnormal levels of lipids, insulin, and blood pressure (BP).[19,20] Barker first proposed the "fetal origins" of adult disease hypothesis, demonstrating that alterations in fetal nutrition causing intrauterine growth restriction were associated with developmental adaptations that predispose to adult cardiovascular and metabolic disease.[21,22] The original concept in growth-restricted term infants[23] has been expanded to concerns about "rapid early catch-up growth" of preterm infants predisposing to increased cardiovascular risk and obesity.[7,23]

The primary objective of this study was to identify the risk for weight-related outcomes at early school age among EPT children born at <28 weeks of gestation, including rates of overweight or obesity, obesity, central obesity, and

BMI	Body mass index
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
CUS	Cranial ultrasound examination
EPT	Extremely preterm
NICHD	National Institute of Child Health and Human Development
PMA	Postmenstrual age

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associated high BP and hypertension. The second objective was to determine risk factors associated with BMI ≥85th percentile and BMI ≥95th percentile, including weight gain velocities from birth to 36 weeks postmenstrual age (PMA), 36 weeks PMA to 18-22 months corrected age, and 18-22 months corrected age to 6-7 years of age. Associations of BMI ≥85th percentile with maternal and neonatal risk factors and 6- to 7-year BP and activity levels were examined. It was hypothesized that increased early weight gain velocity would be associated with overweight, obesity, and central obesity among those born EPT.

Methods

The obesity study was a selective secondary to the National Institute of Child Health and Human Development (NICHD) Neonatal Network SUPPORT Neuroimaging and Neurodevelopmental Outcomes school-age cohort.[24] The children were originally enrolled in SUPPORT, a randomized, multicenter trial of ventilation and oxygenation management strategies for infants born at $24^{0/7}$-$27^{6/7}$ weeks of gestation (ClinicalTrials.gov: NCT00233324).[25,26] The subset of children with anthropometric data at the 6- to 7-year follow-up was eligible (n = 412). Twenty-four children were excluded for severe growth failure associated with short bowel syndrome (n = 2), a congenital syndrome or chromosomal abnormality (n = 9), and missing weight (n = 4) or height data (n = 9) needed to compute BMI percentiles. In the final dataset, 388 of the 412 children (94%) were included. Prenatal and neonatal data from the SUPPORT cohort database including demographics, anthropometrics, and BP obtained at 6 years 4 months, to 7 years 2 months were analyzed.

Measurements at birth, 36 weeks PMA, and 18-22 months corrected age were retrieved for analyses from the Neonatal Research Network database. Fenton growth charts were used at birth and 36 weeks PMA and the Centers for Disease Control and Prevention growth charts were used at 18 months corrected age and 6-7 years of age.[27-28] Standardized methods for measurements were used at all sites.[29] Duplicate measurements of weight, height, head circumference, waist circumference, subcutaneous skinfold measurements, and BP were obtained at 6-7 years of age.

Overweight or obesity was defined as a BMI >85th percentile and obesity as a BMI >95th percentile. BMI was calculated as weight (kilograms)/height (meters squared). A waist circumference >90th percentile was used as an indicator of central adiposity.[30] Skinfolds were categorized as ≥85th percentile (overweight) and ≥95th percentile (obese).[31] Measurements obtained to differentiate central adiposity from peripheral adiposity included triceps, subscapular, and abdominal skinfolds, which are part of a standard assessment for obesity in children.[32]

Skinfolds were measured with a Lange Skinfold Caliper (Cambridge Scientific Industries, Inc, Cambridge, Maryland) using standard techniques. All skinfold measurements were taken twice on the right side. If there was >2 mm difference between measurements, the measurement was taken a third time and the 2 measurements within 2 mm of each other were recorded. Waist circumference was taken horizontally at the level of the narrowest part of the torso with the child standing and relaxed. Head and waist circumferences were measured twice using an inelastic, flexible, retractable metal tape. The head circumference was the largest occipital-frontal measurement obtained with the tape placed superior to the eyebrows. Weight and height were obtained using a standard upright scale. The head was in the Frankfort plane, with subjects fully erect and in stocking feet. Weight gain velocities were calculated as grams per week from birth to 36 weeks PMA, and kilograms per month from 36 weeks PMA to 18-22 months corrected age and 18-22 months corrected age to 6-7 years of age. Site examiners were trained in all measurement techniques.[33] Techniques recommended by the Fourth Task Force on Blood Pressure Control for Children were followed for obtaining BP.[34,35] Children sat in a quiet room with the right arm fully exposed and resting on a supportive surface at heart level. The American Diagnostic Corporation ADC E sphygmomanometer (Hauppauge, New York) automatically measured systolic and diastolic BP, and pulse rate. The appropriate-sized cuff to cover approximately 75% of the upper arm between the top of the shoulder to the olecranon was used. BP was measured twice 2 minutes apart.

BP was classified as normal (average systolic and diastolic BP <90th percentile), high BP (average systolic or diastolic BP of 90th-95th percentile), and high BP or hypertension (average systolic or diastolic BP ≥95th percentile) using updated definitions and nomograms for BP by age and sex for height developed by the Fourth Task Force Report on Blood Pressure.[35]

A brief parent questionnaire of physical and sedentary behavior derived from the NICHD study on growth and calcium intake was completed.[36] The activity questionnaire includes questions that reflect either sedentary screen activity (eg, television or computer time) or active physical activity (eg, sports or dance). Parents reported the number of minutes or hours per day for weekdays and weekends that the child participates in these activities. All site examiners received reliability training in study procedures. Institutional review board approval was obtained, and all parents provided informed consent.

Statistical Analyses

A power analysis indicated the study would have 91% power to detect differences in means for continuous variables between children who were overweight or obese (BMI ≥85th percentile; n = 89) vs not overweight or obese (BMI <85th percentile; n = 310) with an alpha of $P = .05$, assuming a medium-sized effect (Cohen d = 0.5). Bivariate analyses tested for differences in the characteristics of children with a BMI ≥85th percentile vs <85th percentile and for BMI ≥95th percentile vs <85th percentile at 6-7 years, using χ^2 tests and t tests as appropriate. Median tests were used to compare continuous variables with skewed distributions. The association of physical activity and sedentary activity rates with overweight and obesity were also explored. Regression models with generalized estimating equations were conducted to identify antenatal, neonatal, social, and demographic factors that predicted BMI ≥85th percentile and BMI ≥95th percentile, accounting

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