Weight Gain and Height Growth during Infancy, Childhood, and Adolescence as Predictors of Adult Cardiovascular Risk

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Objectives To investigate independent relationships of childhood linear growth (height gain) and relative weight gain to adult cardiovascular disease (CVD) risk traits in Asian Indians.

Study design Data from 2218 adults from the Vellore Birth Cohort were examined for associations of cross-sectional height and body mass index (BMI) and longitudinal growth (independent conditional measures of height and weight gain) in infancy, childhood, adolescence, and adulthood with adult waist circumference (WC), blood pressure (BP), insulin resistance (homeostatic model assessment-insulin resistance [HOMA-IR]), and plasma glucose and lipid concentrations.

Results Higher BMI/greater conditional relative weight gain at all ages was associated with higher adult WC, after 3 months with higher adult BP, HOMA-IR, and lipids, and after 15 years with higher glucose concentrations. Taller adult height was associated with higher WC (men $\beta = 2.32$ cm per SD, women $\beta = 1.63$, both $P < .001$), BP (men $\beta = 2.10$ mm Hg per SD, women $\beta = 1.21$, both $P \leq .001$), and HOMA-IR (men $\beta = 0.08$ log units per SD, women $\beta = 0.12$, both $P \leq .05$) but lower glucose concentrations (women $\beta = -0.03$ log mmol/L per SD $P = .003$). Greater height or height gain at all earlier ages were associated with higher adult CVD risk traits. These positive associations were attenuated when adjusted for adult BMI and height. Shorter length and lower BMI at birth were associated with higher glucose concentration in women.

Conclusions Greater height or weight gain relative to height during childhood or adolescence was associated with a more adverse adult CVD risk marker profile, and this was mostly attributable to larger adult size. *(J Pediatr 2017;180:53-61).*

Cardiovascular disease (CVD) is the leading cause of death globally, and the population incidence of CVD and related metabolic disorders is higher in low- and middle-income countries (LMICs) than in the rest of the world.[1,2] Mortality because of premature CVD is increasing in South Asian countries such as India.[1,3,4]

Growth patterns in early life are important predictors of adult CVD risk factors.[4,5] Lower weight at birth[6,7] and/or during infancy[8] and higher weight or BMI during childhood or adolescence[9-12] are associated with a higher risk of adult hypertension, type 2 diabetes mellitus (T2DM), and CVD. These relationships may be mediated by effects on body composition; weight and BMI at birth and during infancy positively predict adult lean mass more strongly than adult fat mass, and during late childhood and adolescence, they predict fat mass more strongly.[13-15] Few studies have examined associations of height (linear) growth in early life with later CVD risk.

Understanding when in childhood growth relates to later CVD risk may guide the timing of interventions to prevent disease. Identifying specific ages when linear growth and weight (soft tissue) gain predict later outcomes is complicated by the fact that serial measurements of height or weight within an individual are strongly positively correlated, and height and weight are correlated with each other. Two-way conditional growth measures, which are adjusted for prior size, and mutually adjust weight and height for each other, have been developed to overcome these limitations.[14] We have used 2-way conditional growth analysis to study indepen-

BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HOMA-IR	Homeostatic model assessment-insulin resistance
LMIC	Low and middle income countries
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
WC	Waist circumference

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dent relationships of linear growth and weight gain, during defined periods of infancy, childhood, and adolescence, with adult CVD risk markers using data from the Vellore birth cohort in India.

Methods

The Vellore Birth Cohort includes individuals born within defined areas of Vellore town and adjoining rural villages in Tamil Nadu, India during 1969-1973.[9] The current analysis used data from the 2218 cohort members for whom birth measurements were available and who were followed up as young adults during 1998-2002. Height and weight were measured prospectively by trained research staff, using standardized methods, at birth, during infancy (up to 3 months of age), childhood (6-8 years of age), adolescence (10-15 years of age), and adulthood. Children had up to 3 measurements in the first 3 months of age, up to 2 measurements between 6 and 8 years of age, and up to 5 measurements between 10 and 15 years of age. The study was approved by the institutional ethics committee, and all study participants provided written informed consent.

Adult follow-up took place at a median (IQR) age of 28.1 years (27.4, 28.8).[9] Measurements included weight to the nearest 0.1 kg; height to the nearest 1 mm, measured using a Harpenden portable stadiometer (Holtain Ltd, Crymych, Dyfed, Wales); and waist circumference (WC) measured to the nearest 1 mm, midway between the costal margin and iliac crest in expiration. Body mass index (BMI) was calculated using the formula weight (kg)/length or height (m) squared. Information was collected on place of residence (both current and at birth), attained education level, current tobacco and alcohol use, physical activity, and socioeconomic status. Education was recorded in 7 groups from no schooling to a professional qualification. Participants were defined as current tobacco users or nonusers. Frequency and quantity of consumption of beer, wine, and spirits were converted into units of alcohol per week. A score was derived as a summary estimate of daily physical activity as described previously.[10] A 6-point scale ranging from "almost entirely sedentary" to "heavy physical work" was used to classify work-related activity. In addition, the scoring included time spent in domestic and leisure activities and daily mode of transport (walking, cycling). Time periods for each activity were multiplied by metabolic constants derived from published tables of the relative energy expenditure of each task, and summed to create the final physical activity score. Socioeconomic status was assessed by recording possession of up to 15 household items.[11] Details of anthropometry and CVD risk factors measurements are described elsewhere.[12]

Data Analyses

Analysis Sample. In selecting ages for the growth analysis, we aimed to include (in addition to birth and adulthood) infancy, childhood, and adolescence. The exact ages selected were based upon availability of data. No infant data were collected before March 1, 1971 or in December 1973, and therefore, we excluded births at these times (n = 326), leaving 1892. We also excluded 7 cohort members without birth length and 7 without adult height and weight, leaving 1878.

Among the 1878, infant measurements were available for 1613 (median [IQR] 2.9 months [2.0, 3.0]), childhood measurements for 1680 (6.4 years of age [5.9, 6.9]), and adolescent measurements for 1108 (14.9 years of age [14.4, 19.4]) (**Figure 1**; available at www.jpeds.com). All measurements were converted into within-cohort age- and sex-specific z scores [(subject mean-cohort mean)/cohort SD]. Exact values at age 3 months, and age 6.5 and 15 years were then obtained by interpolation of the z scores, using the nearest measurements to that age and within 2 months for the infant value and 2 years for the childhood and adolescent values, and back-transformation to the units of measurement.

We examined the associations of weight and height z scores separately, at each age, with each CVD risk marker, using linear regression, first adjusted for adult age alone (model 1) and then by additional adjustment for adult body size (BMI and height, model 2). Model 1 ("forward-looking" approach) addresses the question: What is the net association of size at each age with the adult outcome? Model 2 ("backward-looking" approach) addresses the question: Given that this person has achieved a particular adult BMI and height, is there any remaining effect on the outcome of size at earlier ages, or do the earlier measurements have all their effect through their contribution to adult size? Both models were adjusted for year of birth and sociodemographic variables. We used interaction tests to examine whether associations between body size and cardiovascular risk markers differed between the sexes, and because there were more statistically significant interactions than expected by chance, all analyses were stratified by sex.

We constructed sex-specific and height- and weight-specific conditional variables, which are standardized residuals derived from regressing size z scores at each age on prior size measures.[16] Conditional height is current height accounting for all prior height and weight measures. Conditional relative weight gain is current weight accounting for current height and all prior weight and height measures. For example, adult conditional relative weight was derived by regressing adult weight on adult height, and weight and height or length at age 15 and 6.5 years, 3 months, and birth.

Conditional relative weight and height gain variables represent children's deviation from expected size based on their own prior measures and on the growth of the other children in the cohort, and can be interpreted as representing greater or less than expected soft tissue gain and linear growth respectively. For example, a child with a positive conditional relative weight at 6.5 years of age is heavier than expected given his/her current height and prior size and, thus, had a faster rate of soft tissue gain from age 3 months to 6.5 years. Again, we created "forward-looking" models adjusted only for adult age (model 1), and "backward-looking" models further adjusted for adult BMI and height (model 2). We included 907 participants who had data at all selected ages for conditional analysis. Analyses were undertaken using SPSS v 22 (SPSS Inc,