



Universiteit  
Leiden  
The Netherlands

## **Long-term consequences of differences in early growth : epidemiological aspects**

Euser, A.M.

### **Citation**

Euser, A. M. (2009, December 8). *Long-term consequences of differences in early growth : epidemiological aspects*. Retrieved from <https://hdl.handle.net/1887/14485>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/14485>

**Note:** To cite this publication please use the final published version (if applicable).

# 8

## **Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm**

A.M. Euser

M.J.J. Finken

M.G. Keijzer-Veen

E.T.M. Hille

J.M. Wit

F.W. Dekker

on behalf of the Dutch POPS-19 Collaborative Study Group

*Am J Clin Nutr* 2005; 81: 480-487

## **Abstract**

### **Background**

Increasing evidence indicates that adult body composition is associated with prenatal and infancy weight gain, but the relative importance of different time periods has not been elucidated.

### **Objective**

The objective was to study the association between prenatal, early postnatal, and late infancy weight gain and body mass index (BMI), fat mass, and fat distribution in young adulthood.

### **Design**

We included 403 men and women aged 19 y from a Dutch national prospective follow-up study who were born at <32 wk of gestation. BMI, waist circumference, and waist-to-hip ratio SD scores and subscapular-to-triceps ratio, percentage body fat, fat mass, and fat-free mass at age 19 y were studied in relation to birth weight SD scores, weight gain from preterm birth until 3 mo postterm (early postnatal weight gain), and weight gain from 3 mo until 1 y postterm (late infancy weight gain).

### **Results**

Birth weight SD scores were positively associated with weight, height, BMI SD scores, and fat-free mass at age 19 y but not with fat mass, percentage body fat, or fat distribution. Early postnatal and late infancy weight gain were positively associated with adult height, weight, BMI, waist circumference SD scores, fat mass, fat-free mass, and percentage body fat but not with waist-to-hip ratio SD scores or subscapular-to-triceps ratio.

### **Conclusions**

In infants born very preterm, weight gain before 32 wk of gestation is positively associated with adult body size but not with body composition and fat distribution. More early postnatal and, to a lesser extent, late infancy weight gain are associated with higher BMI SD scores and percentage body fat and more abdominal fat at age 19 y.

## **Introduction**

Obesity is a major health problem throughout the world. Numerous studies have shown an association between obesity and various cardiovascular disease risk factors, such as diabetes, hypertension, and dyslipidemia.<sup>1-3</sup> Obesity is also associated with an increased risk of death.<sup>4</sup>

Fetal life and the early postnatal period have been suggested to be important for the development of adult obesity.<sup>5,6</sup> The Dutch famine studies have shown that reduced maternal calorie intake during the first 2 trimesters of pregnancy might increase the risk of adult obesity.<sup>7,8</sup> The association between birth weight, mainly an indicator of fetal growth during the third trimester, and adult obesity is equivocal.<sup>9</sup> In several studies, a linear positive association was found,<sup>10-12</sup> whereas in others a J- or U-shape association<sup>13,14</sup> or no association<sup>15</sup> was observed. In these studies, obesity was expressed as body mass index (BMI; in kg/m<sup>2</sup>), which includes both fat mass and fat-free mass.

In studies about fat mass and fat distribution, low birth weight has been associated with a more central pattern of fat distribution<sup>16,17</sup> and a lower BMI, mostly because of a lower lean body mass and not a lower fat mass<sup>18-22</sup>. In addition, a rapid rate of weight gain during early infancy has been associated with both a higher BMI<sup>23</sup> and more fatness and a more central pattern of fat distribution in childhood.<sup>6</sup> In certain specific populations, early growth has been positively associated with obesity and lean body mass in adulthood.<sup>24,25</sup> However, the associations between birth weight and adult body composition have not been consistently found in all populations,<sup>26,27</sup> and in various studies the associations became significant only after adjustment for adult BMI.<sup>16,17,21,22</sup> It is still unclear whether the associations found between early postnatal weight gain and fat mass and fat distribution in childhood persist into adulthood, and even less is known about fetal growth during the first 2 trimesters of pregnancy and subsequent adult body composition in humans.

We studied the relation between birth weight and early postnatal weight gain and adult BMI, fat mass, and fat distribution within the scope of the Project On Preterm and Small-for-gestational-age infants (POPS), a national cohort of individuals born very preterm. In this prospective study, birth weight could be used as an indicator of fetal growth during the first 2 trimesters, whereas growth during the third trimester and the period thereafter could be monitored well ex utero. We studied the relative predictive value of weight gain before 32 wk of gestation, during the period from preterm birth until 3 mo postterm (early postnatal weight gain), and from 3 mo until 1 y postterm (late infancy weight gain) for BMI, fat distribution, and body composition at age 19 y.

## Subjects and methods

### Study population

The subjects were participants of the POPS study. The POPS cohort comprises 94% of all live born infants in the Netherlands between 1 January and 31 December 1983 after a gestation of <32 completed weeks, with a birth weight of <1500 g, or both<sup>28</sup>. The physical and psychosocial outcomes of the POPS cohort have been intensely studied over the years.<sup>28,29</sup> In the current study, conducted when the subjects were 19 y of age, only those subjects with a gestational age <32 wk were studied. Subjects with congenital malformations leading to changes in body proportions and body composition (eg, focomely, amely, chromosomal abnormalities, and inborn errors of metabolism) were not eligible for inclusion. The study was approved by the medical ethics committee of all participating centers, and written informed consent was obtained from all participants.

### Measurements

Weight (g), length (cm), and head circumference (cm) were measured at birth and expressed as SD scores to correct for gestational age and sex with the use of Swedish references for very preterm infants.<sup>30</sup> At the ages of 3 mo and 1 y postterm, weight and length were measured at the outpatient clinics of the participating centers by trained physicians and nurses. These measurements were expressed as SD scores with the use of Dutch reference values.<sup>31</sup> Weight gain between birth and the age of 3 mo postterm (early postnatal weight gain) and between the ages of 3 mo and 1 y postterm (late infancy weight gain) were computed as  $\Delta$ -SD scores.

Anthropometric measurements were performed in 10 centers in the Netherlands by 15 nurses and physicians according to standardized procedures when the subjects had reached the age of 19 y. All assessors had received extensive training before the start of the study; during the study, retraining and standardization were carried out at 2-mo intervals to maximize interobserver reliability. The assessors were blinded with respect to the birth weight or duration of gestation of the subjects.

Subjects were measured barefoot while wearing underclothing. Weight was measured on a balance scale to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm with a fixed stadiometer. BMI was calculated as weight in kg/height squared in cm.<sup>2</sup> Waist circumference was measured at the level of the umbilicus after full expiration and hip circumference at the level of the greater trochanter, both with the use of a flexible tape measuring to 0.1 cm accuracy. The waist-to-hip ratio was calculated. Four skinfold-thickness measurements were taken in duplicate with a calibrated skinfold caliper on the left side of the body at the triceps, biceps, subscapular, and iliacal regions according to guidelines of the World Health

Organization (biceps and subscapular)<sup>32</sup> and Falkner and Tanner (triceps and iliacal).<sup>33</sup> The sum of the 4 skinfold thicknesses was used as a measurement of overall subcutaneous fatness. The ratio of subscapular-to-triceps-skinfold thickness was calculated as an index of truncal to peripheral adiposity.<sup>34</sup> Fat mass and the corresponding fat-free mass were computed by using the equations of Durnin and Rahaman.<sup>35</sup> All outcome measures at age 19 y, except for the derived outcomes, were expressed as SD scores according to recent Dutch references.<sup>31,36,37</sup>

Multivariate linear regression analyses were performed with SPSS 11.0 software (SPSS Inc, Chicago) to assess associations between prenatal, early postnatal, and late infancy weight gain and the outcome measures at age 19 y. To disentangle the effects of birth weight, early postnatal weight gain, and late infancy weight gain on adult outcomes, early postnatal weight gain was corrected for birth weight, and late infancy weight gain was corrected for both the effect of birth weight and the effect of early postnatal weight gain. This correction was performed by entering the variables mentioned above into multivariate regression models. An interaction term, computed as the product of birth weight (SD scores) and early postnatal weight gain ( $\Delta$ -SD scores) and late infancy weight gain ( $\Delta$ -SD scores), respectively, was introduced to assess whether the effect of early postnatal and late infancy weight gain on outcome measures at age 19 y was different for those individuals with low birth weights compared with those with higher birth weights. The relative importance of weight gain during the various time periods was studied by comparing the changes in explained variance ( $R^2$ ) for each period.

Because it was not possible to use an SD score for variables derived from skinfold thicknesses, regression analyses with these outcome measures were corrected for sex. The analyses with waist and hip circumferences, fat mass, and fat-free mass at age 19 y as outcomes were also adjusted for variations in adult body size by adjusting for current height (SD scores). The analyses with height (SD scores) at age 19 y as the outcome measure were adjusted for target height (SD scores) computed as (midparental height  $\pm$  6.5 cm) + 4.5 cm (estimated secular trend per generation). All analyses were repeated with adjustment for the possible confounders race (white versus nonwhite), socioeconomic status (measured on a 6-point scale in which 1 was lowest and 6 was highest), and physical activity (measured on a 3-point scale).

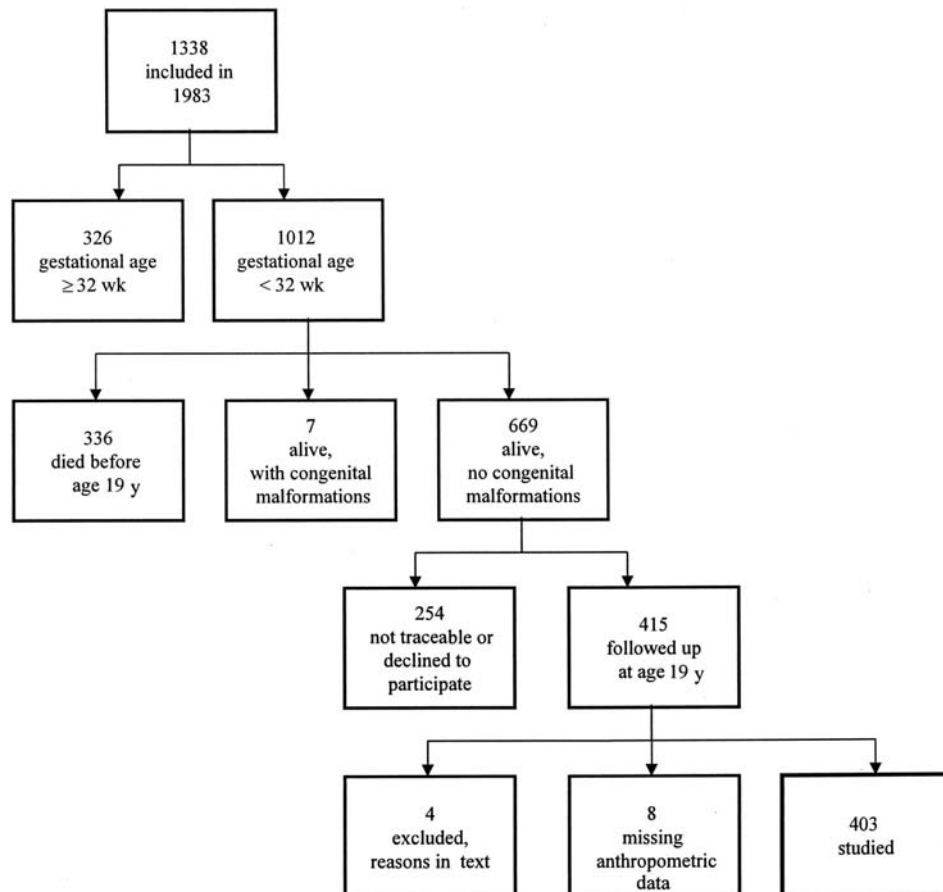
## **Results**

In 1983, 1012 infants who were born before 32 wk of gestation were included in the POPS cohort; 669 without congenital malformations were still alive at age 19 y. Of these subjects, 415 (194 males and 221 females) gave informed consent for the present study (response rate

62%). No anthropometric measurements were performed in 8 subjects either because these subjects were wheelchair bound or because no calibrated instruments were available. Four subjects were excluded from the analyses because of medical conditions or because they were taking medication that could lead to aberrations in body proportions and body composition: 2 subjects used oral corticosteroids, 1 woman had anorexia nervosa, and 1 woman was pregnant at the time of the study. The study population thus included 403 subjects in whom anthropometric measurements were performed at age 19 y (Figure 1).

Characteristics of the subjects are given in Table 1. Nonresponse was higher among males, nonwhites, and those with a mother with a low educational level. Mean birth weight (SD scores) and gestational age did not differ significantly between responders and nonresponders.

**Figure 1.** Flow chart of the study sample



The anthropometric characteristics of the response group are provided in Table 2 as absolute values and SD scores. For both males and females, the mean values for height, weight, and BMI were lower than the means of the Dutch reference population of 19-y-olds, whereas the mean values for waist circumference, waist-to-hip ratio, and the sum of the skinfold thicknesses were greater than the Dutch population means.

**Table 1.** Birth and neonatal characteristics of infants born very preterm

Characteristic	Responders ( <i>n</i> = 403) <sup>1</sup>	Nonresponders ( <i>n</i> = 254) <sup>1</sup>
Demographic		
Sex (% male)	46.4	65.7 <sup>2</sup>
Race (% white)	87.7	80.2 <sup>3</sup>
Low-educational-level mother (%)	38.9	56.5 <sup>2</sup>
Obstetric		
Multiple birth (%)	22.8	21.7
Hypertension during pregnancy (%)	17.6	15.7
Diabetes mellitus gravidarum (%)	5.0	4.3
Smoking during pregnancy (%)	28.0	29.5
Drugs and alcohol intoxication (%) <sup>4</sup>	52.0	52.0
Elective delivery (%)	19.4	13.4 <sup>3</sup>
Birth		
Gestational age (wk)	29.7 ± 1.5 <sup>5</sup> (25.7–31.9) <sup>6</sup>	29.8 ± 1.5 (25.4–31.9)
Birth weight (g)	1316 ± 336 (560–2580)	1347 ± 274 (610–2000)
(SD score)	-0.13 ± 1.0 (-2.98–2.70)	-0.091 ± 0.88 (-3.60–1.66)
Birth length (cm)		
(cm)	39.1 ± 3.4	39.6 ± 2.9 <sup>3</sup>
(SD score)	-0.12 ± 1.2	-0.062 ± 1.13
Head circumference at birth		
(cm)	27.4 ± 2.1	27.6 ± 1.9
(SD score)	0.029 ± 1.2	-0.091 ± 1.0
Postnatal		
Weight at 3 mo		
(kg)	5.1 ± 0.90	5.3 ± 0.88
(SD score)	-0.94 ± 1.3	-0.90 ± 1.4
Weight at 1 y		
(kg)	8.9 ± 1.2	9.1 ± 1.4
(SD score)	-0.98 ± 1.2	-0.94 ± 1.4

- 1 The sample size was slightly less for some variables.
- 2,3 Significantly different from responders (chi-square test for dichotomous variables and two-sample *t* tests for continuous variables): 2 ; *P* < 0.001, 3 ; *P* < 0.05.
- 4 Smoking, drinking alcohol, or using soft drugs, hard drugs, or methadone during pregnancy.
- 5  $\bar{x} \pm$  SD (all such values).
- 6 Range (all such values).



**Table 2.** Characteristics of the response group at age 19 year by sex

	Males ( <i>n</i> = 187) <sup>a</sup>	Females ( <i>n</i> = 216) <sup>a</sup>	<i>P</i> <sup>b</sup>
Height			
(cm)	179.4 ± 7.9 <sup>c</sup>	166.4 ± 7.1	0.001
(SD score)	-0.55 ± 1.1	-0.60 ± 1.1	0.633
Weight			
(kg)	69.9 ± 12.1	60.5 ± 10.6	0.001
(SD score)	-0.41 ± 1.2	-0.48 ± 1.4	0.583
BMI			
(kg/m <sup>2</sup> )	21.7 ± 3.1	21.8 ± 3.4	0.659
(SD score)	-0.10 ± 1.2	-0.17 ± 1.2	0.569
Waist circumference			
(cm)	80.2 ± 8.9	76.6 ± 7.9	0.001
(SD score)	0.24 ± 1.1	0.73 ± 0.92	0.001
Hip circumference			
(cm)	92.1 ± 8.1	94.2 ± 9.4	0.017
(SD score)	-0.22 ± 1.2	0.025 ± 1.1	0.037
Waist-to-hip ratio	0.87 ± 0.054	0.82 ± 0.063	0.001
Waist-to-hip ratio (SD score)	0.72 ± 0.92	0.90 ± 0.93	0.055
Sum of skinfold thicknesses			
(mm)	41.3 ± 20.6	62.6 ± 22.4	0.001
(SD score)	1.7 ± 2.8	1.1 ± 1.6	0.012

a The sample size was slightly less for some variables.

b Two-sample *t* tests.

c  $\bar{x} \pm$  SD (all such values).

### Prenatal, early postnatal, and late infancy weight gain and adult anthropometry

The associations between prenatal, early postnatal, and late infancy weight gain and the anthropometric outcomes at age 19 y are shown in Table 3. Birth weight (SD scores) was positively associated with adult height, weight, BMI, and waist circumference (SD scores), although the 95% CIs for the latter 2 variables almost included zero. There was also a positive association between birth weight (SD scores) and both fat mass and fat-free mass but not between birth weight (SD scores) and percentage body fat at age 19 y. When adjusted for current height (SD scores), the association between birth weight (SD scores) and waist circumference disappeared. The regression coefficient of the association between birth weight (SD scores) and fat-free mass decreased, and the association between birth weight (SD scores) and fat mass became nonsignificant after correction for current height (SD scores). No significant associations were found between birth weight (SD scores) and the waist-to-hip ratio (SD scores), the sum of skinfold thicknesses (SD scores), and the subscapular-to-triceps ratio at age 19 y.

**Table 3.** Linear regression analyses of anthropometric measures at age 19 y with birth weight (SD score), early postnatal weight gain, and late infancy weight gain<sup>1</sup>

Outcome measures at age 19 y	Birth weight (SD score)			Early postnatal weight gain (Δ-SDS) adjusted for birth weight (SD score)			Late infancy weight gain (Δ-SDS) adjusted for birth weight (SD score) and for early postnatal weight gain (Δ-SD score)		
	N	β	95% CI	N	β	95% CI	N	β	95% CI
Height (SD score)	403	0.366	0.265 to 0.466	373	0.238	0.150 to 0.325	351	0.422	0.310 to 0.535
Height (SD score) adjusted for target height (SD score)	401	0.299	0.218 to 0.381	371	0.202	0.132 to 0.273	351	0.240	0.143 to 0.337
Weight (SD score)	403	0.369	0.248 to 0.489	373	0.321	0.215 to 0.427	351	0.445	0.311 to 0.580
BMI (SD score)	403	0.152	0.036 to 0.268	373	0.196	0.092 to 0.300	351	0.215	0.078 to 0.356
Waist circumference (SD score)	399	0.106	0.005 to 0.207	369	0.173	0.082 to 0.263	347	0.218	0.096 to 0.339
Waist circumference (SD score) adjusted for height at age 19 y (SD score)	399	0.00546	-0.098 to 0.109	369	0.111	0.020 to 0.203	347	0.138	0.009 to 0.267
Hip circumference (SD score)	399	0.155	0.042 to 0.268	369	0.173	0.072 to 0.273	347	0.288	0.153 to 0.424
Hip circumference (SD score) adjusted for height at age 19 y (SD score)	399	0.0208	-0.093 to 0.135	369	0.0879	-0.012 to 0.188	347	0.166	0.025 to 0.307
Sum of 4 skinfold thicknesses (SD score)	390	0.0535	-0.170 to 0.277	361	0.190	-0.015 to 0.394	340	0.286	0.011 to 0.561
Fat mass (kg) <sup>2</sup>	390	0.826	0.264 to 1.389	361	0.873	0.370 to 1.376	340	1.275	0.614 to 1.936
Fat mass (kg) adjusted for height at age 19 y (SD score) <sup>2</sup>	390	0.331	-0.252 to 0.914	361	0.599	0.091 to 1.108	340	0.961	0.258 to 1.665
Fat-free mass (kg) <sup>2</sup>	390	2.181	1.582 to 2.779	361	1.639	1.116 to 2.161	340	2.429	1.178 to 3.081
Fat-free mass (kg) adjusted for height at age 19 y (SD score) <sup>2</sup>	390	0.811	0.310 to 1.312	361	0.855	0.420 to 1.290	340	1.202	0.605 to 1.798
Percentage body fat (%) <sup>2</sup>	390	0.176	-0.329 to 0.682	361	0.479	0.022 to 0.936	340	0.651	0.033 to 1.269

<sup>1</sup> Waist-to-hip ratio (SD score), subscapular-to-triceps ratio, and the interaction terms between birth weight and later weight gain were not significant and thus were not reported.

<sup>2</sup> Adjusted for sex.

**Table 4.** Explained variance ( $R^2$ ) and change in explained variance ( $R^2$  change) for the outcome measures at age 19 y, which were significantly associated with birth weight (SD score), early postnatal weight gain, and late infancy weight gain ( $\Delta$ -SDS), or both according to a stepwise model in which the independent variables were included in chronologic order

Outcome measures at age 19 y	n	$R^2$ change (%)			Sex	Total $R^2$ (%)
		Target height (SD score)	Height at age 19 y (SD score)	Birth weight (SD score)		
Height (SD score)	351	37.5 <sup>a</sup>	—	6.2 <sup>a</sup>	—	51.5
Weight (SD score)	351	—	—	9.6 <sup>a</sup>	—	28.0
BMI (SD score)	351	—	—	2.7 <sup>a</sup>	—	10.1
Waist circumference (SD score)	347	—	8.8 <sup>a</sup>	0.0	—	12.2
Sum of 4 skinfold thicknesses (SD score)	340	—	—	0.1	—	3.1
Fat mass (kg)	340	—	5.4 <sup>a</sup>	0.2	25.2 <sup>a</sup>	34.0
Fat-free mass (kg)	340	—	18.1 <sup>a</sup>	0.7 <sup>a</sup>	60.1 <sup>a</sup>	80.8
Percentage body fat (%)	340	—	—	0.0	64.7 <sup>a</sup>	65.8

<sup>a</sup>  $P < 0.05$ .

Early postnatal weight gain and late infancy weight gain were both positively associated with height, weight, BMI, and waist circumference (SD scores), fat mass, fat-free mass, and percentage body fat at age 19 y. Late infancy weight gain was also positively associated with the adult sum of skinfold thicknesses (SD scores). The coefficients of waist circumference, fat mass, and fat-free mass in relation to early postnatal and late infancy weight gain diminished after correction for current height (SD scores) but remained significant. When adjusted for target height (SD scores), the associations between prenatal, early postnatal, and late infancy weight gain and adult height (SD scores) remained significant but decreased in magnitude. No significant associations were found between early postnatal and late infancy weight gain and the waist-to-hip ratio (SD scores) or subscapular-to-triceps ratio in young adulthood.

No significant interaction was found between birth weight (SD scores) and early postnatal weight gain or between birth weight (SD scores) and late infancy weight gain with regard to any of the outcome measures at age 19 y. Correction for race, socioeconomic status, sex, and physical activity did not significantly change the results of the abovementioned analyses (data not shown).

#### **Relative contributions of weight gain during different time periods**

For the anthropometric outcomes at age 19 y that were associated with weight gain during early life, the percentages of variance explained by weight gain during the different time periods are presented in Table 4. For current height (SD scores), 37.5% of the variance was explained by target height (SD scores). Birth weight explained 6.2% of the variance in current height not explained by target height, whereas early postnatal weight gain explained another 4.5% of current height variance not explained by target height or birth weight. Late infancy weight gain explained 3.3% of the variance of current height not explained by the abovementioned variables. So, for current height (SD scores), adjusted for target height (SD scores), the largest change in  $R^2$  values was observed for the effect of birth weight (SD scores).

For adult weight, the effect of birth weight on  $R^2$  change equaled the effect of early postnatal weight gain. For BMI and waist circumference (SD scores) and fat mass, fat-free mass, and percentage body fat, the largest increase in  $R^2$  - apart from adjustments for sex and current height (SD scores) - was observed with the input of early postnatal weight gain into the model. The percentages of variance explained by early postnatal and late infancy weight gain were larger for adult fat mass than for adult fat-free mass.

## Discussion

This study describes the results of a large-scale prospective study on the relation between birth weight, postnatal weight gain, and anthropometric variables at the age of 19 y in subjects born very preterm and provides exclusive information about the predictive value of weight gain during the first 2 trimesters of pregnancy for adult body composition.

In our study there might have been an interference of the effects of possible programming (ie, the lifelong changes in structure or function of body systems that follow a specific insult in early life) and the effects of prematurity on BMI and body composition in young adulthood. We studied only children with a gestational age <32 wk and corrected birth weight for gestational age, which facilitated a valid comparison within the cohort. The results may not be generalizable to infants born at term but do provide useful information about fetal growth restriction in infants born very preterm. We did not separately address the effect of gestational age on adult outcomes, because this interesting issue provides sufficient data for a different study.

Inherent to the population studied, perinatal mortality was high, especially in those infants with a shorter gestational age and to a lesser extent in those with a lower absolute birth weight. However, no significant difference in birth weight (SD scores) was found between those who died and those who survived; therefore, confounding by selective mortality seems unlikely. The same reasoning can be applied to the response and the nonresponse groups. Some subjects had missing data on weight at 3 mo or 1 y, but these missing data were not related to any of the outcome measures.

We found some differences between anthropometric characteristics at age 19 y between the male and the female participants. Whereas the differences in absolute values were expected, the different SD scores for a few outcomes were not. However, because these sex differences were found in unplanned post hoc analyses, the results should be interpreted very cautiously. Adjustment for sex did not change the conclusions of the study.

To determine fat mass and distribution we used skinfold thicknesses, which are known to be prone to interobserver variation.<sup>38</sup> However, although skinfold-thickness measurements tend to overestimate fat mass somewhat compared with a direct method such as dual-energy X-ray absorptiometry (DXA), Fewtrell et al<sup>39</sup> concluded from their study on prematurity and body fatness at ages 8–12 y that the same associations were found with both methods. The correlations between the anthropometric data of Durnin and dual-photon absorptiometry are 0.76 and 0.83 for males and females, respectively.<sup>40</sup> A study of the reproducibility of the skinfold-thickness measurements used in the POPS-19 study

showed that the reliability of the skinfold-thickness measurements was relatively low, but the reliability of the derived estimates of body composition was much higher (intraclass correlation coefficients ranged from 0.55 to 0.98), with a high intraobserver reliability (intraclass correlation coefficient > 0.99) (AM Euser, MJJ Finken, S le Cessie, JM Wit, FW Dekker, unpublished observations, 2004). Because the birth weights of participants did not substantially differ between centers, this relatively low interobserver reliability will have only attenuated the associations between birth weight and body composition at age 19 y.

We found that birth weight was positively associated with weight, height, and BMI at age 19 y. These findings are consistent with those of studies in populations born at term.<sup>11,12</sup> Our study indicates that the positive association between birth weight and adult BMI is determined as early as the first 2 trimesters of pregnancy. This finding conflicts with the results of the Dutch famine studies, which suggest that maternal malnourishment during early gestation predisposes to later obesity in the offspring.<sup>7,8</sup> Our study does not confirm the J- or U-shape relation between birth weight and adult BMI found in some studies,<sup>13,41,42</sup> which might form a biological link between low birth weight and adult diseases. This suggests that either the associations mentioned above are established during the third trimester of pregnancy or that there is another link between fetal growth and adult disease. Singhal et al<sup>18</sup> proposed that this link might be formed by fat-free mass. However, though fat-free mass was significantly associated with birth weight, our data show no significant association between birth weight and percentage body fat in adulthood.

Although prenatal weight gain was not associated with percentage body fat, more early postnatal weight gain was associated with both a higher BMI and a higher percentage body fat at age 19 y. The higher BMI found agrees with the findings of earlier studies in which a positive association between early growth and adult BMI and obesity was found.<sup>13,43</sup> Our study showed that this association was independent of birth weight and that the higher BMI was partly accounted for by a higher percentage body fat, at least in premature infants. So far, only a few studies have addressed the relation between early growth and adult fat mass and distribution. From our results it may be concluded that the positive associations found by Ong et al<sup>6</sup> and Stettler et al<sup>24</sup> between early catch-up growth and fatness in childhood persist into young adulthood. This agrees with a study by Li et al<sup>25</sup> about early postnatal growth in length and adult fat-free mass in a Guatemalan population.

Moreover, we also found that a greater postnatal weight gain was associated with a higher adult waist circumference, both when adjusted and unadjusted for current height (SD scores). Fetal weight gain was also positively associated with waist circumference (SD scores), but after adjustment for current body height (SD scores), the association completely disappeared;

this finding indicates that the increase in waist circumference with higher birth weight reflects mainly an increase in body size and not solely an increase in visceral fat. Prenatal and postnatal weight gain were not significantly associated with waist-to-hip ratio or subscapular-to-triceps ratio, although a tendency for low birth weight to be associated with a higher waist-to-hip ratio and a subscapular-to-triceps ratio was observed. This finding agrees with the results of Fall et al<sup>13</sup> and Li et al<sup>25</sup>. In some studies, low birth weight and early growth have been associated with a more truncal and abdominal fat pattern<sup>13,16,17</sup> but only after adjustment for current BMI. Although adjustment for current body size in fetal origins studies should always be interpreted cautiously, it might be arguable for some adult disease outcomes.<sup>44</sup> However, we think it is theoretically incorrect to adjust for current BMI -which includes current fat mass- in analyses with fat mass and fat distribution as outcomes. If correction for current body proportions is applied, an index independent of body fat should be used.

The associations found between birth weight, early postnatal weight gain, and late infancy weight gain and adult BMI and body composition might be explained by perinatal programming.<sup>45</sup> However, it is also possible that genes that influence prenatal, perinatal, and adult determinants underlie the associations found. More research is required about the possible mechanisms of programming of body proportions and body composition.

In conclusion, gestation, the period from birth until 3 mo postterm, and the period from 3 mo until 1 y postterm seem to be important predictors of body size and body mass in young adulthood in infants born very preterm. Greater weight gain during these periods is associated with greater height, weight, BMI, and fat-free mass at age 19 y. Birth weight in infants born very preterm is not associated with fat distribution. However, early postnatal weight gain and late infancy weight gain are -independently of birth weight or current height- associated with a more abdominal pattern of fat distribution and a higher percentage body fat. The relative effect of weight gain from birth until 3 mo postterm on adult fat mass and fat distribution is more pronounced than is the effect of weight gain from 3 mo until 1 y postterm.

### **Acknowledgements**

The participants of the Dutch POPS-19 Collaborative Study Group are as follows: TNO Prevention and Health, Leiden, Netherlands (ETM Hille, CH de Groot, H Kloosterboer-Boerrigter, AL den Ouden, A Rijpstra, SP Verloove-Vanhorick, and JA Vogelaar); Emma Children's Hospital AMC, Amsterdam (JH Kok, A Ilsen, M van der Lans, WJC Boelen-van der Loo, T Lundqvist, and HSA Heymans); University Hospital Groningen, Beatrix Children's Hospital, Groningen (EJ Duiverman, WB Geven, ML Duiverman, LI Geven, and EJLE Vrijlandt); University Hospital Maastricht, Maastricht (ALM Mulder and A Gerger); University Medical Center St Radboud,

Nijmegen, Netherlands (LAA Kollée, L Reijmers, and R Sonnemans); Leiden University Medical Center, Leiden, Netherlands (JM Wit, FW Dekker, and MJJ Finken); Erasmus MC Rotterdam–Sophia Children’s Hospital, University Medical Center, Rotterdam, Netherlands (N Weisglas-Kuperus, MG Keijzer-Veen, AJ van der Heijden, and JB van Goudoever); VU University Medical Center, Amsterdam (MM van Weissenbruch, A Cranendonk, HA Delemarre-van de Waal, L de Groot, and JF Samsom); Wilhelmina Children’s Hospital, UMC, Utrecht, Netherlands (LS de Vries, KJ Rademaker, E Moerman, and M Voogsgaard); Máxima Medical Center, Veldhoven, Netherlands (MJK de Kleine, P Andriessen, CCM Dielissen-van Helvoirt, and I Mohamed); Isala Clinics, Zwolle, Netherlands (HLM van Straaten, W Baerts, GW Veneklaas Slots-Kloosterboer, and EMJ Tuller-Pikkemaat); Royal Effatha Guyot Group, Zoetermeer, Netherlands (MH Ens-Dokkum); and the Association for Parents of Premature Babies (GJ van Steenbrugge).

MJJF, JMW, and FWD developed the analytic plan. AME, MJJF, and MGK-V contributed to the data collection. ETMH was responsible for the data management. AME conducted the data analyses and was primarily responsible for writing the manuscript. All authors provided substantive and editorial comments on several drafts of the manuscript. None of the authors had any financial or personal conflict of interest with respect to the material reported in this article.



## References

1. Kopelman PG. Obesity as a medical problem. *Nature* 2000; 404:635-643.
2. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289:76-79.
3. Paeratakul S, Lovejoy JC, Ryan DH, Bray GA. The relation of gender, race and socioeconomic status to obesity and obesity comorbidities in a sample of US adults. *Int J Obes Relat Metab Disord* 2002; 26:1205-1210.
4. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999; 341:1097-1105.
5. Dietz WH. Periods of risk in childhood for the development of adult obesity--what do we need to learn? *J Nutr* 1997; 127:1884S-1886S.
6. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 2000; 320:967-971.
7. Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* 1976; 295:349-353.
8. Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr* 1999; 70:811-816.
9. Rogers I. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes Relat Metab Disord* 2003 Jul 19; 27:755-777.
10. Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Size at birth, childhood growth and obesity in adult life. *Int J Obes Relat Metab Disord* 2001; 25:735-740.
11. Pietilainen KH, Kaprio J, Rasanen M, Winter T, Rissanen A, Rose RJ. Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship. *Am J Epidemiol* 2001; 154:21-29.
12. Sorensen HT, Sabroe S, Rothman KJ, Gillman M, Fischer P, Sorensen TI. Relation between weight and length at birth and body mass index in young adulthood: cohort study. *BMJ* 1997; 315:1137.
13. Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 1995 Feb 18; 310:428-432.
14. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* 1996; 94:3246-3250.
15. Allison DB, Paultre F, Heymsfield SB, Pi-Sunyer FX. Is the intra-uterine period really a critical period for the development of adiposity? *Int J Obes Relat Metab Disord* 1995; 19:397-402.
16. Barker M, Robinson S, Osmond C, Barker DJ. Birth weight and body fat distribution in adolescent girls. *Arch Dis Child* 1997; 77:381-383.
17. Law CM, Barker DJ, Osmond C, Fall CH, Simmonds SJ. Early growth and abdominal fatness in adult life. *J Epidemiol Community Health* 1992; 46:184-186.
18. Singhal A, Wells J, Cole TJ, Fewtrell M, Lucas A. Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease? *Am J Clin Nutr* 2003; 77:726-730.
19. Weyer C, Pratley RE, Lindsay RS, Tataranni PA. Relationship between birth weight and body composition, energy metabolism, and sympathetic nervous system activity later in life. *Obes Res* 2000; 8:559-565.
20. Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR, Davis WW. Muscularity and fatness of infants and young children born small- or large-for-gestational-age. *Pediatrics* 1998; 102:E60.
21. Loos RJ, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young women: a prospective twin study. *Am J Clin Nutr* 2002; 75:676-682.

22. Loos RJ, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young adult men--a prospective twin study. *Int J Obes Relat Metab Disord* 2001; 25:1537-1545.
23. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics* 2002; 109:194-199.
24. Stettler N, Kumanyika SK, Katz SH, Zemel BS, Stallings VA. Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. *Am J Clin Nutr* 2003; 77:1374-1378.
25. Li H, Stein AD, Barnhart HX, Ramakrishnan U, Martorell R. Associations between prenatal and postnatal growth and adult body size and composition. *Am J Clin Nutr* 2003; 77:1498-1505.
26. Matthes JW, Lewis PA, Davies DP, Bethel JA. Body size and subcutaneous fat patterning in adolescence. *Arch Dis Child* 1996; 75:521-523.
27. Peralta-Carcelen M, Jackson DS, Goran MI, Royal SA, Mayo MS, Nelson KG. Growth of adolescents who were born at extremely low birth weight without major disability. *J Pediatr* 2000; 136:633-640.
28. Verloove P, Verwey RA, Brand R, Keirse MJ. Importance of gestational age. *Lancet* 1986; 1:1494.
29. Walther FJ, den Ouden AL, Verloove-Vanhorick SP. Looking back in time: outcome of a national cohort of very preterm infants born in The Netherlands in 1983. *Early Hum Dev* 2000; 59:175-191.
30. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand* 1991 Aug -Sep 1991;756-762.
31. Fredriks AM, Van BS, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res* 2000; 47:316-323.
32. WHO Expert Committee. Physical status: the use and interpretation of anthropometry. *World Health Organ Tech Rep Ser* 1995; 854:1-452.
33. Cameron N. The methods of auxological anthropometry. In: Falkner F, Tanner J, editors. *Human growth - a comprehensive treatise*. New York: Plenum Press; 1986. 26-28.
34. Haffner SM, Stern MP, Hazuda HP, Pugh J, Patterson JK. Do upper-body and centralized adiposity measure different aspects of regional body-fat distribution? Relationship to non-insulin-dependent diabetes mellitus, lipids, and lipoproteins. *Diabetes* 1987; 36:43-51.
35. Durnin JVG, Rahaman MM. Assessment of Amount of Fat in Human Body from Measurements of Skinfold Thickness. *British Journal of Nutrition* 1967; 21:681-&.
36. Fredriks AM. *Growth diagrams 1997: Fourth Dutch Nation-wide Survey*. [ Leiden University, Netherlands; 2004.
37. Gerver W, De Bruin R. *Paediatric morphometrics: a reference manual (second extended edition)*. Utrecht, Netherlands: Wetenschappelijke Uitgeverij Bunge; 2001.
38. Fuller NJ, Jebb SA, Goldberg GR, Pullicino E, Adams C, Cole TJ et al. Inter-observer variability in the measurement of body composition. *Eur J Clin Nutr* 1991; 45:43-49.
39. Fewtrell MS, Lucas A, Cole TJ, Wells JC. Prematurity and reduced body fatness at 8-12 y of age. *Am J Clin Nutr* 2004; 80:436-440.
40. Pierson RN, Jr., Wang J, Heymsfield SB, Russell-Aulet M, Mazariegos M, Tierney M et al. Measuring body fat: calibrating the rulers. Intermethod comparisons in 389 normal Caucasian subjects. *Am J Physiol* 1991; 261:E103-E108.
41. Parsons TJ, Power C, Manor O. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *BMJ* 2001; 323:1331-1335.
42. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE et al. Birth weight and adult hypertension and obesity in women. *Circulation* 1996; 94:1310-1315.

## Chapter 8

---

43. Eriksson J, Forsen T, Osmond C, Barker D. Obesity from cradle to grave. *Int J Obes Relat Metab Disord* 2003; 27:722-727.
44. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. *BMJ* 1999; 319:245-249.
45. Barker DJ. In utero programming of chronic disease. *Clin Sci (Lond)* 1998; 95:115-128.