CLINICAL STUDY

Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study

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Abstract

Objective: To examine whether infant growth rates are influenced by fetal growth characteristics and are associated with the risks of overweight and obesity in early childhood.

Design: This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward.

Methods: Fetal growth characteristics (femur length (FL) and estimated fetal weight (EFW)) were assessed in the second and third trimesters and at birth (length and weight). Infant peak weight velocity (PWV), peak height velocity (PHV), and body mass index at adiposity peak (BMIAP) were derived for 6267 infants with multiple height and weight measurements.

Results: EFW measured during the second trimester was positively associated with PWV and BMIAP during infancy. Subjects with a smaller weight gain between the third trimester and birth had a higher PWV. FL measured during the second trimester was positively associated with PHV. Gradual length gain between the second and third trimesters and between the third trimester and birth were associated with higher PHV. Compared with infants in the lowest quintile, the infants in the highest quintile of PWV had strongly increased risks of overweight/obesity at the age of 4 years (odds ratio (95% confidence interval): 15.01 (9.63, 23.38)).

Conclusion: Fetal growth characteristics strongly influence infant growth rates. A higher PWV, which generally occurs in the first month after birth, was associated with an increased risk of overweight and obesity at 4 years of age. Longer follow-up studies are necessary to determine how fetal and infant growth patterns affect the risk of disease in later life.

European Journal of Endocrinology 165 623–630

Introduction

The inverse relationship between birth weight and adverse metabolic phenotypes in adulthood has been well established (1–3). Increasing evidence suggests that infant growth patterns, such as rapid postnatal weight gain, are also risk factors for diseases in later life (4, 5). Recent data from the Northern Finland Birth Cohort 1966 Study suggest that infant growth characteristics such as the peak weight velocity (PWV) and peak height velocity (PHV) are predictors of increased blood pressure, waist circumference, and body mass index (BMI) at the age of 31 years (6). Also, BMI at the adiposity peak (BMIAP), which occurs at around 9 months of age, was positively associated with BMI at the age of 31 years (7). Growth rate in early postnatal life is highly dependent on birth weight, since

smaller babies tend to catch-up and heavier babies tend to catch-down during the first months of postnatal life (8). Birth weight is a crude measure of fetal growth as different fetal growth patterns may lead to the same birth weight (9). Growth restriction during different critical periods of fetal growth can have different metabolic consequences in adult life (10). An adverse environment has been demonstrated to influence fetal growth as early as the 10th week of pregnancy (11). Infant growth rates and patterns might be intermediates in the association between impaired fetal growth and the increased risks of obesity and metabolic diseases in later life. However, the associations between fetal growth characteristics and early postnatal growth rates are not known.

Therefore, we examined in a prenatally recruited prospective cohort study among 6267 children whether

infant growth rates are influenced by fetal growth characteristics and are associated with the risks of overweight and obesity in early childhood.

Methods

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study of 9897 children and their parents from early fetal life onward. This study is designed to identify early determinants of growth, development, and health from fetal life until young adulthood and has previously been described in detail (12). Pregnant women were asked to enroll between 2001 and 2005, and enrollment was aimed to be in the first trimester but was allowed until birth. The study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam. All participants gave written informed consent.

Population for analysis

In total, 9897 children and their parents were enrolled in the study. Of those, 8880 mothers were enrolled during pregnancy. These mothers gave birth to 8638 singleton live births (Fig. 1). Of these children, 13% ($n=1143$) lived outside the study area for postnatal follow-up and 14% ($n=1228$) had fewer than three postnatal measurements, which is necessary for the infant growth modeling, leaving $n=6267$ subjects for the analyses. Of these children, 85% ($n=5341$) were available for the analyses regarding overweight and obesity at the age of 4 years.

Figure 1 Population for analysis.

Fetal growth measurements and birth outcomes

In a dedicated research facility, we measured fetal crown-rump length (CRL) in the first trimester and fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) in the second and third trimesters to the nearest millimeter using standardized ultrasound procedures (13). Estimated fetal weight (EFW) was calculated using the formula of Hadlock ($\log_{10} \text{EFW} = 1.5662 - 0.0108 (\text{HC}) + 0.0468 (\text{AC}) + 0.171 (\text{FL}) + 0.00034 (\text{HC})^2 - 0.003685 (\text{AC} \times \text{FL})$) (14). SDS for all fetal growth characteristics were constructed on data from the study group (13). Ultrasound examinations were performed using an Aloka model SSD-1700 (Tokyo, Japan) or the ATL-Philips Model HDI 5000 (Seattle, WA, USA). For first trimester CRL, gestational age was based on the first day of the last menstrual period. Analyses were limited to women who had a CRL measurement between 10 weeks 0 days and 13 weeks 6 days, with a known and reliable first day of last menstrual period and a menstrual cycle between 24 and 32 days ($n=1377$) (11). Fetal growth measurements in the second and third trimesters were available for 6004 and 6181 children respectively. For second trimester, third trimester, and birth, gestational age was based on first trimester CRL according to the standard obstetric practice. Date of birth, birth weight and length, and infant sex were obtained from community midwives and hospital registries. Birth length was only available for 4164 individuals (66.4%), since birth length is not routinely measured in obstetric practices in the Netherlands. Gestational age-adjusted SDS for birth weight and length were constructed using growth standards from Niklasson *et al.* (15).

Postnatal growth measurements and derived infant growth parameters

Well-trained staff in the community health centers obtained postnatal growth characteristics (weight and length) using standardized procedures and BMI (kg/m^2) was calculated (12). The ages at which the children were measured were based on the national health care program in the Netherlands: 1 month; 2 months; 3 months; 4 months; 6 months; 11 months; 14 months; 18 months; 24 months; 36 months; and 48 months. The median number of postnatal growth measurements was 5 (90% range: 3–8). Overweight and obesity were defined as described by Cole *et al.* (16).

PWV and PHV PWV and PHV were derived from the postnatal data using the Reed1 model for boys and girls separately using the previously described procedure (6, 17). The Reed1 model (18) was chosen since it showed a better fit to the early growth data than the Kouchi, Carlberg, and Count models, and it showed an equally good fit to the Reed2 model which has one more

parameter than the Reed1 model. The difference compared with the simpler models, for example, the Count model, is that the Reed1 model allows the velocity to peak after birth, whereas other models force it to peak at birth. In the first couple of weeks after birth, weight may drop up to 10% in normal individuals. The PWV is thus usually not in the first weeks after birth, but slightly later. Therefore, the Reed1 model is more realistic (especially for weight) and more flexible. The Reed1 model was fitted by sex on all weight and height measurements taken at 0–3 years of age, including birth weight and length. We assumed both a fixed and a random component for all four parameters in the model. For each person, the first derivative of the fitted distance curve was taken to get the weight or height velocity curve. Subsequently, the maximum of this curve was taken to obtain the PWV or PHV in infancy. The Reed1 model is a four-parameter extension of the three-parameter Count model (19) and its functional form is (18):

$$Y = A + Bt + C\ln(t) + D/t$$

Since this model is not defined at birth ($t=0$), it was modified for this study in the same way as in Simondon *et al.* (20):

$$Y = A + Bt + C\ln(t + 1) + D/(t + 1)$$

where t , postnatal age; Y , weight or height reached at age t and A , B , C , and D the function parameters.

Of the function parameters, A is related to the baseline weight or height at birth, B to the linear component of the growth velocity, C to the decrease in the growth velocity over time, and D to the inflection point that allows growth velocity to peak after birth rather than exactly at birth. The Reed1 model is linear in its constants (19). Having two measurements was inadequate to capture the shape of the growth curve, and therefore, we restricted all association analyses to those with a minimum of three measurements per person.

Adiposity peak For BMIAP, a cubic mixed effects model was fitted on log(BMI) from 14 days to 1.5 years, using sex as a covariate (6). Modelization of BMI growth was performed from the age of 14 days onward, since 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. We assumed autoregressive AR(1) within-person correlation structure between the measurements. Then, BMI was derived for each individual at the point where the curve reaches its maximum, i.e. at infant adiposity peak.

Covariates

At enrollment, data regarding maternal age, pre-pregnancy weight, parity, smoking, and paternal height and weight were obtained by questionnaires (12). Both parents were asked to provide details regarding the country of birth of their parents. This information was used to classify the ethnic background of the child according to Statistics Netherlands, as described previously in detail (21). Maternal height was measured at our research center and BMI was calculated as weight (kg)/height (m)². We obtained information regarding breastfeeding duration by postnatal questionnaires at the ages of 2, 6, and 12 months. Mothers were asked whether they ever breastfed their child and, if so, at what age they stopped breastfeeding.

Table 1 Parental and child characteristics ($n=6267$). Values are means (s.d.), percentages or medians (90% range).

Characteristics	Values
Maternal characteristics	
Age (years)	30.3 (5.1)
Weight (kg)	67.0 (52.0–94.0)
Height (cm)	167.7 (7.4)
Body mass index (kg/m ²)	23.7 (19.4–33.3)
Educational level	
Primary (%)	9.2%
Secondary (%)	42.6%
Higher (%)	48.2%
Smoked during pregnancy (% yes)	23.9%
Parity (% primiparous)	56.3%
Paternal characteristics	
Age (years)	33.1 (5.4)
Weight (kg)	83.0 (65.0–106.0)
Height (cm)	182.2 (7.8)
Body mass index (kg/m ²)	24.9 (20.2–31.1)
Fetal and child characteristics	
Sex (% males)	50.6%
Ethnicity	
Caucasian (%)	66.5%
Turkish (%)	7.6%
Surinamese (%)	7.0%
Moroccan (%)	6.1%
Other/mixed (%)	13.8%
First trimester	
Gestational age (weeks)	12.4 (10.0–13.9)
Crown-rump length (mm)	60.9 (11.4)
Second trimester	
Gestational age (weeks)	20.5 (18.9–22.7)
Estimated fetal weight (g)	380 (91)
Femur length (mm)	33.4 (3.5)
Third trimester	
Gestational age (weeks)	30.4 (28.9–32.2)
Estimated fetal weight (g)	1623 (254)
Femur length (mm)	57.4 (3.0)
Birth	
Gestational age (weeks)	40.1 (37.1–42.1)
Weight (g)	3442 (543)
Length (cm)	50.2 (2.4)
Infancy	
Number of postnatal measurements	5 (3–8)
Peak weight velocity (PWV; kg/year)	12.3 (9.1–16.1)
Age at peak weight velocity (PWV; months)	0.8 (0.6–1.0)
Peak height velocity (PHV; cm/year)	48.5 (38.7–64.9)
Age at peak height velocity (PHV; months)	0.6 (0.2–1.0)
Adiposity peak, body mass index (kg/m ²)	17.6 (0.8)
Breastfeeding duration (months)	3.5 (0.5–12.0)

Statistical analysis

First, using multivariate linear regression models and adjusting for covariates, we assessed the associations of CRL in the first trimester, EFW in the second and third trimesters, and birth weight with infant PWV and BMIAP. The covariates in the model were fetal ethnicity, maternal age, maternal educational level, maternal pre-pregnancy BMI, maternal smoking, paternal BMI, parity, duration of breastfeeding, and number of postnatal measurements. The covariates were based on whether they were associated with the postnatal growth parameters. The interaction parameters 'fetal growth-sex' and 'fetal growth-smoking' were not associated with postnatal growth and were therefore not included in the models. Using similar models, we then examined whether weight change (in SDS) between the second and third trimesters (second trimester weight gain), and between the third trimester and birth (third trimester weight gain), was associated with infant PWV and BMIAP. Subsequently, similar analyses were repeated for the associations of (femur) length with PHV and BMIAP. Since fetal body length cannot be measured, FL in the second and third trimesters was used as a proxy for body length (22). Finally, using multivariate logistic regression models, we assessed whether PWV, PHV, and BMIAP were associated with the risks of overweight and obesity during infancy at the age of 4 years (16). To distinguish between antenatal and postnatal determinants, this model was subsequently additionally adjusted for birth weight. For this purpose, PWV, PHV, and BMIAP were stratified into quintiles and the lowest quintile was used as the reference category. Analyses were performed using the Statistical Package of Social Sciences version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) and R version 2.10.1 (The R Foundation for Statistical Computing).

Results

Subject characteristics are shown in Table 1. Of all the children, 67% were of Caucasian ethnicity. The mean maternal age was 30.3 years, the median maternal weight was 67.0 kg, and the mean maternal height was 167.7 cm.

There were no significant associations between first trimester CRL and PWV, PHV, and BMIAP (Table 2). EFW measured during the second trimester was positively associated with PWV and BMIAP (both *P* value for linear trend <0.05; Table 3). Also, we found a positive association between birth weight and BMIAP (*P* value for linear trend <0.0001), while the association between birth weight and PWV was inverse (*P* value for linear trend <0.05). Weight gain between both the second and third trimesters and the third

Table 2 The association of first trimester crown-rump length (CRL) with peak weight velocity (PWV), peak height velocity (PHV), and BMI at adiposity peak (BMIAP). Median age at measurement in first trimester (in weeks): 12.4 (90% range: 10.0–13.9). Values represent geometric means (s.d.). Model is adjusted for sex, age, fetal ethnicity, age of mother, menstrual cycle duration, maternal pre-pregnancy BMI, maternal educational level, maternal smoking, paternal BMI, parity, duration of breastfeeding, and number of postnatal measurements.

CRL first trimester (SDS)	PWV (kg/year; <i>n</i> =1376)	PHV (cm/year; <i>n</i> =1349)	BMIAP (kg/m ² ; <i>n</i> =1282)
1st quintile	11.79 (1.18)	48.79 (1.16)	17.45 (0.78)
2nd quintile	11.95 (1.19)	48.30 (1.17)	17.59 (0.79)
3rd quintile	12.08 (1.19)	48.94 (1.17)	17.58 (0.82)
4th quintile	12.02 (1.20)	49.00 (1.17)	17.57 (0.84)
5th quintile	11.95 (1.19)	48.35 (1.17)	17.56 (0.75)
<i>P</i> value for linear trend	0.32	0.85	0.65

trimester and birth was positively associated with BMIAP (both *P* values for linear trends <0.0001). Infants with a smaller weight gain between the third trimester and birth had a higher PWV (*P* value for linear trend <0.0001). Prenatal growth parameters were not associated with the ages of PWV and PHV (data not shown).

FL measured during the second trimester was positively associated with PHV and negatively associated with BMIAP (both *P* value for linear trend <0.05; Table 4). At birth, these associations were both reversed where length was negatively associated with PHV and positively associated with BMIAP (*P* values for linear trends <0.0001). Gradual length gain between both the second and third trimesters and between the third trimester and birth was associated with higher PHV after birth (*P* values for linear trends <0.05). Length gain between the third trimester and birth was positively associated with BMIAP (*P* value for linear trend <0.0001).

Table 5 shows the associations between PWV, PHV, and BMIAP with the risks of overweight and obesity at the age of 4 years. Subjects in the highest quintile of PWV had an increased risk of being overweight/obese at the age of 4 years (odds ratios (95% confidence interval (CI)): 15.01 (9.63, 23.38)). There was no association between PHV and the risk of overweight or obesity at the age of 4 years. These results did not materially change after additional adjustment for birth weight. The ages at PWV and PHV were not associated with the risk of obesity at the age of 4 years (data not shown).

Discussion

We demonstrated strong associations between fetal growth characteristics and infant growth rates. The direction and size of the associations were dependent on

Table 3 The association of estimated fetal weight (EFW) with peak weight velocity (PWV) and BMI at adiposity peak (BMIAP). Values represent geometric means (s.d.). Model is adjusted for sex, age, fetal ethnicity, age of mother, maternal pre-pregnancy BMI, maternal educational level, maternal smoking, paternal BMI, parity, duration of breastfeeding, and number of postnatal measurements. Median age at measurement in the second trimester (in weeks): 20.5 (90% range: 18.9–22.7). Median age at measurement in the third trimester (in weeks): 30.4 (90% range: 28.9–32.2). Median age at measurement at birth (in weeks): 40.1 (90% range: 37.1–42.1).

EFW	PWV (kg/year)	BMIAP (kg/m ²)
Second trimester (SDS)		
<i>n</i>	5943	5421
1st quintile	12.02 (1.19)	17.52 (0.80)
2nd quintile	12.01 (1.18)	17.56 (0.80)
3rd quintile	12.12 (1.18)	17.60 (0.80)
4th quintile	12.22 (1.19)	17.64 (0.82)
5th quintile	12.16 (1.16)	17.68 (0.77)
<i>P</i> value for linear trend	<0.05	<0.05
Third trimester (SDS)		
<i>n</i>	6114	5598
1st quintile	12.00 (1.18)	17.41 (0.80)
2nd quintile	12.09 (1.19)	17.53 (0.80)
3rd quintile	12.18 (1.18)	17.64 (0.77)
4th quintile	12.12 (1.20)	17.67 (0.81)
5th quintile	12.16 (1.19)	17.80 (0.79)
<i>P</i> value for linear trend	0.47	<0.0001
Birth weight (SDS)		
<i>n</i>	6265	5705
1st quintile	12.16 (1.18)	17.25 (0.78)
2nd quintile	12.23 (1.19)	17.46 (0.76)
3rd quintile	12.18 (1.19)	17.62 (0.76)
4th quintile	12.08 (1.19)	17.74 (0.76)
5th quintile	11.86 (1.20)	17.95 (0.79)
<i>P</i> value for linear trend	<0.05	<0.0001
Weight change from second to third trimester (SDS)		
<i>n</i>	5829	5332
1st quintile	12.16 (1.18)	17.50 (0.78)
2nd quintile	12.09 (1.19)	17.55 (0.79)
3rd quintile	12.08 (1.19)	17.59 (0.82)
4th quintile	12.11 (1.19)	17.63 (0.80)
5th quintile	12.05 (1.19)	17.75 (0.81)
<i>P</i> value for linear trend	0.09	<0.0001
Weight change from third trimester to birth (SDS)		
<i>n</i>	6141	5596
1st quintile	12.39 (1.18)	17.43 (0.82)
2nd quintile	12.15 (1.19)	17.54 (0.78)
3rd quintile	12.14 (1.19)	17.64 (0.78)
4th quintile	12.09 (1.18)	17.71 (0.79)
5th quintile	11.78 (1.19)	17.78 (0.80)
<i>P</i> value for linear trend	<0.0001	<0.0001

the timing of the fetal growth variation. EFW measured during the second trimester was positively associated with both PWV and BMIAP during infancy. Gradual weight and height gain between the third trimester and birth were associated with higher PWV and PHV respectively. Both higher PWV and BMIAP during infancy were strongly positively associated with increased risks of overweight and obesity at the age of 4 years.

To our knowledge, this is the first study that has examined the associations of infant growth rates with both fetal growth characteristics and the risks of overweight and obesity in childhood. Analyses were performed in a large sample that made our study well powered. Furthermore, data were available for a large number of covariates. A limitation might be that 16.4% of the children had fewer than three postnatal measurements and were therefore not included in the analyses. A minimum of three measurements was set for the postnatal growth modeling. Birth weight and birth length were lower in children without postnatal data available for analyses (70.6 (95% CI: 42.8, 98.4) g and 0.26 (95% CI: 0.06, 0.46) cm respectively). Also, birth length was missing in 33.6% of our sample, since this measurement is not a part of the routine obstetric practice in the Netherlands. Subjects without birth length measurements had a slightly smaller FL in the second and third trimesters ($P=0.07$ and $P=0.04$ respectively) and a lower PHV (-0.60 (95% CI: -1.05 , -0.16) cm/year). Smaller babies at birth are more likely to show lower growth rates in the third trimester and increased growth rates during early infancy than normal size newborns. Therefore, we expect that this selection most likely will lead to an underestimation of inverse associations between growth rates in the third trimester and peak growth velocity during infancy.

Recently, it was demonstrated in a population-based study from Finland that both PWV and PHV in the first months after life were associated with increased risks of higher blood pressure and BMI in adulthood (6). Previously, catch-up growth or upward growth re-alignment in the first 2 years of postnatal life was shown to be associated with an adverse adult metabolic phenotype (5, 23). Moreover, it has been shown that children who were born small-for-gestational-age and had a rapid weight gain in the first 3 months of life were at increased risk of development of risk factors for cardiovascular disease and type 2 diabetes (24). It seems that rapid weight gain in the first months immediately after birth may be of greater importance than catch-up growth during the first 2 years (25). Adaptations in early postnatal growth rates are influenced by a drive to compensate for prenatal fetal growth restriction or growth acceleration caused by the maternal–uterine environment (26). In our study, we indeed found that there was a strong negative association between weight or height gain from the third trimester until birth and PWV and PHV during infancy. In contrast, growth in weight and height measured in the second trimester was positively associated with PWV and PHV respectively. Body stature and size are known to be a highly heritable trait, with a large genetic component (27, 28). It could be hypothesized that the fetus grows along its growth curve during the first half of pregnancy but that this curve is more susceptible to maternal–uterine factors during late pregnancy. After birth, however, the child may continue along its original genetically

Table 4 The association of femur length with PHV and BMI at adiposity peak (BMIAP). Values represent geometric means (s.d.). Model is adjusted for sex, age, fetal ethnicity, age of mother, maternal pre-pregnancy BMI, maternal educational level, maternal smoking, paternal BMI, parity, duration of breastfeeding, and number of postnatal measurements. Median age at measurement in the second trimester (in weeks): 20.5 (90% range: 18.9–22.7). Median age at measurement in the third trimester (in weeks): 30.4 (90% range: 28.9–32.2). Median age at measurement at birth (in weeks): 40.1 (90% range: 37.1–42.1).

	PHV (cm/year)	BMIAP (kg/m ²)
Femur length		
Second trimester (SDS)		
<i>n</i>	5802	5448
1st quintile	48.89 (1.16)	17.67 (0.82)
2nd quintile	49.45 (1.18)	17.63 (0.76)
3rd quintile	48.73 (1.17)	17.62 (0.80)
4th quintile	49.48 (1.18)	17.55 (0.84)
5th quintile	49.28 (1.17)	17.54 (0.79)
<i>P</i> value for linear trend	<0.05	<0.05
Third trimester (SDS)		
<i>n</i>	5993	5619
1st quintile	49.53 (1.18)	17.64 (0.82)
2nd quintile	49.21 (1.18)	17.66 (0.81)
3rd quintile	49.41 (1.17)	17.60 (0.79)
4th quintile	49.18 (1.17)	17.61 (0.79)
5th quintile	48.45 (1.16)	17.54 (0.80)
<i>P</i> value for linear trend	0.47	<0.01
Birth length (SDS)		
<i>n</i>	4125	3833
1st quintile	56.26 (1.20)	17.46 (0.78)
2nd quintile	50.52 (1.16)	17.51 (0.80)
3rd quintile	48.51 (1.14)	17.62 (0.78)
4th quintile	46.76 (1.14)	17.66 (0.79)
5th quintile	43.22 (1.14)	17.77 (0.79)
<i>P</i> value for linear trend	<0.0001	<0.0001
Length change from second to third trimester (SDS)		
<i>n</i>	5717	5369
1st quintile	49.82 (1.19)	17.57 (0.83)
2nd quintile	49.56 (1.17)	17.60 (0.79)
3rd quintile	49.01 (1.17)	17.61 (0.81)
4th quintile	48.71 (1.16)	17.62 (0.77)
5th quintile	48.53 (1.16)	17.62 (0.81)
<i>P</i> value for linear trend	<0.05	0.66
Length change from third trimester to birth (SDS)		
<i>n</i>	4007	3789
1st quintile	55.47 (1.20)	17.42 (0.77)
2nd quintile	50.39 (1.16)	17.56 (0.79)
3rd quintile	48.40 (1.15)	17.56 (0.79)
4th quintile	47.04 (1.15)	17.70 (0.80)
5th quintile	44.10 (1.15)	17.81 (0.74)
<i>P</i> value for linear trend	<0.001	<0.0001

determined growth curve or may deviate from this due to compensatory accelerated or decelerated growth as a response to decreased or increased fetal third trimester growth respectively. Finally, the first trimester CRL was not associated with any of the derived postnatal growth parameters. We have previously described that the first trimester CRL is associated with prenatal and early postnatal growth but that these associations are much stronger before birth than after birth (11). Thus, though

the first trimester analyses were not nearly as well powered as the analyses of later pregnancy, this lack of associations is most likely due to the fact that there is no relationship between the first trimester growth and PWV, PHV, or BMIAP.

The relationship between obesity during infancy and during later life (both childhood and adulthood) is complex. In the study of Rolland-Cachera *et al.* (29), the authors found a twofold increased risk of being obese at the age of 21 years if the individual was also obese at the age of 1 year. This would be similar with our current study, where we find a strong association between BMIAP (which occurs at around 0.75 years) and obesity at the age of 4 years. Also, in the Northern Finland Birth Cohort Study 1966, it was also found that BMIAP was associated with higher BMI at 31 years of age (7). The phenomenon where children tend to stay more or less in the same percentile of growth is also called tracking. In contrast, the study of Eriksson *et al.* (30) shows an inverse relationship between BMI at the age of 1 year and obesity in adulthood. These findings are in line with our previous study regarding the association between obesity gene *FTO* and BMI during early life (31). Here, we found that the obesity risk allele

Table 5 The association of PWV, PHV, and BMI at adiposity peak (BMIAP) with the risk of overweight/obesity at the age of 4 years. Overweight/obesity based on standard definitions established by Cole *et al.* (16). Values represent odds ratios (95% confidence interval) based on multivariate logistic regression. Model 1 is adjusted for sex, age, fetal ethnicity, age of mother, maternal pre-pregnancy BMI, maternal educational level, maternal smoking, paternal BMI, parity, duration of breastfeeding, and number of postnatal measurements. Model 2 is additionally adjusted for birth weight (SDS).

	Overweight/obesity	
	Model 1	Model 2
PWV (kg/year)		
1st quintile	Reference	Reference
2nd quintile	2.70 (1.74, 4.19) [†]	2.79 (1.79, 4.34) [†]
3rd quintile	3.77 (2.43, 5.84) [†]	4.06 (2.61, 6.31) [†]
4th quintile	6.00 (3.88, 9.29) [†]	6.49 (4.18, 10.09) [†]
5th quintile	15.01 (9.63, 23.38) [†]	16.33 (10.43, 25.55) [†]
<i>P</i> for linear trend	<0.0001	<0.0001
PHV (cm/year)		
1st quintile	Reference	Reference
2nd quintile	1.14 (0.83, 1.56)	1.25 (0.91, 1.71)
3rd quintile	1.01 (0.73, 1.40)	1.18 (0.84, 1.64)
4th quintile	0.82 (0.58, 1.16)	0.96 (0.67, 1.37)
5th quintile	1.00 (0.70, 1.41)	1.26 (0.88, 1.82)
<i>P</i> for linear trend	0.57	0.35
BMIAP (kg/m ²)		
1st quintile	Reference	Reference
2nd quintile	3.46 (1.68, 7.14) [†]	3.49 (1.69, 7.12) [†]
3rd quintile	7.66 (3.86, 15.21) [†]	7.75 (3.84, 15.42) [†]
4th quintile	16.65 (8.54, 32.48) [†]	16.96 (8.64, 33.28) [†]
5th quintile	47.28 (24.26, 92.12) [†]	48.38 (24.57, 95.27) [†]
<i>P</i> for linear trend	<0.0001	<0.0001

[†]*P*<0.001.

was associated with lower BMIAP (at the age of about 0.75 years) (31). This finding may reflect rapid early weight gain or sometimes called catch-up growth. The most plausible explanation for this apparent contradiction is that there are actually two phenomena occurring simultaneously, namely tracking and early rapid weight gain. The most convincing evidence for this theory is the study of Parsons *et al.* (32) using data from the 1958 Birth Cohort. In this study, they found the association between birth weight and BMI in adulthood to be J-shaped. Children in the lower ranges of (birth) weight in early life tend to show rapid weight gain in early life, which ultimately may lead to obesity in adulthood. On the other side of the spectrum, children in the upper ranges tend to track and continue to have a high BMI in adulthood. In our study, EFW measured during the second trimester was positively associated with BMIAP. Also, birth weight itself was strongly positively associated with BMI at the age of 4 years (data not shown). Based on the data from the current study, it could be hypothesized that fetuses that show third trimester growth restriction in late pregnancy, which might lead to a lower birth weight, show rapid weight gain postnatally and thus are at increased risk of developing obesity in later life. In contrast, fetuses that grow in the highest percentiles for weight, from the second trimester onward, are more likely to continue following this curve during postnatal life, which could ultimately lead to a higher BMI as adults.

In conclusion, we demonstrated strong associations between fetal growth characteristics and infant growth rates. EFW measured during the second trimester was positively associated with a higher PWV during infancy. Both gradual weight gain and height gain between the third trimester and birth were strongly associated with higher postnatal PWV and PHV respectively. Higher PWV, which generally occurs in the first month after birth, was a strong predictor of childhood overweight and obesity. Results from our study suggest that studies relating to birth size with outcomes in later life should take the longitudinal fetal and infant growth measures into account. Longer follow-up studies are necessary to determine how infant growth patterns affect the risk of disease in later life.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The general design of Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (I), the Ministry of Health, Welfare and Sport and the Ministry of Youth and Families. V W V Jaddoe received additional grants from the Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159).

Acknowledgements

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. Furthermore, we acknowledge Medical Research Council, MRC, UK (velocity modelling work) and the Academy of Finland and Biocenter Oulu, University of Oulu, Finland.

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Received 21 January 2011

Revised version received 6 July 2011

Accepted 20 July 2011