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Early infant growth velocity patterns and cardiovascular and metabolic outcomes in childhood

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Abstract

Objective—To evaluate the impact of infant growth on childhood health, we examined the associations of detailed longitudinal infant weight velocity patterns with childhood cardiovascular and metabolic outcomes.

Study Design—In a population-based prospective cohort study among 4,649 children, we used repeated growth measurements between 0 and 3 years to derive peak weight velocity (PWV), age at adiposity peak (AGEAP) and body mass index at adiposity peak (BMIAP). At the age of 6 years, we measured blood pressure, left ventricular mass, and cholesterol, triglycerides and insulin concentrations and define children with clustering of risk factors. We assessed the associations using two multivariable linear regression models.

Results—A 1-standard deviation score (SDS) higher infant PWV was associated with higher diastolic blood pressure (0.05 SDS (95% Confidence Interval (CI) 0.02, 0.09)), and lower left ventricular mass (-0.05 SDS (95% CI -0.09, -0.01), independently of body size. A 1-SDS higher BMIAP was associated with higher systolic (0.12 (95% CI 0.09, 0.16) and diastolic blood pressure (0.05 (95% CI 0.01, 0.08)), but these associations were explained by childhood BMI. We did not observe associations of PWV, BMIAP and AGEAP with cholesterol and insulin concentrations. Higher PWV and AGEAP were associated with higher risk of clustering of cardiovascular risk factors in childhood (p-values<0.05).

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.

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Keywords

cohort; infancy; growth patterns; cardiovascular risk factors

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Introduction

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) Especially rapid weight gain in the first 3 months of life is associated with risk factors of CVD in early adulthood.(5, 6) Similarly, excessive weight gain in infancy is associated with increased blood pressure in early adulthood.(7) We have previously observed that specific fetal and infant weight gain were associated with various cardiovascular properties at 6 years.(8)

Early growth velocity patterns can be studied in more detail by deriving specific growth measures from longitudinal data. Repeatedly measured anthropometric data enable construction of infant weight growth indices, such as infant peak weight velocity (PWV), body mass index at adiposity peak (BMIAP) and age at adiposity peak (AGEAP).(9, 10) We have previously reported that these measures are strongly related to childhood adiposity. Higher infant PWV and BMIAP were associated with higher childhood BMI, body fat percentage, android/gynoid fat mass ratio and pre-peritoneal 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)

We examined in a population-based prospective cohort study among 4,649 children followed from fetal life onwards, the associations of infant PWV, BMIAP and AGEAP with childhood cardiovascular and metabolic outcomes, including blood pressure, left ventricular mass, and total-, HDL-, and LDL-cholesterol, triglycerides, and insulin concentrations and clustering of cardiovascular risk factors.

Methods

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards 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 the Erasmus MC (MEC-2007-413). Written informed consent was obtained from all mothers.

Infant growth measures were available in 6,523 children participating in the preschool phase of the study. We excluded 1,797 children who did not have at least 3 infant growth measurements, which were necessary for infant growth modeling. Of the remaining 4,726

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children, 4,681 participated in the follow-up studies at the age of 6 years. Cardiovascular and metabolic outcomes were measured in 4,649children (**Figure 1;** online).

Longitudinal infant growth velocity patterns

Gestational age and sex adjusted standard deviation scores for birth weight and length were calculated using North-European growth charts.(17) Childhood length and weight were measured according to standardized procedures at birth, at the ages of 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 with Dutch reference growth charts.(18) As previously described, these growth measures were used to construct longitudinal weight and body mass index growth patterns, and derive infant PWV, AGEAP and BMIAP.(9, 10) Briefly, infant PWV was derived using the Reed1 model for boys and girls separately.(19) The model was fitted by sex on all weight measurements taken at 0-3 years of age, 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 14 days to 1.5 years, using sex as a covariate. Modeling of BMI growth was performed from the age of 14 days onwards, because children may 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 where the curve reaches its maximum, which gives BMIAP and AGEAP.

Childhood cardiovascular and metabolic properties

Children visited our research center for follow up measurements at the median age of 6years (95% range 5.6 – 7.3). We measured blood pressure at the right brachial artery, four times with one minute intervals, using the validated automatic sphygmonanometer Datascope Accutor PlusTM(Paramus, NJ, USA).(20) We calculated the mean value by using the last three blood pressure measurement of 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 and varied between 0.91 to 0.99 and 0.78 to 0.96, respectively.(23) Thirty-minutes fasting blood samples were collected to measure total-, HDL-, and LDL-cholesterol, triglycerides, and insulin concentrations, using Cobas 8000 analyser (Roche, Almere, the Netherlands). Quality control samples demonstrated intra and inter assay coefficients of variation ranging from 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 three 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 was used as proxy for waist circumference, because waist circumference was

not available. Total body fat mass and android fat mass were measured using a Dual-energy X-ray absorptiometry (DXA) scanner (iDXA, GE-Lunar, 2008, Madison, WI, USA) and analyzed with the enCORE software v.12.6.(25)

Covariates

Maternal age, and pre-pregnancy BMI were assessed at enrollment in the study. Information on maternal educational level, smoking, alcohol consumption, and folic acid supplement use during pregnancy was obtained by questionnaires.(15) Information on gestational hypertensive disorders was obtained from midwife and hospital registries.(26) Child´s ethnicity (European, Non-European) was classified by the countries of birth of the parents. At the age of 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-Wallice and Chi-square tests. Also, we explored correlations between early growth measures and cardiovascularproperties using Pearson correlation coefficients. Second, we assessed the associations of infant PWV, AGEAP and BMIAP with childhood cardiovascular and metabolic outcomes using two multivariable linear regression models, respectively. The basic model was adjusted for child age and sex, while the confounder model was additionally adjusted for covariates selected on their associations with the outcome of interest based on previous studies or a change in effect estimate of >10%. For blood pressure and metabolic outcomes, we additionally 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 analyses for multiple testing, because of the strong correlation between the different exposures and outcomes. Metabolic risk factors that were not normally distributed were log-transformed or root-transformed. We constructed standard deviation scores (SDS)(SDS=(observed value-mean/SD)) of determinants and metabolic outcomes. We constructed height adjusted SDS for the blood pressure and body surface area adjusted SDS for the left ventricular mass using Generalized Additive Models for Location, Size and Shape (GAMLSS) using R, version 3.2.0 (R Core Team, Vienna, Austria).(27–30) We tested the interaction of PWV, AGEAP and BMIAP with sex, ethnicity and gestational age and weight at birth, in relation to cardiovascular variables. Because interaction between AGEAP and sex on systolic and diastolic blood pressure was significant, we performed the regression analyses stratified by sex. To reduce the possibility of potential bias associated with missing data, missing values in covariates were imputed using the multiple imputations procedure with five imputations and these datasets were analyzed together.(31) Statistical analyses were performed using SPSS version 21.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

Results

Subject characteristics

Table I shows the subject characteristics according to sex. Girls had lower infant PWV and BMIAP (all p values <0.01) than boys. At the age of 6 years, boys had higher height, weight and left ventricular mass, whereas girls had higher blood pressure, android fat mass percentages, total-cholesterol and triglycerides concentrations and higher percentage of clustering of cardiovascular risk factors (all p-values <0.05). Subject characteristics before imputation are shown online in Table II, while Table III and Table IV (online) show Pearson correlation coefficients between infant PWV, AGEAP and BMIAP and childhood cardiovascular and metabolic properties, respectively.

Infant growth velocity patterns and cardiovascular outcomes

Table V shows that a 1-SDS increase of infant PWV was associated with higher diastolic blood pressure (0.06 SDS (95% Confidence Interval (CI) 0.02, 0.09)), and lower left ventricular mass (-0.05 SDS (95% CI -0.09, -0.01), independently of current body size. The positive association of PWV with systolic blood pressure was explained by current childhood BMI. A 1-SDS higher infant BMIAP was associated with higher systolic (0.12 (95% CI 0.09, 0.16), and diastolic blood pressure (0.05 (95% CI 0.01, 0.08), but these associations were explained by current childhood BMI. The associations of infant PWV and BMIAP with childhood blood pressure tended to be stronger in girls. Infant AGEAP was not associated with cardiovascular outcomes. **Table VI** (online) shows results from the basic models adjusted for child's age and sex only.

Infant growth velocity patterns and metabolic outcomes

Table VII (online) shows in the models adjusted for current BMI that a 1-SDS higher AGEAP was associated with lower triglycerides concentrations (-0.05 SDS (95% CI -0.10, -0.01)), and this association tended to be stronger in boys. Infant PWV and BMIAP were not associated with any of the metabolic outcomes. None of the infant growth patterns were associated with childhood LDL and HDL cholesterol concentrations or with LDL/total cholesterol ratio (results are not shown). We did not observe any association of infant growth velocity patterns with metabolic properties in the basic models adjusted for child's age and sex (**Table VIII;** online).

Infant growth velocity patterns and risk of clustering of cardiovascular risk factors

Table IX shows that, after adjusting for covariates, higher infant PWV and AGEAP were associated with higher risk of clustering of cardiovascular risk factors (Odds Ratio (OR) 1.13 (95% CI 1.01, 1.26) and OR 1.11 (95% CI 1.00, 1.22), respectively). BMIAP was with borderline significance associated with the risk of clustering of cardiovascular risk factors (OR 1.11 (95% CI 1.00, 1.22)).

Discussion

We observed in a large population-based prospective cohort study that early infant growth velocity patterns are associated with certain cardiovascular outcomes, but not consistently

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with metabolic outcomes. The observed associations of infant growth patterns with childhood blood pressure tended to be stronger in girls than in boys. Higher infant growth velocity patterns were also associated with an increased risk of clustering of cardiovascular risk factors.

Methodological considerations

The main strength of our study is the population-based prospective cohort design, including a large number of subjects whom we studied from early fetal life onwards. The repeated infant growth measures enabled us to study the effects of infant growth velocity patterns on the cardiovascular and metabolic properties. However, some limitations need to be discussed. Of the total group of singleton live born children with information on growth, follow-up measurements were available in 71%. Loss to follow-up would lead to selection bias if the associations of early infant growth measures with childhood cardiovascular and metabolic measures would be different between those included and those not included in the final analyses.(32) A limitation is that blood lipids and insulin concentrations were measured in blood samples that were collected in 30 minutes-fasting states. According to studies in adults, fasting time has little influence on cholesterol levels, but concentrations of triglyceride and insulin vary more substantially with differences in fasting time.(33, 34) The measurement error for triglycerides and insulin levels in our study population could have led to non-differential misclassification, and this may have resulted in an underestimation of our effect estimates for associations with triglycerides and insulin levels. Finally, although we performed adjustments for a large number of potential maternal and childhood confounders, residual confounding still might have occurred, as in any observational study.

Interpretation of main findings

A pattern of rapid growth in early life is associated with a higher risk of CVD in later life.(1) A study among 2,285 Japanese adolescents aged 13 to 14 years shows that rapid weight gain during early childhood predicts high blood pressure and unfavorable lipid concentrations.(14) Moreover, data from five birth cohort studies showed that faster relative weight gain during early infant life was associated with an increased risk of elevated blood pressure in adulthood.(35) In line with these studies, we showed that early infant growth patterns are associated with cardiovascular variables in childhood. However, we did not find an association with metabolic variables.

Most previous studies used change in weight or length between two time points as indicator of growth. More detailed infant growth patterns can be derived from the longitudinally collected anthropometric measures, such as PWV, BMIAP and AGEAP. Previously, a study in Germany among 1127 children up to the age of 10 years, reported that higher PWV in infancy is associated with an increase in systolic and diastolic blood pressure after adjustment for confounders, including BMI.(36) However, another cohort study among 2822 children in the Netherlands showed that the association of BMIAP with blood pressure at the age of 6 years was mediated by current BMI.(37) In the same study, it has been shown that timing of BMI peak seemed not to be associated as strongly as magnitude of BMI peak with blood pressure.(37) In line with these studies, we observed an association of infant PWV and BMIAP with childhood blood pressure, which could be explained by current BMI. The

association of infant PWV and BMIAP and diastolic blood pressure in our study was independent from current BMI in girls. Also, in the present study, infant AGEAP was not associated with childhood blood pressure.

Fetal and early life growth patterns may also influence cardiac structures in children and adults.(38, 39) A previous study examined the effect of early infant weight on left ventricular mass among 290 men born in East Hertfordshire, England. They reported that low weight at 1 year was associated with higher left ventricular mass in adulthood.(39) In line with this study, we observed that higher PWV leads to lower left ventricular mass, relative to current body size. Recent study suggests that fat mass is a minor predictor of left ventricular mass, while lean body mass is a much stronger predictor.(40) Therefore, the association between higher PWV and lower left ventricular mass might be explained by a different body composition of children with and without increased PWV, relative to current body surface area (BSA).

Several studies have been performed focused on the associations of infant weight gain with metabolic outcomes. A study among1,999 subjects showed that a slower increase in BMI during the first 6 months after birth was associated with an atherogenic lipid profile in adult life.(41) An additional study among 396 men aged 58 years reported that the combination of being born small followed by a rapid weight gain was associated with the occurrence of risk factors included in the metabolic syndrome, and that growth patterns during infancy and childhood correlate with insulin levels later in life.(42) In our study, we only observed an inverse association of infant AGEAP with triglycerides concentrations after adjusting for current BMI. This observation was not consistent with other results and may be a chance finding. Also, our observation may be explained by the strong positive association of BMI with triglycerides. Results from a study among 128 subjects suggest that rapid weight gain during infancy predicted clustering of metabolic risk factors at age 17 years.(43). Consistently with these results, our results showed higher risk of clustering of cardiovascular risk factors in children with higher PWV and AGEAP. Thus, the increased risk for clustering seemed to be mainly driven by the increased blood pressure and adiposity, and not by the metabolic risk factors.

Although the observed effect estimates infant growth on cardiovascular and metabolic outcomes are small and without clinical relevance for individuals, the results from this study may be important on a population based level. These results are especially important from an etiological perspective and give an important contribution to the field of developmental origins of cardiovascular disease. They suggest that infant growth influence cardiovascular development and might predispose individuals to cardiovascular disease in adulthood. We have shown that infant weight gain patterns may most importantly affect blood pressure and adiposity in childhood. Future research should focus on whether these changes in early childhood are associated with cardiovascular morbidity and mortality at later ages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject characteristics (N = 4,649)

Maternal characteristics	Total (N=4,649)	Boys (N=2,323)	Girls (N=2,326)	*P value*
Age, y	31.0 (4.9)	31.1 (4.9)	31.0 (4.8)	0.31
Body mass before pregnancy, kg/m^2	22.6 (18.1, 34.2)	22.7 (18.0, 33.9)	22. 6 (18.1, 34.6)	0.51
Maternal education, n (%)				0.70
Low/middle	2275 (48.9)	1130 (48.6)	1145 (49.2)	
Higher	2380 (51.1)	1197 (51.4)	1183 (50.8)	
Folic acid intake during pregnancy, n (%)				0.18
No use	1056 (22.7)	548 (23.5)	508 (21.8)	
Start in the first 10 weeks	1453 (31.2)	739 (31.8)	714 (30.7)	
Start periconceptional	2146 (46.1)	1040 (44.7)	1107 (47.6)	
Alcohol consumption during pregnancy, n				0.51
No	1983 (42.6)	980 (42.1)	1004 (43.1)	
Yes	2672 (57.4)	1347 (57.9)	1324 (56.9)	
Smoking during pregnancy, n(%)				0.22
No	3555 (76.4)	1768 (76.0)	1787 (76.8)	
Yes	1100 (23.6)	559 (24.01)	541 (23.2)	
Systolic blood pressure, mmHg	115.3 (12.0)	115.7 (12.04)	115.8 (11.9)	0.80
Diastolic blood pressure, mmHg	68.2 (9.4)	68.1 (9.3)	68.3 (9.5)	0.61
Gestational hypertensive disorders[a]	282 (6.1)	127 (5.5)	155 (6.7)	0.13
Birth and infant characteristics				
Ethnicity, European, n (%)				0.49
European	3518 (75.7)	1751 (75.4)	1769 (76.1)	
Non-European	1131 (24.3)	572 (24.6)	557 (23.9)	
Gestational age at birth unit, weeks	40.1 (36.0, 42.3)	40.1 (36.0, 42.3)	40.1 (36.0, 42.1)	0.23
Birth weight, grams	3459 (535)	3523 (545)	3390 (516)	**<0.001**
Preterm birth <37 weeks at delivery, n (%)	193 (4.1)	98 (4.2)	95 (4.1)	0.88
Peak weight velocity (kg/year)	12.2 (2.1)	13.2 (2.0)	11.3 (1.77)	**<0.001**
Age at adiposity peak (months)	8.4 (7.8, 9.6)	8.4 (7.8,9.6)	8.6 (7.8,9.6)	0.99
Body mass index at adiposity peak (kg/m^2)	17.6 (16.1, 19.2)	17.8 (16.3, 19.4)	17.3 (15.9,19.0)	**<0.001**
Child characteristics at 6 years				
Age, y	6.0 (5.6, 7.3)	6.0 (5.6, 7.4)	6.0 (5.6, 7.2)	0.29
Height, cm	118.9 (0.1)	119.3 (5.6)	118.4 (5.6)	**<0.001**
Weight, kg	22.2 (17.4, 32.4)	22.6 (17.6, 32.2)	22.0 (17.2, 32.4)	**0.01**
Body mass index, kg/m^2	15.8 (13.6, 20.7)	15.8 (13.7, 20.6)	15.8 (13.5, 20.8)	0.70
Android fat mass (%)	3.7 (0.9)	3.6 (0.8)	4.0 (1.0)	**<0.001**
Systolic blood pressure, mmHg	102.5 (8.2)	101.9 (7.7)	103.0 (8.5)	**<0.001**
Diastolic blood pressure, mmHg	60.6 (6.8)	59.9 (6.6)	61.2 (6.8)	**<0.001**
Left ventricular mass, grams	52.8 (11.2)	55.2 (11.4)	50.4 (10.3)	**<0.001**
Total cholesterol, mmol/l	4.2 (0.6)	4.1 (0.6)	4.3 (0.6)	**<0.001**
Triglycerides, mmol/l	1.0 (0.4, 2.4)	1.0 (0.4, 2.3)	1.1 (10.4, 2.5)	**<0.001**

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Maternal characteristics	Total (N=4,649)	Boys (N=2,323)	Girls (N=2,326)	*P value*
Insulin, U/l	114.0 (17.8, 398.3)	114.7 (16.2, 385.5)	112.6 (19.1, 422.2)	0.05
Clustering of risk factors, N (%)	743 (24.8)	355 (22.9)	388 (27)	**0.01**

Values are means (SD), medians (95% range). Values represent the results based on imputed data. Characteristics based on original data are shown in Supplemental Table S1.

[a]Pre-eclampsia or pregnancy induced hypertension.

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Table 2

Associations of infant growth velocity measures with childhood cardiovascular outcomes (N=4,649).

	SDS difference in childhood cardiovascular outcomes (95% Confidence Interval)		
	Systolic blood pressure	**Diastolic blood pressure**	**Left ventricular mass**
Total group			
PWV (1 SDS = 2.1 kg/year)	0.09 (0.05, 0.12) **	0.06 (0.02, 0.09) **	-0.05 (-0.09, -0.01) **
BMI model - PWV (1 SDS = 2.1 kg/year)	0.01 (-0.02, 0.05)	0.05 (0.01, 0.09) *	NA
AGEAP (1 SDS = 0.5 months)	0.02 (-0.02, 0.05)	0 (-0.03, 0.03)	0.01 (-0.02, 0.05)
BMI model - AGEAP (1 SDS = 0.5 months)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	NA
BMIAP (1 SDS = 0.8 kg/m^2)	0.12 (0.09, 0.16) **	0.05 (0.01, 0.08) *	-0.02 (-0.06, 0.01)
BMI model – BMIAP (1 SDS = 0.8 kg/m^2)	0.04 (0.00, 0.08)	0.04 (0.00, 0.08)	NA
Boys			
PWV (1 SDS = 2.0 kg/year)	0.07 (0.03, 0.12) **	0.04 (-0.01, 0.09)	-0.05 (-0.10, -0.00) *
BMI model - PWV (1 SDS = 2.0 kg/year)	0.00 (-0.05, 0.05)	0.02 (-0.03, 0.07)	NA
AGEAP (1 SDS = 0.5 months)	-0.03 (-0.07, 0.02)	-0.03 (-0.08, 0.01)	0.03 (-0.01, 0.08)
BMI model - AGEAP (1 SDS = 0.5 months)	-0.04 (-0.09, 0.00)	-0.04 (-0.08, 0.01)	NA
BMIAP (1 SDS = 0.8 kg/m^2)	0.14 (0.09, 0.19) **	0.03 (-0.02, 0.08)	-0.03 (-0.08, 0.03)
BMI model – BMIAP (1 SDS = 0.8 kg/m^2)	0.05 (0.00, 0.11)	0.00 (-0.06, 0.06)	NA
Girls			
PWV (1 SDS = 1.8 kg/year)	0.10 (0.04, 0.16) **	0.08 (0.02, 0.14) **	-0.05 (-0.10, 0.01)
BMI model - PWV (1 SDS = 1.8 kg/year)	0.03 (-0.04, 0.09)	0.09 (0.02, 0.15) **	NA
AGEAP (1 SDS = 0.5 months)	0.06 (0.01, 0.11) *	0.04 (-0.01, 0.09)	-0.01 (-0.06, 0.04)
BMI model - AGEAP (1 SDS = 0.5 months)	0.04 (-0.01, 0.09)	0.04 (-0.01, 0.09)	NA
BMIAP (1 SDS = 0.8 kg/m^2)	0.11 (0.05, 0.16) **	0.06 (0.01,0.12) *	-0.02 (-0.07, 0.03)
BMI model – BMIAP (1 SDS = 0.8 kg/m^2)	0.03 (-0.03, 0.09)	0.07 (0.01, 0.13) *	NA

Abbreviations: N: number, SDS: standard deviation scores, BMI: body mass index, PWV: peak weight velocity, AGEAP: age at adiposity peak, BMIAP: body mass index at adiposity peak, NA not applicable. Values are linear regression coefficients (95% CI) based on multiple linear regression models and reflect the change in outcome per SDS increase in each infant growth characteristics.

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Confounder model is adjusted for maternal factors: pre-pregnancy body mass index, educational level, smoking during pregnancy, use of alcohol during pregnancy, folic acid supplement use during pregnancy, systolic and diastolic blood pressure at intake and gestational hypertensive disorders, and child factors: age, sex (total group), ethnicity, birth weight and gestational age at birth. BMI model for systolic and diastolic blood pressure was additionally adjusted for childhood BMI. Models adjusted for child's age and sex only are given in Supplementary Materials Table S4. For blood pressure we used height adjusted standard deviation scores, whereas for left ventricular mass, we used body surface area adjusted standard deviation scores. P<0.05 for interaction between AGEAP and sex on systolic and diastolic blood pressure.

* P value <0.05, ** P value <0.01.

Table 3

Associations of infant growth velocity patterns with childhood metabolic outcomes (N=3,136).

	Total cholesterol	Triglycerides	Insulin
Total group			
PWV (1 SDS = 2.1 kg/year)	0.03 (-0.02, 0.07)	-0.00 (-0.05, 0.04)	0.04 (-0.01, 0.08)
BMI model - PWV (1 SDS = 2.1 kg/year)	-0.00 (-0.05, 0.05)	-0.03 (-0.07, 0.02)	-0.03 (-0.08, 0.02)
AGEAP (1 SDS = 0.5 months)	-0.03 (-0.07, 0.01)	-0.05 (-0.09, -0.01) *	-0.00 (-0.04, 0.04)
BMI model - AGEAP (1 SDS = 0.5 months)	-0.04 (-0.08, 0.00)	-0.05 (-0.10, -0.01)**	-0.02 (-0.06, 0.02)
BMIAP (1 SDS = 0.8 kg/m^2)	0.02 (-0.02, 0.07)	0.02 (-0.03, 0.06)	0.04 (-0.01, 0.08)
BMI model - BMIAP (1 SDS = 0.8 kg/m^2)	-0.02 (-0.07, 0.03)	-0.01 (-0.06, 0.04)	-0.05 (-0.10, -0.00)
Boys			
PWV (1 SDS = 2.0 kg/year)	0.04 (-0.02, 0.09)	0.00 (-0.05, 0.07)	0.01 (-0.04, 0.07)
BMI model - PWV (1 SDS = 2.0 kg/year)	0.01 (-0.06, 0.07)	-0.02 (-0.08, 0.05)	-0.03 (-0.09, 0.03)
AGEAP (1 SDS = 0.5 months)	-0.02 (-0.08, 0.03)	-0.06 (-0.11, -0.00)	0.00 (-0.05, 0.06)
BMI model - AGEAP (1 SDS = 0.5 months)	-0.03 (-0.08, 0.02)	-0.07 (-0.12, -0.01) *	-0.01 (-0.06, 0.05)
BMIAP (1 SDS = 0.8 kg/m^2)	0.02 (-0.04, 0.08)	0.01 (-0.05, 0.07)	0.02 (-0.05, 0.08)
BMI model - BMIAP (1 SDS = 0.8 kg/m^2)	-0.03 (-0.09, 0.05)	-0.03 (-0.10, 0.05)	-0.05 (-0.12, 0.02)
Girls			
PWV (1 SDS = 1.8 kg/year)	0.02 (-0.06, 0.09)	-0.02 (-0.09, 0.05)	0.07 (0.00, 0.15)
BMI model - PWV (1 SDS = 1.8 kg/year)	-0.02 (-0.10, 0.06)	-0.05 (-0.07, -0.02)	-0.03 (0.11, 0.05)
AGEAP (1 SDS = 0.5 months)	-0.04 (-0.10, 0.02)	-0.04 (-0.10, 0.02)	-0.01 (-0.08, 0.05)
BMI model - AGEAP (1 SDS = 0.5 months)	-0.05 (-0.11, 0.02)	-0.04 (-0.10, 0.04)	-0.04 (-0.10, 0.03)
BMIAP (1 SDS = 0.8 kg/m^2)	0.02 (-0.04, 0.09)	0.02 (-0.04, 0.09)	0.06 (-0.01, 0.13)
BMI model - BMIAP (1 SDS = 0.8 kg/m^2)	-0.01 (-0.09, 0.07)	0.01 (-0.06, 0.08)	-0.06 (-0.13, 0.02)

Abbreviations: N: number, SDS: standard deviation scores, BMI: body mass index, PWV: peak weight velocity, AGEAP: age at adiposity peak, BMIAP: body mass index at adiposity peak. Values are linear regression coefficients (95% CI) based on multiple linear regression models and reflect the change in outcome per SDS increase in each infant growth characteristics. Model adjusted for maternal factors: pre-pregnancy body mass index, educational level, smoking during pregnancy, use of alcohol during pregnancy, folic acid supplement use during pregnancy, systolic and diastolic blood pressure at intake and gestational hypertensive disorders, and child factors: age, sex, ethnicity, birth weight and gestational age at birth. All models were additionally adjusted for childhood BMI. Models adjusted for child's age and sex only are given in Supplementary Material Table S5. P<0.05 for interaction between AGEAP and sex on systolic and diastolic blood pressure.

* P value <0.05

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Table 4

Associations of infant growth velocity patterns with clustering of cardiovascular risk factor (N=2,990).

	Odds Ratio for clustering for cardiovascular risk factors (95% CI)
PWV (1 SDS = 2.1 kg/year)	1.13 (1.01 – 1.26) *
AGEAP (1 SDS = 0.5 months)	1.11 (1.00 - 1.22) *
BMIAP (1 SDS = 0.8 kg/m^2)	1.11 (1.00-1.24)

Abbreviations: N: number, SDS: standard deviation scores, BMI: body mass index PWV: peak weight velocity, AGEAP: age at adiposity peak, BMIAP: body mass index at adiposity peak. Models are adjusted for maternal factors: pre-pregnancy body mass index, educational level, income, smoking during pregnancy, use of alcohol during pregnancy, folic acid supplement use during pregnancy, systolic and diastolic blood pressure at intake and gestational hypertensive disorders, and child factors: age, sex, ethnicity, birth weight and gestational age;

* P value <0.05;