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

Fetal and infant growth and the risk of obesity

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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 onwards.

Methods:

Fetal growth characteristics (femur length and estimated fetal weight) were assessed in second and third trimester 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 6 267 infants with multiple height and weight measurements.

Results:

Estimated fetal weight measured during second trimester was positively associated with PWV and BMIAP during infancy. Subjects with a smaller weight increase between 3rd trimester and birth had a higher PWV. Femur length measured during second trimester was positively associated with PHV. Slower length gain between second and third trimester and between third trimester and birth were associated with higher PHV. As compared to infants in the lowest quintile, those in the highest quintile of PWV had strongly increased risks of overweight/obesity at the age of 4 years (Odds Ratio (95% CI): 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.

Keywords: fetal growth, childhood obesity, cohort, growth rates, pediatrics

INTRODUCTION

The inverse relationship between birth weight and adverse metabolic phenotypes in adulthood has been well established [1-3]. Increasing evidence suggest that also infant growth patterns such as rapid postnatal weight gain are risk factors for diseases in later life [4, 5]. Recent data from the Northern Finnish 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 of 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 6 267 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 9 897 children and their parents from early fetal life onwards. This study is designed to identify early determinants of growth, development and health from fetal life until young adulthood and has been described previously in detail [12]. Pregnant women were asked to enrol between 2001 and 2005, and enrolment was aimed for in first trimester but was allowed until birth. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. All participants gave written informed consent.

Population for analysis

In total, 9 897 children and their parents were enrolled in the study. Of those, 8 880 mothers were enrolled during pregnancy. These mothers gave birth to 8 638 singleton live births (Figure 1). Of these children, 13 percent (n=1 143) lived outside the study area for postnatal follow-up, and 14 percent (n=1 228) children had fewer than three postnatal measurements, which is necessary for the infant growth modelling, leaving n=6 267 subjects for the analyses. Of these children, 85 percent (n=5 341) were available for the analyses regarding overweight and obesity at the age of 4 years.

Fetal growth measurements and birth outcomes

In a dedicated research facility, we measured fetal crown-rump length (CRL) in first trimester and fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) in second and third trimester to the nearest millimeter using standardized ultrasound procedures [13]. Estimated fetal weight (EFW) was calculated using the formula by Hadlock ($\log_{10}$ EFW = 1.5662 – 0.0108 (HC) + 0.0468 (AC) + 0.171 (FL) + 0.00034 $(HC)^2$ – 0.003685 (AC * FL)) [14]. Standard deviation scores 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 days 6 days, with a known and reliable first day of last menstrual period and a menstrual cycle between 24 and 32 days (n=1,377) [11]. Fetal growth measurements in second and third trimester were available in 6,004 and 6,181 children, respectively. For second trimester, third trimester and birth, gestational age was based on first trimester CRL according to standard obstetric practice. Date of birth, birth weight and length and infant sex were obtained from community midwife and hospital registries. Birth length was only available in 4,164 individuals (66.4%), since birth length is not routinely measured in obstetric practices in the Netherlands. Gestational age adjusted standard deviation scores (SDS) for birth weight and length, were constructed using growth standards from Niklasson [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].

Peak weight velocity and peak height velocity

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 to 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 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 4-parameter extension of the 3-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]. Modelisation of BMI growth was performed from the age of 14 days onwards, since children may lose up to 10% of their body weight in the first two 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 enrolment, data regarding maternal age, pre-pregnancy weight, parity, smoking and paternal height and weight was 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 ethnic background of the child according to Statistics Netherlands, as previously described in detail [21]. Maternal height was measured at our research center and body mass index (BMI) was calculated (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.

Statistical analysis

First, using multivariate linear regression models and adjusting for covariates, we assessed the associations of crown-rump length in first trimester, estimated fetal weight in second and third trimester 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 second trimester and third trimester (second trimester weight gain), and between third trimester and birth (third trimester weight gain), were 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, femur length in second and third trimester 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 additional 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 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). Estimated fetal weight measured during 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 second and third trimester, and between third trimester and birth were both positively associated with BMIAP (both p-values for linear trends <0.0001). Infants with a smaller weight gain between 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).

Femur length measured during 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). Slower length gain between second and third trimester, and between third trimester and birth were both associated with higher PHV after birth (p-values for linear trends <0.05). Length gain between 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 (OR (95% 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 the timing of the fetal growth variation. Estimated fetal weight measured during second trimester was positively associated with both PWV and BMIAP during infancy. Slower weight and height gain between 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 modelling. Birth weight and birth length were lower in children without postnatal data available for analyses (70.6 (95% CI: 42.8, 98.4) grams 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 femur length in second and third trimester (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 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 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 two 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 two 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 third trimester until birth, and PWV and PHV during infancy. In contrast, growth in weight and height measured at 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 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, first trimester crown-rump length was not associated with any of the derived postnatal growth parameters. We have previously described that first trimester crown-rump length is associated with pre- 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 assocations are most likely due to the fact that there is no relationship between 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. the authors found a two-fold increased risk of being obese at the age of 21 years if the individual was also obese at the age of 1 year [29]. 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 Finnish Birth Cohort Study 1966, it was also found that BMI at adiposity peak 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. shows an inverse relationship between BMI at the of 1 year and obesity in adulthood [30]. 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 was associated with an 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. 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 [32]. 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 body mass index in adulthood. In our study, estimated fetal weight measured during 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 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 second trimester onwards are more likely to continue following this curve during postnatal life, which ultimately could lead to a higher BMI as adults.

In conclusion, we demonstrated strong associations between fetal growth characteristics and infant growth rates. Estimated fetal weight measured during second trimester was positively associated with a higher PWV during infancy. Both slower weight gain and height gain between 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 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

All authors have no conflict of interest to declare.

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Table 1. Parental and child characteristics (n=6 267)

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 (grams)	380 (91)
Femur length (mm)	33.4 (3.5)
Third trimester	
Gestational age (weeks)	30.4 (28.9 – 32.2)
Estimated fetal weight (grams)	1 623 (254)
Femur length (mm)	57.4 (3.0)
Birth	
Gestational age (weeks)	40.1 (37.1 – 42.1)
Weight (grams)	3 442 (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/m2)	17.6 (0.8)
Breastfeeding duration (months)	3.5 (0.5 – 12.0)

Values are means (standard deviation), percentages or medians (90% range).

Table 2: The association of first trimester crown-rump length with peak weight velocity, peak heigth velocity and body mass index at adiposity peak.

Crown-rump length 1st trimester (SDS)	Peak weight velocity (PWV) (kg/year) (n=1,376)	Peak height velocity (PHV) (cm/year) (n=1,349)	Adiposity peak (BMI) (kg/m^2) (n=1,282)
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)
p-value for linear trend	0.32	0.85	0.65

Median age at measurement in first trimester (in weeks): 12.4 (90% range: 10.0 – 13.9)
Values represent geometric means (standard deviation).
Model is adjusted for sex, age, fetal ethnicity, age of mother, menstrual cycle duration, maternal pre-pregnancy body mass index, maternal educational level, maternal smoking, paternal body mass index, parity, duration of breastfeeding and number of postnatal measurements.
SDS: Standard Deviation Score

Table 3. The association of (estimated fetal) weight with peak weight velocity and body mass index at adiposity peak

Estimated fetal weight 2nd trimester (SDS)	**Peak weight velocity (PWV) (kg/year) (n=5 943)**	**Adiposity peak (BMI) (kg/m^2) (n=5 421)**
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)
p-value for linear trend	< 0.05	<0.05
Estimated fetal weight 3rd trimester (SDS)	**Peak weight velocity (PWV) (kg/year) (n=6 114)**	**Adiposity peak (BMI) (kg/m^2) (n=5 598)**
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)
p-value for linear trend	0.47	< 0.0001
Birth weight (SDS)	**Peak weight velocity (PWV) (kg/year) (n=6 265)**	**Adiposity peak (BMI) (kg/m^2) (n=5 705)**
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)
p-value for linear trend	< 0.05	< 0.0001
Weight change from 2nd	**Peak weight velocity**	**Adiposity peak (BMI)**

to 3rd trimester (SDS)	(PWV) (kg/year) (n=5 829)	(kg/m^2) (n=5 332)
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)
p-value for linear trend	0.09	< 0.0001
Weight change from 3rd trimester to birth (SDS)	**Peak weight velocity (PWV) (kg/year) (n=6 141)**	**Adiposity peak (BMI) (kg/m^2) (n=5 596)**
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)
p-value for linear trend	< 0.0001	< 0.0001

Median age at measurement in second trimester (in weeks): 20.5 (90% range: 18.9 – 22.7)
Median age at measurement in 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)
Values represent geometric means (standard deviation).
Model is adjusted for sex, age, fetal ethnicity, age of mother, maternal pre-pregnancy body mass index, maternal educational level, maternal smoking, paternal body mass index, parity, duration of breastfeeding and number of postnatal measurements.
SDS: Standard Deviation Score.

Table 4. The association of (femur) length with peak height velocity and body mass index at adiposity peak

Femur length 2nd trimester (SDS)	Peak height velocity (PHV) (cm/year) (n=5 802)	Adiposity peak (BMI) (kg/m^2) (n=5 448)
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)
p-value for linear trend	< 0.05	< 0.05
Femur length 3rd trimester (SDS)	**Peak height velocity (PHV) (cm/year) (n=5 993)**	**Adiposity peak (BMI) (kg/m^2) (n=5 619)**
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)
p-value for linear trend	0.47	< 0.01
Birth length (SDS)	**Peak height velocity (PHV) (cm/year) (n=4 125)**	**Adiposity peak (BMI) (kg/m^2) (n=3 833)**
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)
p-value for linear trend	< 0.0001	< 0.0001
Length change from 2nd	**Peak height velocity**	**Adiposity peak (BMI)**

to 3rd trimester (SDS)	(PHV) (cm/year) (n=5 717)	(kg/m²) (n=5 369)
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)
p-value for linear trend	< 0.05	0.66
Length change from 3rd trimester to birth (SDS)	**Peak height velocity (PHV) (cm/year) (n=4 007)**	**Adiposity peak (BMI) (kg/m²) (n=3 789)**
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)
p-value for linear trend	< 0.001	< 0.0001

Median age at measurement in second trimester (in weeks): 20.5 (90% range: 18.9 – 22.7)
Median age at measurement in 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)
Values represent geometric means (standard deviation).
Model is adjusted for sex, age, fetal ethnicity, age of mother, maternal pre-pregnancy body mass index, maternal educational level, maternal smoking, paternal body mass index, parity, duration of breastfeeding and number of postnatal measurements.
SDS: Standard Deviation Score.

Table 5. The association of peak weight velocity, peak height velocity and body mass index at adiposity peak with the risk of overweight/obesity[16] at the age of 4 years.

Peak weight velocity (PWV) (kg/year)	Model 1: Overweight/Obesity	Model 2: Overweight/Obesity
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)***
p for linear trend	< 0.0001	< 0.0001
Peak height velocity (PHV) (cm/year)	**Model 1: Overweight/Obesity**	**Model 2: Overweight/Obesity**
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)
p for linear trend	0.57	0.35
Body mass index at adiposity peak (BMIAP) (kg/m^2)	**Model 1: Overweight/Obesity**	**Model 2: Overweight/Obesity**
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)***
p for linear trend	< 0.0001	< 0.0001

Overweight/obesity based on standard definitions established by Cole et al [16].
Values represent odds ratio's (95% confidence interval) based on multivariate logistic regression.
Model 1 is adjusted for sex, age, fetal ethnicity, age of mother, maternal pre-pregnancy body mass index, maternal educational level, maternal smoking, paternal body mass index, parity, duration of breastfeeding and number of postnatal measurements.
Model 2 is additionally adjusted for birth weight (standard deviation score).
** p<0.05, ** p<0.01, *** p<0.001*

Figure 1. Population for analysis.