Early Infant Growth Velocity Patterns and Cardiovascular and Metabolic Outcomes in Childhood

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Objective To evaluate the impact of infant growth on childhood health by examining the associations of detailed longitudinal infant weight velocity patterns with childhood cardiovascular and metabolic outcomes.

Study design In a population-based prospective cohort study of 4649 children, we used repeated growth measurements at age 0-3 years to derive peak weight velocity (PWV), age at adiposity peak (AGEAP), and body mass index at adiposity peak (BMIAP). At age 6 years, we measured blood pressure, left ventricular mass, and cholesterol, triglyceride, and insulin concentrations and defined children with clusters of risk factors. We assessed associations using 2 multivariable linear regression models.

Results A 1-SDS-higher infant PWV was associated with higher diastolic blood pressure (0.05 SDS; 95% CI, 0.02-0.09) and lower left ventricular mass (–0.05 SDS; 95% CI, –0.09 to –0.01), independent of body size. A 1-SDS-higher BMIAP was associated with higher systolic (0.12; 95% CI, 0.09-0.16) and diastolic (0.05; 95% CI, 0.01-0.08) blood pressure, but these associations were explained by childhood BMI. We did not observe any associations of PWV, BMIAP, and AGEAP with cholesterol and insulin concentrations. Higher PWV and AGEAP were associated with elevated risk of clustering of cardiovascular risk factors in childhood ($P < .05$).

Conclusion Infant weight velocity patterns are associated with cardiovascular outcomes. Further studies are needed to explore the associations with metabolic outcomes and long-term consequences. *(J Pediatr 2017;186:57-63).*

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Rapid growth in early life is associated with an increased cardiovascular risk profile later in life.[1] Previous studies suggest that subjects with higher cardiovascular disease (CVD) risk were small at birth, but had accelerated childhood growth.[2-4] In particular, rapid weight gain in the first 3 months of life is associated with risk factors for CVD in early adulthood.[5,6] Similarly, excessive weight gain in infancy is associated with elevated blood pressure in early adulthood.[7] We previously reported that specific fetal and infant weight gains were associated with various cardiovascular properties at age 6 years.[8]

Early growth velocity patterns can be studied in more detail by deriving specific growth measures from longitudinal data. Repeated measurements of anthropometric data enable the construction of infant weight growth indices, including infant peak weight velocity (PWV), body mass index at adiposity peak (BMIAP), and age at adiposity peak (AGEAP).[9,10] We previously reported that these measures are strongly related to childhood adiposity, with higher infant PWV and BMIAP associated with higher childhood BMI, body fat percentage, android/gynoid fat mass ratio, and preperitoneal abdominal fat area.[9,11] An increasing number of studies suggest that growth velocity patterns during early infancy are associated with cardiovascular risk later in life, but studies on the association between more detailed growth indices and cardiovascular and metabolic factors are lacking.[12,13] We hypothesized that infant growth velocity patterns are associated with cardiovascular risk in school-aged children.[14]

AGEAP	Age at adiposity peak
BMI	Body mass index
BMIAP	Body mass index at adiposity peak
CVD	Cardiovascular disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
PWV	Peak weight velocity

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In a population-based prospective cohort study of 4649 children followed from fetal life onward, we examined associations of infant PWV, BMIAP, and AGEAP with childhood cardiovascular and metabolic outcomes, including blood pressure; left ventricular mass; total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol concentrations; triglyceride levels; insulin concentration; and clustering of cardiovascular risk factors.

Methods

This study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onward in Rotterdam, The Netherlands.[15,16] Of all eligible children in the study area, 61% participated in the study at birth.[15] The study protocol was approved by the local Medical Ethical Committee of Erasmus MC (MEC-2007-413). Written informed consent was obtained from all mothers.

Infant growth measures were available for 6523 children who participated in the preschool phase of the study. We excluded 1797 children who did not have at least 3 infant growth measurements, required for infant growth modeling. Of the remaining 4726 children, 4681 participated in the follow-up studies at age 6 years. Cardiovascular and metabolic outcomes were measured in 4649 children (**Figure**; available at www.jpeds.com).

Gestational age- and sex-adjusted SDSs for birth weight and length were calculated using northern European growth charts.[17] Childhood length and weight were measured according to standardized procedures at birth and at age 1, 2, 3, 4, 6, 11, 14, 18, 24, and 36 months. The median number of postnatal growth measurements was 5 (full range, 3-11).[15] Age- and sex-adjusted SDS for all growth characteristics were obtained from Dutch reference growth charts.[18] As described previously, these growth measures were used to construct longitudinal weight and BMI growth patterns, and to derive infant PWV, AGEAP, and BMIAP values.[9,10] In brief, infant PWV was derived using the Reed1 model for boys and girls separately.[19] The model was fitted by sex on all weight measurements recorded at age 0-3 years, including birth weight. The first derivative of the fitted distance curve was taken to obtain the weight velocity curve. To obtain the infant PWV, the maximum of this curve was taken. This value reflects the maximum rate of growth in infancy. For infant BMIAP, a cubic mixed-effects model was fitted on log(BMI) from age 14 days to 1.5 years, using sex as a covariate. Modeling of BMI growth was performed from age 14 days onward, because children can lose up to 10% of their body weight in the first 2 weeks of life. When fitting the model, age was centralized to 0.75 years. In addition to fixed effects, we included random effects for the constant and the slope in the model. Subsequently, BMI was derived for each individual at the point at which the curve reaches its maximum, which yields BMIAP and AGEAP.

Children visited our research center for follow-up measurements at a median age of 6 years (95% CI, 5.6-7.3 years). We measured blood pressure at the right brachial artery, 4 times at 1-minute intervals, using a validated automatic sphygmomanometer (Accutorr Plus; Datascope, Paramus, New Jersey).[20] We calculated the mean value using the last 3 blood pressure measurements for each participant. M-mode echocardiographic measurements were performed, and left ventricular mass was computed using the formula derived by Devereux.[21,22] Intraobserver and interobserver intraclass correlation coefficients were calculated previously as 0.91-0.99 and 0.78-0.96, respectively.[23] Thirty-minute fasting blood samples were collected to measure cholesterol (total, HDL, and LDL), triglycerides, and insulin concentrations, using a cobas 8000 analyzer (Roche, Almere, The Netherlands). Quality control samples demonstrated intra-assay and interassay coefficients of variation of 0.77%-1.39% and 0.87%-2.40%, respectively.

We defined children with clustering of cardiovascular risk factors using the previously described definition of childhood metabolic syndrome phenotype, which means having 3 or more of the following components: android fat mass % ≥75th percentile; systolic or diastolic blood pressure ≥75th percentile, HDL cholesterol ≤ 25th percentile or triglycerides ≥75th percentile, and insulin level ≥75th percentile.[24] Percentiles were derived from the study population. We used android fat mass as percentage of total body fat mass, which served as proxy for waist circumference, which was not available. Total body fat mass and android fat mass were measured using a dual-energy X-ray absorptiometry (DXA) scanner (Lunar iDXA; GE Healthcare, Madison, Wisconsin) and analyzed with the enCORE software version 12.6.[25]

Maternal age and prepregnancy BMI were recorded at study enrollment. Information on maternal educational level, smoking, alcohol consumption, and folic acid supplement use during pregnancy was obtained via questionnaire.[15] Information on gestational hypertensive disorders was obtained from midwife and hospital registries.[26] Child's ethnicity (European, non-European) was classified by the birth countries of the parents. At age 6 years, we measured height and weight and calculated BMI. We obtained sex- and age-specific SDS based on Dutch reference growth curves.[18]

Statistical Analyses

First, we compared characteristics between boys and girls using one-way ANOVA, Kruskal-Wallace and χ^2 tests. We also explored correlations between early growth measures and cardiovascular properties using Pearson correlation coefficients. Second, we assessed the associations of infant PWV, AGEAP, and BMIAP with childhood cardiovascular and metabolic outcomes using 2 multivariable linear regression models. The basic model was adjusted for child age and sex, whereas the confounder model was also adjusted for covariates selected based on their associations with the outcome of interest based on previous studies or a change in the effect estimate of >10%. For blood pressure and metabolic outcomes, we also created a third model controlling for current childhood BMI. Finally, we used logistic regression models to examine the associations of infancy PWV, AGEAP, and BMIAP with the risk of clustering of cardiovascular risk factors. We did not adjust these