Original Article

Peak growth velocity in infancy is positively associated with blood pressure in school-aged children

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Objectives: Rapid growth velocity in early life may be a risk factor for obesity, elevated blood pressure, and adverse metabolic markers in childhood, but results are not consistent. We analysed the association between peak growth velocity during the first 2 years of life and blood pressure, fasting glucose and insulin at 10 years of age.

Methods: A prospective German birth cohort (LISAplus) provided data on growth, blood pressure, glucose, and insulin for 1127 children up to the age of 10 years. All children had a birth weight of at least 2500 g. Growth was modelled using nonlinear mixed-effect Reed1 models. Associations between peak growth velocities and metabolic outcomes were calculated with linear regression models. Potential confounders were sequentially adjusted for.

Results: Higher peak height velocity (PHV) and peak weight velocity (PWV) in infancy were associated with significant increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in children at 10 years. For each 10.2 cm/year [2 standard deviation (SD)] increase in PHV, SBP increased by 2.94 mmHg [95% confidence interval (CI) 1.34, 4.54] after adjustment for potential confounders including birth weight and body mass index. A 5.1 kg/year (2 SD) higher PWV was associated with a 2.13 mmHg (95% CI 0.51, 3.74) increase in SBP and a 1.91 mmHg (95% CI 0.52, 3.30) increase in DBP. No consistent associations were found between PHV or PWV and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index after multiple adjustments.

Conclusions: Blood pressure and metabolic outcomes at school age may be associated with growth patterns in early life, regardless of relative weight during school age.

Keywords: blood glucose, blood pressure, child, cohort studies, growth, infant, insulin

Abbreviations: HOMA-IR, Homeostasic Model Assessment for Insulin Resistance; PHV, peak height velocity; PWV, peak weight velocity

INTRODUCTION

High body mass index (BMI) during childhood was shown to increase the risk of cardiovascular disease in later life in a large prospective cohort [1]. However, in a systematic review of 16 studies no independent effect of childhood obesity was found after taking adulthood BMI into account [2]. Recently, Tzoulaki *et al.* [3] found significant positive associations between peak height velocity (PHV) in infancy and systolic and diastolic blood pressure (SBP and DBP, respectively) at the age of 31 years after adjustment for adulthood BMI; and between peak weight velocity (PWV) and SBP in adulthood. In this study, data from 3778 individuals from the Northern Finland Birth Cohort 1966 Study were analysed. In the Cebu Longitudinal Health and Nutrition Survey (Cebu) early weight velocity was found to be associated with adult BMI and waist circumference, but no direct effects on insulin resistance were found [4].

To date, no study has investigated the association between peak growth velocities during infancy and blood pressure, as well as fasting insulin and glucose levels at school age. Therefore, we analysed postnatal peak growth velocity in infancy and associations with SBP and DBP, as well as fasting blood glucose and insulin levels at the age of 10 years within the prospective birth cohort 'Influence of life-style factors on the development of the immune system and allergies in East and West Germany Plus the influence of traffic emissions and genetics' study (LISAplus).

MATERIALS AND METHODS

Study population

In the LISAplus study, parents of neonates admitted to maternity hospitals in Munich, Leipzig, Wesel, and

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Bad Honnef, Germany were recruited. In total, 3097 healthy neonates with a birth weight over 2500 g were recruited between December 1997 and January 1999. LISAplus was designed as a population-based study and follow-ups were completed at the age of 6, 12 and 18 months and 2, 4, 6 and 10 years [5,6]. Fifty-seven percent of the children recruited at birth were followed until the age of 10 years; and 1127 children who participated in the clinical examination at 10 years of age and had valid growth and blood pressure measurements were analysed here.

Height and weight measurements were obtained at birth, at days 3–10 (weight only), at weeks 4–6, months 3–4, 6–7, 10–12 and 21–24 via medical records. Analyses were restricted to singletons with at least three postnatal growth measurements. At the age of 10 years, SBP and DBP were measured twice (the second measurement was used) in a sitting position from the right arm after 5 min of rest during a clinical examination at the study centres. Fasting blood glucose and insulin measurements were taken in a subset of children ($n = 213$). Blood glucose was measured using the standard laboratory methods of the individual hospital. The measurement of insulin in serum was performed by the fully mechanized system Liaison (DiaSorin). The lower limit of detection for this method was 3.5 pmol/l. Quality control samples demonstrated intra and interassay coefficients of variation below 5.8%. For the glucose and insulin analysis, one child was excluded because they had diabetes (type 1 or type 2). The regional ethics committees approved the study and parents gave written informed consent.

Statistical analysis

Growth modelling was performed as described previously [3,7] using Reed1 nonlinear random-effects models to fit weight and height growth curves for each individual based on their longitudinal growth data. Peak height and peak weight velocities during infancy defined as the first 2 years of life were calculated by the derivates of the parametric growth curves. Two children were excluded because their peak weight velocity exceeded the mean peak weight velocity of the total sample and 4 standard deviations (SDs). For sensitivity analyses height velocity and weight velocity at age 1 and 2 years were obtained from the individual growth curves and we calculated relative weight loss or gain per day just after birth from the first two measurements of weight.

To ensure comparability, we applied identical models that included a similar set of potential confounding factors from a recently published adult cohort [3].

Differences in the study characteristics between children included in the present study and children who were not followed were tested using χ^2-tests and Mann–Whitney test.

The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index [8] was calculated by HOMA-IR = [glucose (mmol/l) × insulin (mU/l)]/22.5.

Glucose and insulin levels, as well as the HOMA-IR index were log-transformed due to their skewed distributions. Subsequently, linear regression models were fitted to test the association between BMI, SBP and DBP, fasting blood glucose, fasting blood insulin, and HOMA-IR at the age of 10 years and peak height and peak weight velocity in infancy. Results are presented as β coefficients with CI and P value for BMI, SBP, and DBP; and as mean ratios with CI and P value for the log-transformed outcomes (fasting insulin, fasting glucose and HOMA-IR).

For the total population four models were sequentially adjusted for sex and study centre (model 1); sex, study centre, maternal age, maternal height and weight before pregnancy, parental educational level as socioeconomic status, gestational age, paternal height and weight, parental diabetes and hypertension (model 2); all model 2 confounders and birth weight and breastfeeding (model 3); and all model 3 confounders and BMI at 10 years (model 4). All analyses were additionally stratified by sex (without adjustment for sex). To examine deviations from linearity generalized additive models were used. Displayed P values are based on two-sided testing. All statistical analyses were performed using R 2.13.0 [9].

RESULTS

Table 1 shows the basic characteristics of the study population. PHV and PWV were moderately correlated (Pearson correlation coefficient $r = 0.51$). The mean age at PHV was 0.60 (SD 0.14) months and the mean age at PWV was 0.53 (SD 0.17) months. Children participating in the present study had a higher birth weight, a longer breastfeeding duration, a higher socioeconomic status and an older mother, who was less likely to smoke compared to children not participating (Supplementary Table 1, http://links.lww.com/HJH/A164).

Peak weight velocity was strongly related to BMI at the age of 10 years with no differences between sexes, even after additional adjustment for birth weight and breastfeeding, whereas the association between PHV and BMI was less pronounced. This association was significant in the total population after adjustment for birth weight, based on a significant association in females. The impact of PWV and PHV on BMI in the later life was driven by a significant positive association of both indices with both height and weight at 10 years (data not shown). There was no significant interaction between birth weight and growth velocities in any of the models. SBP at the age of 10 years was significantly associated with PHV and PWV in infancy after adjustment for several confounders (Table 2), whereas the association between DBP and PHV was restricted to males. Effect sizes for the association of blood pressure and PWV were higher than with PHV with different levels of adjustments (model 1–3), but more attenuated by adjustment for BMI at the age of 10 years (model 4) (Fig. 1).

Sensitivity analyses of height and weight velocities at age 1 and 2 years (Supplementary Tables 2 and 3, http://links.lww.com/HJH/A164) revealed very similar findings. The correlations of peak velocities and velocities at age 1 year were moderate to high (0.66 for PHV and height velocity; 0.44 for PWV and weight velocity) and moderate to low at age 2 years (0.47 for PHV and height velocity; 0.16 for PWV and weight velocity 2). Table 2 shows the analyses of peak height and weight velocities in regard to fasting glucose and insulin levels, as well as HOMA-IR. PWV was statistically significant inverse associated with fasting

TABLE 1. Characteristics of the study population, stratified by males ($n = 588$) and females ($n = 539$) and a total of 1127 children

	No. of participants	Mean (SD) or %		
		Total ($n = 1127$)	Males ($n = 588$)	Females ($n = 539$)
Study centre, (%) Munich	531	47.1	48.3	45.8
Leipzig	330	29.3	28.7	29.9
Bad Honnef	150	13.3	12.6	14.1
Wesel	116	10.3	10.4	10.2
Sex, male (%)	588	52.2		
Birth weight (kg)	1127	3.5 (0.4)	3.6 (0.4)	3.4 (0.4)
Birth length (cm)	1104	51.6 (2.4)	52.0 (2.4)	51.2 (2.3)
Gestational age (weeks)	1110	39.9 (1.2)	39.9 (1.2)	39.9 (1.2)
Exclusive breastfeeding (%) no	194	17.5	18.1	16.8
1–4 months	359	32.3	32.9	31.7
>4 months	558	50.2	49.0	51.5
Maternal smoking[a], (%) nonsmoker	994	92.4	92.7	92.0
Light smoker (1–10 cigarettes/day)	69	6.4	6.6	6.2
Heavy smoker (>10 cigarettes/day)	13	1.2	0.7	1.8
Maternal weight before pregnancy (kg)	1117	64.5 (11.5)	64.5 (11.2)	64.6 (12.0)
Maternal height (cm)	1116	168.4 (5.8)	168.6 (6.0)	168.3 (5.7)
Maternal age (years)	1126	31.7 (4.2)	31.8 (4.3)	31.5 (4.2)
Paternal weight (kg)	969	84.2 (12.4)	83.8 (11.9)	84.5 (13.0)
Paternal height (kg)	998	181.3 (6.7)	181.3 (6.9)	181.3 (6.6)
Parental diabetes, yes (%)	31	3.0	3.3	2.7
Parental hypertension, yes (%)	167	16.4	17.6	15.0
Socioeconomic status at birth[b] (%) low	1119	3.1	3.3	3.0
medium	1119	25.9	24.3	27.7
high	1119	71.0	72.4	69.3
Peak height velocity (0–2 years) (cm/year)	1127	46.7 (5.1)	48.2 (4.6)	45.0 (5.1)
Peak weight velocity (0–2 years) (kg/year)	1127	12.9 (2.5)	14.0 (2.3)	11.7 (2.2)
BMI at the age of 10 years	1125	17.3 (2.5)	17.3 (2.6)	17.2 (2.4)
Insulin at the age of 10 years (mU/l)[c]	211	7.1 (1.9)	6.6 (1.9)	7.6 (1.8)
Glucose at the age of 10 years (mmol/l)[c]	212	4.9 (1.1)	4.9 (1.1)	4.8 (1.1)
Systolic BP at the age of 10 years (mmHg)	1127	108.8 (10.6)	108.4 (10.5)	109.2 (10.7)
Diastolic BP at the age of 10 years (mmHg)	1127	64.2 (9.2)	63.8 (8.7)	64.8 (9.8)

BP, blood pressure; LISAplus, Life Style-Immune System-Allergy study.
[a]After third month of pregnancy.
[b]Defined as highest educational level of father or mother.
[c]Geometric mean.

glucose and HOMA-IR, but only after adjustment for BMI at age 10 years (Table 3, model 4). No significant associations between PWV and any of the fasting blood outcomes were found when the models were not adjusted for BMI at the age of 10 years (Table 3, models 1–3). There were also no significant associations between PHV with fasting blood insulin or glucose levels and with HOMA-IR.

A cross-sectional analysis of our data revealed a strong positive association between BMI and insulin, glucose and HOMA-IR at age of 10 years and no association or effect modification in regard to the relative weight loss or gain per day just after birth (data not shown).

DISCUSSION

In this prospective birth cohort elevated SBP and DBP levels were observed in children who grew quickly during infancy, regardless of relative weight at school age.

Adjustment for several potential confounders, including maternal age, maternal height and weight before pregnancy, maternal smoking during pregnancy, gestational age, breast-feeding, height and weight of the father, parental hypertension and diabetes, birth weight, and socioeconomic status, attenuated the association. There was no consistent, statistically significant association between PWV and PHV with insulin and glucose levels as well as HOMA-IR. However, these outcomes were reduced with increasing PWV if concomitant BMI was used as an additional confounding factor.

To our knowledge, this is the only cohort study to have examined PHV and PWV from fitted growth curves over the first 2 years of life in relation to blood pressure and metabolic risk factors in childhood. Because different growth patterns after birth may lead to the same averaged weight gain or height increase during a predefined time window, we believe that the investigation of accelerated growth is important.

The timing and magnitude of PHV and PWV can be estimated by the individual growth curves fitted over the first 2 years of life, even if the peaks occur between two weight or height measurements. Furthermore this period is a critical window of tissue and organ development in which several regulatory mechanisms continue to develop after birth.

A possible limitation is related to a potential bias caused by loss for follow-up. Parents of children who participated

TABLE 2. Regression coefficients for the associations between BMI, SBP and DBP at age 10 years and peak weight and height velocities in infancy ($n = 1127$)

		Model 1[c]			Model 2[d]			Model 3[e]			Model 4[f]		
Outcome	Effect for	β	CI	*P* value	β	CI	*P* value	β	CI	*P* value	β	CI	*P* value
BMI	PWV[a]												
	Total	1.41	1.10, 1.72	<0.001	1.28	0.95, 1.60	<0.001	1.26	0.93, 1.60	<0.001			
	Males	1.42	0.98, 1.86	<0.001	1.21	0.77, 1.65	<0.001	1.23	0.78, 1.68	<0.001			
	Females	1.40	0.96, 1.85	<0.001	1.35	0.85, 1.85	<0.001	1.31	0.79, 1.82	<0.001			
	PHV[b]												
	Total	0.27	−0.05, 0.59	0.094	0.25	−0.09, 0.58	0.149	0.42	0.07, 0.77	0.019			
	Males	0.10	−0.38, 0.57	0.691	0.11	−0.36, 0.58	0.657	0.27	−0.22, 0.77	0.282			
	Females	0.42	−0.00, 0.84	0.052	0.36	−0.12, 0.84	0.139	0.54	0.03, 1.04	0.040			
SBP	PWV[a]												
	Total	3.36	2.03, 4.70	<0.001	3.56	1.99, 5.13	<0.001	3.42	1.82, 5.02	<0.001	2.13	0.51, 3.74	0.010
	Males	3.02	1.25, 4.80	0.001	3.01	1.02, 5.00	0.003	2.93	0.90, 4.97	0.005	1.77	−0.28, 3.82	0.091
	Females	3.79	1.78, 5.81	<0.001	4.49	1.94, 7.03	0.001	4.21	1.61, 6.81	0.002	2.79	0.16, 5.43	0.039
	PHV[b]												
	Total	2.98	1.67, 4.29	<0.001	2.97	1.42, 4.52	<0.001	3.40	1.77, 5.04	<0.001	2.94	1.34, 4.54	<0.001
	Males	2.94	1.08, 4.79	0.002	3.55	1.48, 5.62	0.001	3.91	1.74, 6.09	<0.001	3.64	1.52, 5.76	0.001
	Females	2.96	1.10, 4.83	0.002	1.92	−0.45, 4.29	0.113	2.48	−0.05, 5.02	0.056	1.85	−0.63, 4.34	0.145
DBP	PWV[a]												
	Total	2.34	1.17, 3.50	<0.001	2.88	1.54, 4.22	<0.001	2.84	1.47, 4.21	<0.001	1.91	0.52, 3.30	0.007
	Males	2.10	0.62, 3.59	0.006	2.29	0.63, 3.95	0.007	2.22	0.53, 3.91	0.010	1.26	−0.45, 2.97	0.149
	Females	2.60	0.76, 4.44	0.006	3.54	1.29, 5.79	0.002	3.59	1.30, 5.88	0.002	2.85	0.49, 5.20	0.018
	PHV[b]												
	Total	1.28	0.13, 2.43	0.029	1.19	−0.14, 2.53	0.079	1.39	−0.02, 2.80	0.053	1.05	−0.34, 2.43	0.140
	Males	1.96	0.41, 3.52	0.014	2.10	0.37, 3.84	0.018	2.47	0.65, 4.29	0.008	2.25	0.47, 4.02	0.014
	Females	0.54	−1.17, 2.26	0.534	−0.28	−2.37, 1.82	0.795	−0.45	−2.69, 1.79	0.693	−0.84	−3.07, 1.39	0.462

CI, confidence interval.
[a]All estimates are for a 10.2 cm/year (2-SD) increase in peak height velocity.
[b]All estimates are for a 5.1 kg/year (2-SD) increase in peak weight velocity.
[c]Adjusted for sex (in the analysis for the total population) and study centre.
[d]Adjusted for all variables in model 1 and parental education, maternal age, maternal height and weight before pregnancy, smoking during pregnancy, gestational age at birth, paternal height and weight, parental diabetes and hypertension.
[e]Adjusted for all variables in model 2 and birth weight and breastfeeding.
[f]Adjusted for all variables in model 3 and body mass index at age 10 years.

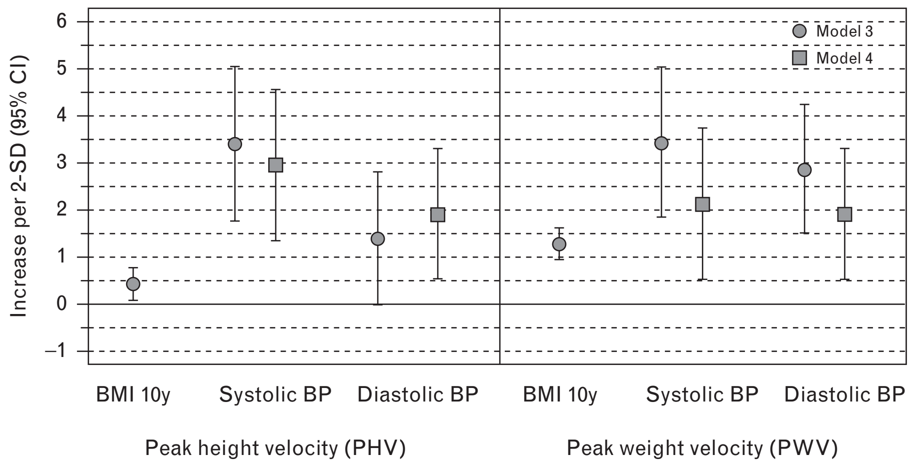

FIGURE 1 Comparison of the regression coefficients for the associations of peak weight and height velocities with (model 3) and without (model 4) adjustment for BMI at age 10 years. BMI, body mass index.

in the clinical examination at 10 years had higher socioeconomic status compared to those who did not. As socioeconomic status did not serve as an effect modifier in our study, results are considered as not likely to be biased. In addition, PHV and PWV in the original cohort were similar to those in the study population. Therefore we think that neither the power of the study nor the magnitude of the effect estimates was affected much by this.

Body mass index and blood pressure

There is extensive evidence regarding the association between weight gain during infancy and being overweight or obese in childhood, adolescence, and adulthood ([10,11]). This study supports previous findings that high PWV is a risk factor for increased BMI later in life independently of additional co-factors such as low birth weight [12], prenatal exposure to environmental tobacco smoke [13] or maternal weight gain during pregnancy [14]. In addition to the effect of PWV we found also associations for PHV which is consistent with previous studies in adults [15].

Although the association between BMI and blood pressure has been well documented in several cross-sectional studies in children [16], no single study has investigated peak growth velocity in infancy and blood pressure in childhood. A small number of studies have reported these associations for adults [3,4] and we consider our findings to be consistent with these adult studies. Compared to an adult study [3], differences occurred when the effect estimates on blood pressure were adjusted for BMI at the age of blood pressure measurement. We found that effect estimates for PWV were only attenuated when BMI at 10 years was added to the adjusted model (model 4), whereas BMI adjustment in the adult study removed the statistical significance of the effect estimate. This suggests that the association between PWV and blood pressure is less influenced by concomitant BMI in childhood versus that in adulthood. PWV in early childhood seems to be a risk factor for elevated BP apart from concurrent BMI levels and the age of blood pressure measurement. In our study, PWV was also strongly related to BMI at 10 years, and the association with blood pressure was attenuated more by the adjustment for BMI compared to PHV. However, higher concurrent BMI did not completely explain the elevated blood pressure in children who grew quickly during infancy.

There has been some controversy regarding the foetal origins hypothesis in the literature. Several observational and interventional studies have investigated effects of low birth weight on blood pressure later in life [17] and the heterogeneity in the relationship and possible publication bias have also been discussed [18]. In general, the effect of catch-up growth [19] seems to be stronger compared to foetal growth [20] or birth weight.

In our study, we did not observe any effect modification in the relationship between early peak infancy growth and metabolic outcomes by birth weight in full-term (birth weight >2500 g, gestational age >37 weeks) newborns. Our findings suggest that the effect of rapid infant growth on blood pressure and BMI was partly independent of intrauterine growth (measured by birth weight and gestational age) as shown previously for other risk factors [21]. Moreover, effect estimates for blood pressure were higher in childhood compared to the published effect estimates in adults. We speculate that the higher effect size and significance, with albeit a smaller sample size, were due to less confounding by life-style factors like active smoking, alcohol consumption and individual socioeconomic status.

Insulin and glucose levels

Adverse effects of rapid infant growth and weight gain on insulin sensitivity have been previously observed in adolescents born prematurely [22]. Singhal *et al.* [23] showed that weight gain in the first 2 weeks after birth was highly influential on the effect of concurrent BMI and a risk factor for insulin resistance in adolescents born preterm. In the subset of our cohort in which fasting glucose and insulin levels were measured, we did not find a similar association. Apart from the small sample sizes, that lead to a lack of power and are too small to draw any definitive conclusion, the differing results might be caused by the exclusion of preterm or low-birth-weight newborns from our study. Recently, Slining *et al.* [4] found no direct

TABLE 3. Mean ratios for the associations between fasting glucose and insulin levels, and HOMA at age 10 years and peak weight and height velocities in infancy ($n = 213$)

Outcome	Effect for	Model 1[c]			Model 2[d]			Model 3[e]			Model 4[f]		
		MR	CI	*P* value	MR	CI	*P* value	MR	CI	*P* value	MR	CI	*P* value
Insulin	PWV[a]												
	Total	1.00	0.83, 1.20	0.987	1.02	0.81, 1.28	0.871	0.99	0.79, 1.25	0.940	0.82	0.66, 1.02	0.076
	Males	0.98	0.76, 1.26	0.850	1.11	0.84, 1.47	0.457	1.07	0.80, 1.43	0.664	0.89	0.67, 1.18	0.410
	Females	1.03	0.79, 1.35	0.815	0.89	0.59, 1.36	0.595	0.98	0.63, 1.51	0.918	0.87	0.58, 1.31	0.498
	PHV[b]												
	Total	1.07	0.88, 1.29	0.506	1.06	0.85, 1.33	0.587	1.03	0.80, 1.31	0.826	0.96	0.76, 1.20	0.709
	Males	1.10	0.84, 1.44	0.486	1.16	0.86, 1.57	0.341	1.10	0.78, 1.54	0.587	1.07	0.78, 1.45	0.686
	Females	1.01	0.77, 1.32	0.960	0.92	0.65, 1.30	0.627	0.96	0.65, 1.39	0.814	1.01	0.71, 1.44	0.944
Glucose	PWV[a]												
	Total	0.98	0.96, 1.01	0.207	0.98	0.95, 1.00	0.096	0.98	0.95, 1.01	0.137	0.97	0.94, 1.00	0.031
	Males	0.98	0.95, 1.01	0.242	0.97	0.94, 1.01	0.175	0.98	0.94, 1.02	0.246	0.97	0.93, 1.01	0.118
	Females	0.99	0.95, 1.03	0.642	0.99	0.94, 1.05	0.773	1.00	0.94, 1.06	0.910	0.98	0.93, 1.04	0.563
	PHV[b]												
	Total	0.99	0.97, 1.02	0.568	0.99	0.96, 1.01	0.297	0.98	0.95, 1.01	0.280	0.98	0.95, 1.01	0.201
	Males	0.99	0.96, 1.03	0.709	0.97	0.94, 1.01	0.208	0.97	0.93, 1.02	0.232	0.97	0.93, 1.02	0.225
	Females	0.99	0.96, 1.03	0.677	1.00	0.95, 1.04	0.887	0.99	0.95, 1.04	0.821	0.99	0.94, 1.04	0.726
HOMA	PWV[a]												
	Total	0.94	0.78, 1.15	0.572	0.93	0.72, 1.19	0.549	0.90	0.70, 1.15	0.403	0.71	0.56, 0.90	0.005
	Males	0.96	0.73, 1.25	0.759	1.07	0.78, 1.46	0.687	1.01	0.73, 1.41	0.950	0.82	0.60, 1.12	0.221
	Females	0.93	0.70, 1.23	0.603	0.74	0.47, 1.16	0.191	0.81	0.52, 1.29	0.383	0.67	0.44, 1.02	0.070
	PHV[b]												
	Total	1.08	0.89, 1.32	0.446	1.03	0.82, 1.31	0.777	1.01	0.78, 1.31	0.951	0.94	0.74, 1.20	0.631
	Males	1.17	0.88, 1.56	0.285	1.15	0.83, 1.59	0.401	1.09	0.76, 1.58	0.633	1.09	0.78, 1.52	0.598
	Females	0.96	0.72, 1.26	0.756	0.86	0.60, 1.22	0.394	0.91	0.62, 1.34	0.644	0.95	0.67, 1.35	0.778

CI, confidence interval; HOMA-IR, Homeostasic Model Assessment for Insulin Resistance; MR, mean ratio; PHV, peak height velocity; PWV, peak weight velocity.
[a]All estimates are for a 10.2 cm/year (2-SD) increase in peak height velocity.
[b]All estimates are for a 5.1 kg/year (2-SD) increase in peak weight velocity.
[c]Adjusted for sex (in the analysis for the total population) and study centre.
[d]Adjusted for all variables in model 1 and parental education, maternal age, maternal height and weight before pregnancy, smoking during pregnancy, gestational age at birth, paternal height and weight, parental diabetes and hypertension.
[e]Adjusted for all variables in model 2 and birth weight and breastfeeding.
[f]Adjusted for all variables in model 3 and body mass index at age 10 years.

effects of early growth velocities between birth and age 4 months on insulin resistance in adults in a community-based cohort (mean gestational age 39 weeks), but small indirect effects were mediated through adult BMI and waist circumference. In our study, the inverse association between PWV and HOMA-IR was only significant after adjustment for BMI at age 10 years, which is in line with the results of Slining *et al.* [4]. Although this should be cautiously interpreted because BMI and PWV are strongly related, one might speculate that whereas PWV/PHV contributes to higher BMI at later age, this contribution is neutral from metabolic point of view and that other determinants of high BMI (e.g. nutrition or ETS in childhood) are detrimental for metabolic features.

In conclusion, our results on PHV and PWV and blood pressure confirmed those of the previous studies in adult cohorts [3]. We conclude that high PHV and PWV in early life might have an adverse impact on blood pressure at school age regardless of (low) birth weight and school age BMI.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Referee 1

This is an interesting and important piece of research relating children's peak growth height and weight velocities during the first year of life and blood pressure at age 10 years in a cohort of over 3000 children. A relationship on 213 children for insulin resistance was much less conclusive. A weakness is that only 36% of the cohort was included for the blood pressure analysis and 7% for the insulin resistance analysis due to missing information, reducing the conclusiveness of the results. The study also lacks information on parental risk factors and childhood lifestyle factors which can confound the results.

Referee 2

The paper by Thiering *et al.* addresses an issue of major scientific interest by attempting to identify early life characteristics associated with future development of hypertension and metabolic alterations. Its key strengths include innovative approach to growth velocity assessment (peak growth velocity estimation), extensive subjects' characterization and robust analytic approach. On the downside, while overall sample size is relatively large, the interpretation of study results is affected by a high rate of subjects lost to follow-up. This not only reduced the power of the study but may also have introduced an important bias, as acknowledged by the Authors.