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Hollanders, J.J.

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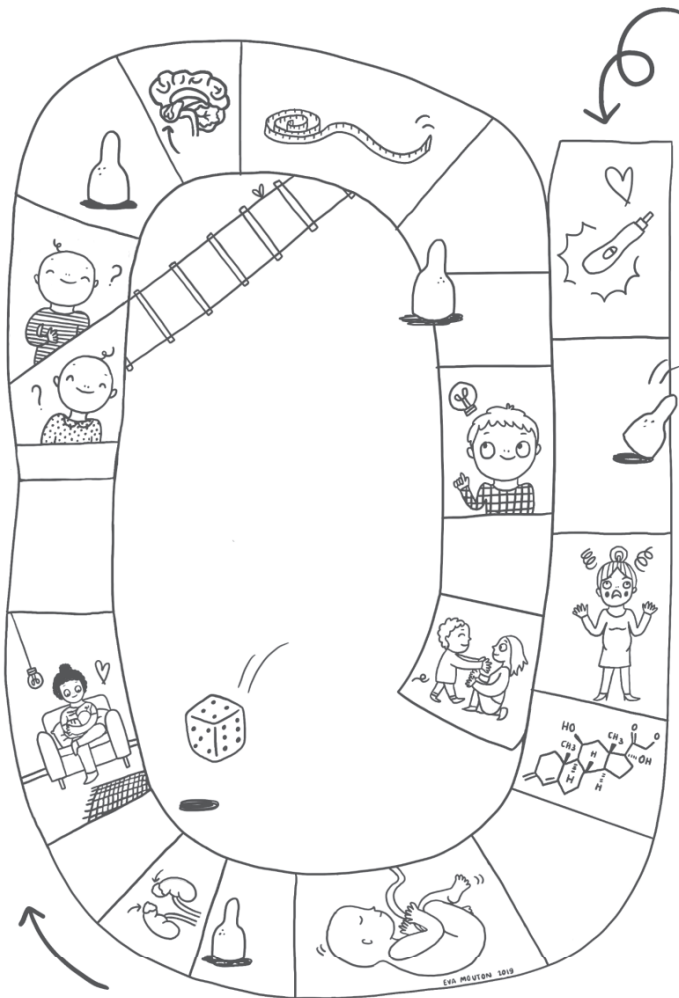
### **E-mail address:**

[vuresearchportal.ub@vu.nl](mailto:vuresearchportal.ub@vu.nl)

# Part 4

## Early-life growth and neurodevelopment





# 13

## Growth pattern and final height of very preterm vs. very low birth weight infants

Jonneke J. Hollanders,  
Sylvia M. van der Pal,  
Paula van Dommelen,  
Joost Rotteveel,  
Martijn J.J. Finken

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## ABSTRACT

### Background

Both very preterm (VP; i.e., gestational age <32 weeks) and very low birth weight (VLBW; i.e., birth weight <1,500 g) are used as inclusion criteria by studies on preterm birth. We aimed to quantify the impact of these entities on postnatal growth until final height.

### Methods

Subjects born VP and/or with VLBW from the Project On Preterm and Small-for-gestational-age infants cohort were classified as follows: (1) VP+/VLBW+ (n=495), (2) VP+/VLBW- (n=207), or (3) VP-/VLBW+ (n=296) infants. Anthropometric data were collected at birth, 3, 6, 12, and 24 months' corrected age, and at 5 and 19 years. At 19 years, 590/998 (59%) of the subjects enrolled in 1983 were followed up.

### Results

Birth size was smallest in the VP-/VLBW+ group compared with the VP+/VLBW+ and VP+/VLBW- groups. During childhood, length, weight, and head circumference SD scores increased in the VP-/VLBW+ group, whereas SD scores in the VP+/VLBW+ and VP+/VLBW- groups either remained stable or decreased. Despite catch-up growth, VP-/VLBW+ infants remained the shortest and lightest at age 19.

### Conclusion

Classification on the basis of VP and VLBW impacts growth, causing different growth patterns for infants born VP+/VLBW+, VP+/VLBW-, or VP-/VLBW+. For future studies, we recommend, at least for industrialized countries, including preterm infants based on gestational age.

## INTRODUCTION

Infants born very preterm (i.e., VP; <32 weeks of gestation) and/or with very low birth weight (i.e., VLBW; <1,500 grams) require admission to a Neonatal Intensive Care Unit (NICU). Early postnatal growth in such infants is often characterized by extrauterine growth retardation (EUGR),<sup>1</sup> caused by a combination of factors, including acute illnesses, glucocorticoid therapy and feeding difficulties. Although the majority of these infants exhibit late postnatal catch-up growth, they often remain short and thin during childhood and adolescence.<sup>2</sup> Moreover, postnatal growth in VP and/or VLBW infants has been associated with a variety of short- and long-term outcomes, such as cognitive functioning,<sup>3,4</sup> motor performance,<sup>4</sup> and body composition.<sup>5</sup>

However, most of the evidence on the long-term consequences of preterm birth on growth comes from studies in infants with VLBW,<sup>6-11</sup> which can be attributed to prematurity, intrauterine growth retardation (IUGR), or both. Before the 1980s, prematurity was often based on birth weight in lieu of reliable ways to estimate gestational age. After the widespread application of ultrasound as a tool to accurately measure pregnancy duration,<sup>12</sup> the majority of studies on preterm infants still used birth weight as an estimate of the degree of prematurity.<sup>6-11</sup>

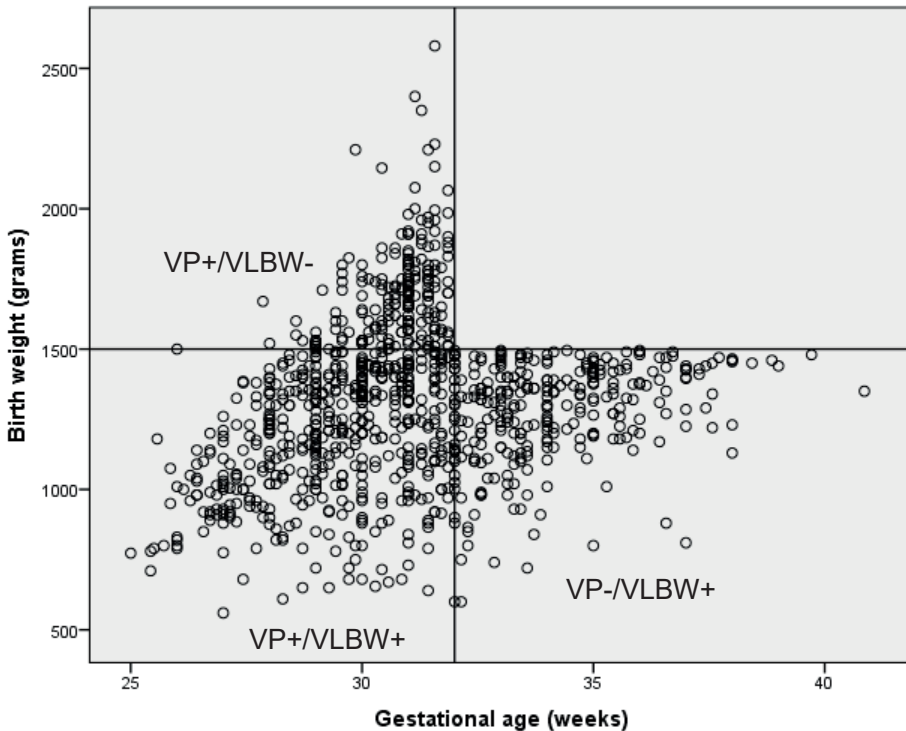
Although it is reasonable to assume that being born VP or with VLBW has different impacts on outcomes, surprisingly, this has been quantified only once before.<sup>13</sup> In comparing VLBW with VP infants, VLBW was associated with an overrepresentation of SGA births and with lower numbers experiencing neonatal morbidities. However, this study did not provide long-term follow-up and, therefore, it is not known whether the differences between these groups could be extended with growth after hospital discharge. Findings from studies in cohorts of infants born either VP or with VLBW that have provided follow-up until adulthood are incomparable because of the different standards of care at the time of birth.<sup>5,7,8,14</sup> The past 30 years were characterized by major changes including widespread use of antenatal glucocorticoid therapy, introduction of synthetic surfactant and more aggressive feeding policies. Such changes have resulted in improved chances for survival. Therefore, caution must be exercised in the comparison of populations born either VP or with VLBW from different birth eras. Consequently, the long-term impact of being born VP or with VLBW can only be studied within the same birth cohort.

Therefore, in this study, we aimed to quantify the impact of being born VP and/or with a VLBW on growth until adulthood. For this purpose, we used the data of the Dutch Project On Preterm and Small-for-gestational-age infants (POPS) cohort, which is, to our knowledge, the only study to date that followed up children born both VP and/or with a VLBW into young adulthood.

## METHODS

### Study population

The POPS cohort comprised 94% (n=1,334) of the infants born alive in the Netherlands in 1983 with a gestational age <32 weeks (VP) and/or with a birth weight <1,500 grams (VLBW). Gestational age was based on last menstrual period, pregnancy testing, and/or ultrasound. Subjects were excluded if they died during their hospital stay (n=340). Thus, 998 subjects were included in this study. The inclusion criteria enabled us to compare groups of: (1) VP+/VLBW+ infants (n=495), (2) VP+/VLBW- infants (n=207), and (3) VP-/VLBW+ infants (n=296) (Figure 1). Approval of the medical ethical committees of all participating centers was obtained.



**Figure 1:** Distribution of our study population, with the three different groups (i.e., VP+/VLBW+, VP+/VLBW- and VP-/VLBW+) indicated

### Growth assessment

Subjects underwent growth assessment at birth, at 3, 6, 12 and 24 months of corrected age, and again at the chronological ages of 5 and 19 years, when all participants had reached final height. Follow-up was done by trained research nurses and/or physicians

according to standardized procedures. At ages 3 months to 2 years, anthropometric data were collected at outpatient clinics. At age 5, research staff made house visits, whereas at age 19 follow-up took place at 1 of the 10 involved research centers. Until the age of 2, length was measured in supine position to the nearest 1 cm. From age 5 onward, standing height was measured to the nearest 1 mm. Weight was measured to the nearest 5 grams at birth, and during the follow-up visits to the nearest 0.1 kg on a balance scale. Head circumference (HC) was measured to the nearest 1 cm up to the age of 5.

Standard deviation scores (SDSs) for length/height, weight, and HC were calculated.<sup>15,16</sup> Subjects with a birth weight and/or length of less than -2 SD were classified as SGA. Body mass index (BMI) was calculated as  $(\text{weight (kg)} / (\text{length (m)})^2)$  and converted to SDS.<sup>17</sup>

### Statistical analysis

SDS of length/height, weight, BMI, and HC were compared between groups using a generalized estimating equation (GEE). The different measurement points were used as an interaction term with the different groups. A *P* value of  $\leq 0.05$  was considered as a significant difference, and 95% confidence intervals (95% CIs) were calculated as described by Figueiras, et al.<sup>18</sup>

## RESULTS

Perinatal characteristics of participants were significantly different between the VP+/VLBW+, VP+/VLBW- and VP-/VLBW+ groups (Table 1). In general, the VP-/VLBW+ group showed significantly less neonatal morbidity and had a better Apgar score after 5 minutes, whereas they were significantly more often SGA and born to mothers with (pre-existent) hypertension and/or who smoked during pregnancy. The VP+/VLBW+ group had significantly more neonatal morbidity, a longer hospital stay, and more days on ventilation compared with the other two groups. The VP+/VLBW- group had the shortest hospital stay. However, ethnicity, marital status, and socio-economic status (SES) were not significantly different between the three groups, and target height SD and maternal height also did not differ between the three groups.

The response rate was different for the several follow-up visits (Figure 2). At age 19, 59% of the infants included for this study were followed up; for the other visits, the response rate was adequate. At age 19, responders were significantly different compared with the non-responders with regard to gender distribution, target height, pre-existent hypertension, ethnicity, and SES, whereas all other perinatal characteristics as well as the distribution of the subjects between the three groups did not differ (Table 2).



**Table 1:** Perinatal characteristics of the surviving subjects in the three groups

	VP+/VLBW+ n=495	VP+/VLBW- n=207	VP-/VLBW+ n=296	Overall P value
Male	250 (50.5)	134 (64.7)	139 (47.0)	<0.001* <sup>‡</sup>
Birth weight (grams)	1,173±214	1,705±178	1,276±178	<0.001* <sup>‡</sup>
Gestational age (weeks)	29.3±1.6	30.8±0.9	34.1±1.7	<0.001* <sup>‡</sup>
PROM	115 (23.2)	56 (27.1)	12 (4.1)	<0.001 <sup>††</sup>
Born via caesarian section	194 (39.2)	52 (25.1)	223 (75.3)	<0.001* <sup>‡</sup>
Apgar score >7 after 5 minutes	384 (77.6)	175 (84.5)	264 (89.2)	<0.001* <sup>†</sup>
Duration of hospital stay (d)	79±32	50±20	62±33	<0.001* <sup>‡</sup>
Days of ventilation (d)	7.5±11.0	3.2±5.1	1.4±7.5	<0.001* <sup>‡</sup>
IRDS	254 (51.3)	99 (47.8)	36 (12.2)	<0.001 <sup>††</sup>
Sepsis	196 (39.8)	60 (29.0)	77 (26.0)	<0.001* <sup>†</sup>
IVH	129 (26.1)	28 (13.5)	18 (6.1)	<0.001* <sup>‡</sup>
NEC	31 (6.3)	9 (4.3)	17 (5.7)	0.608
SGA-status	48 (9.7)	2 (1.0)	235 (79.4)	<0.001* <sup>‡</sup>
Target height (SD) <sup>a</sup>	-0.1±0.8	0.0±0.8	-0.1±0.9	0.203
Maternal height (cm)	166±6.1	167±6.5	166±7.0	0.306
Pre-existent hypertension	16 (3.2)	3 (1.5)	25 (8.6)	<0.001 <sup>††</sup>
Hypertension during pregnancy	104 (21.0)	11 (5.3)	152 (51.4)	<0.001* <sup>‡</sup>
Smoking during pregnancy	145 (29.3)	55 (26.6)	112 (37.8)	0.023 <sup>†‡</sup>
Caucasian maternal ethnicity	417 (84.4)	177 (87.2)	252 (85.7)	0.628
Married (parents)	438 (88.8)	192 (92.8)	249 (84.1)	0.114
Low parental SES	214 (45.1)	75 (37.9)	123 (42.4)	0.228

Values represent mean±SD or n (%). Continuous variables were compared with the one-way ANOVA test when comparing the three groups, and the independent t-test when comparing two groups. Dichotomous variables were compared with the Chi square test.

\* P value <0.05 for VP+/VLBW+ vs. VP+/VLBW-

† P value <0.05 for VP+/VLBW+ vs. VP-/VLBW+

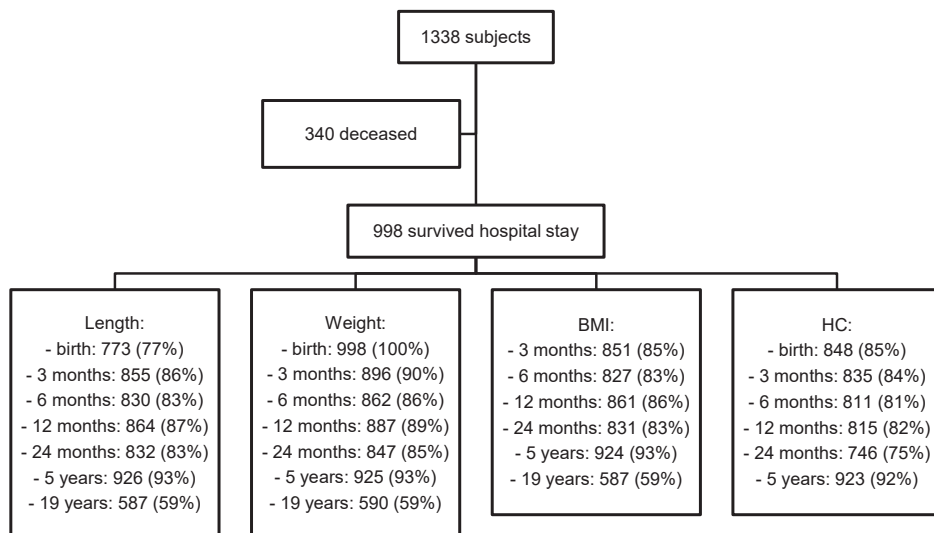
‡ P value <0.05 for VP+/VLBW- vs. VP-/VLBW+

VP: very preterm; VLBW: very low birth weight; PROM: premature rupture of membranes; IRDS: infants respiratory distress syndrome; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; SGA: small-for-gestational-age

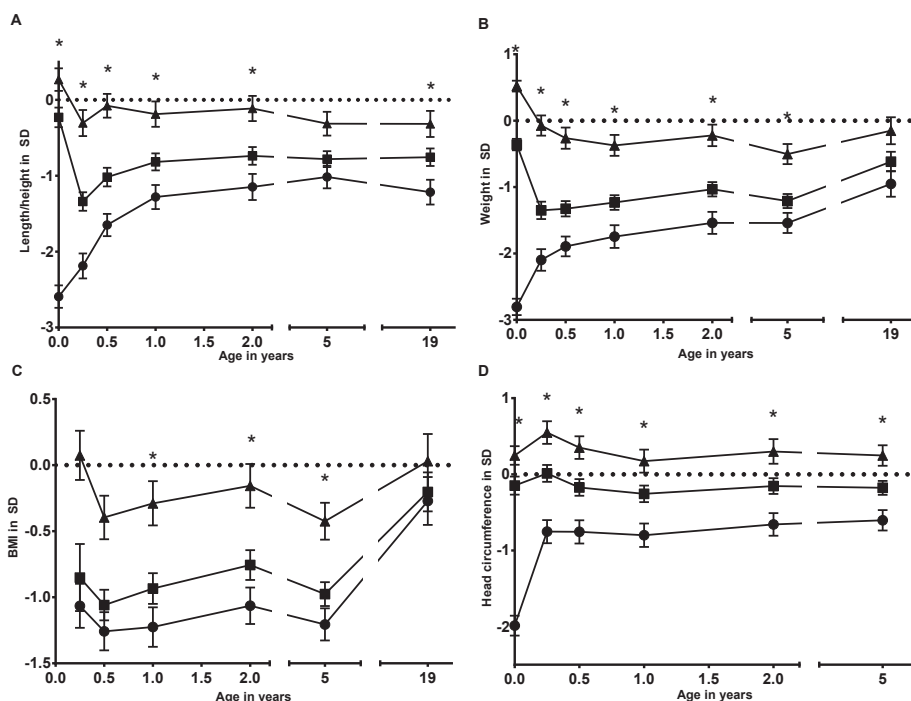
<sup>a</sup> Girls: target height = [(height father in cm + height mother in cm - 13) / 2] + 4.5; boys: target height = [(height father in cm + height mother in cm + 13) / 2] + 4.5

Length/height was significantly different between groups at all ages, except between the VP-/VLBW+ and VP+/VLBW+ group at age 5 (Figure 3A). The VP+/VLBW- group was the tallest at all ages, whereas the VP-/VLBW+ group remained the shortest.

Weight was significantly different between groups at all ages (Figure 3B), except for age 19 between the VP-/VLBW+ and the VP+/VLBW+ groups. Once again, the VP+/VLBW- group consistently had the highest weight, whereas the VP-/VLBW+ group had the lowest.



**Figure 2:** Follow-up response for the different growth parameters at all follow-up visits



**Figure 3:** Growth for length/height (A), weight (B), BMI (C) and head circumference (D), expressed as SD scores, for all three groups

Squares=VP+/VLBW+, triangles=VP+/VLBW-, circles=VP-/VLBW+; the error bars represent 95%CI's.

\* P value <0.05 between all three group, analyzed per measurement point

**Table 2:** Perinatal characteristics of the responders vs. non-responders at age 19

	Responders at age 19 n=590	Non-responders at age 19 n=408	P value
Male	265 (44.9)	258 (63.2)	<0.001
Birth weight (grams)	1301±299	1331±261	0.095
Gestational age (weeks)	31.0±2.5	31.2±2.6	0.265
PROM	105 (17.8)	78 (19.1)	0.596
Born via caesarian section	289 (49.0)	180 (44.1)	0.130
Apgar score >7 after 5 minutes	492 (83.4)	331 (81.1)	0.618
Duration of hospital stay (d)	67.3±30.3	69.9±35.4	0.464
Days of ventilation (d)	4.8±9.5	4.7±9.4	0.840
IRDS	232 (39.3)	157 (38.5)	0.789
Sepsis	193 (32.8)	140 (34.4)	0.592
IVH	95 (16.1)	80 (19.6)	0.152
NEC	36 (6.1)	21 (5.1)	0.523
SGA-status	170 (28.8)	115 (28.3)	0.848
Target height (SD) <sup>a</sup>	0.0±0.8	-0.2±0.9	0.001
Maternal height (cm)	167±6.3	165±6.6	0.006
Pre-existent hypertension	33 (5.6)	11 (2.7)	0.030
Hypertension during pregnancy	168 (28.5)	99 (24.3)	0.140
Smoking during pregnancy	178 (30.2)	134 (32.8)	0.644
Caucasian maternal ethnicity	519 (88.9)	327 (80.3)	<0.001
Married (parents)	529 (89.7)	350 (86.2)	0.324
Low parental SES	208 (35.5)	204 (54.1)	<0.001
VP/VLBW status	302 (51.2)	193 (47.3)	0.392
- VP+/VLBW+	115 (19.5)	92 (22.5)	
- VP+/VLBW-	173 (29.3)	123 (30.1)	
- VP-/VLBW+			

Values represent mean±SD or n (%). Continuous variables were compared with the one-way ANOVA test when comparing the three groups, and the independent t-test when comparing two groups. Dichotomous variables were compared with the Chi square test.

\* P value <0.05 for VP+/VLBW+ vs. VP+/VLBW-

† P value <0.05 for VP+/VLBW+ vs. VP-/VLBW+

‡ P value <0.05 for VP+/VLBW- vs. VP-/VLBW+

VP: very preterm; VLBW: very low birth weight; PROM: premature rupture of membranes; IRDS: infants respiratory distress syndrome; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; SGA: small-for-gestational-age

<sup>a</sup> Girls: target height = [(height father in cm + height mother in cm - 13) / 2] + 4.5; boys: target height = [(height father in cm + height mother in cm + 13) / 2] + 4.5

**Table 3:** Changes in SD scores within the groups for length/height, weight, BMI, and HC over time

	VP+/VLBW+		VP+/VLBW-		VP-/VLBW+	
	$\beta$ (95% CI)	P value	$\beta$ (95% CI)	P value	$\beta$ (95% CI)	P value
<b>Length/height</b>						
Birth - 19 years	-0.5 (-0.7 to -0.4)	<0.001	-0.6 (-0.8 to -0.4)	<0.001	1.4 (1.2 to 1.6)	<0.001
Birth - 3 months	-1.1 (-1.3 to -1.0)	<0.001	-0.6 (-0.8 to -0.4)	<0.001	0.4 (0.2 to 0.6)	<0.001
3 months - 1 year	0.5 (0.4 to 0.6)	<0.001	0.1 (-0.1 to 0.3)	0.20	0.9 (0.8 to 1.0)	<0.001
1 year - 5 years	0.0 (-0.1 to 0.1)	0.43	-0.1 (-0.3 to 0.0)	0.09	0.3 (0.2 to 0.4)	<0.001
5 years - 19 years	0.0 (-0.1 to 0.1)	0.57	0.0 (-0.1 to 0.1)	0.97	-0.2 (-0.3 to -0.1)	0.005
<b>Weight</b>						
Birth - 19 years	-0.3 (-0.4 to -0.1)	0.001	-0.7 (-0.9 to -0.5)	<0.001	1.9 (1.6 to 2.1)	<0.001
Birth - 3 months	-1.0 (-1.1 to -0.9)	<0.001	-0.6 (-0.7 to -0.4)	<0.001	0.7 (0.5 to 0.9)	<0.001
3 months - 1 year	0.1 (0.0 to 0.2)	0.04	-0.3 (-0.5 to -0.1)	<0.001	0.4 (0.2 to 0.5)	<0.001
1 year - 5 years	0.0 (-0.1 to 0.1)	0.59	-0.1 (-0.3 to 0.0)	0.05	0.2 (0.1 to 0.3)	0.001
5 years - 19 years	0.6 (0.5 to 0.7)	<0.001	0.4 (0.2 to 0.5)	<0.001	0.6 (0.4 to 0.8)	<0.001
<b>BMI</b>						
3 months - 19 years	0.6 (0.3 to 1.0)	<0.001	0.0 (-0.3 to 0.2)	0.72	0.8 (0.6 to 1.0)	<0.001
3 months - 1 year	-0.1 (-0.3 to 0.2)	0.52	-0.4 (-0.6 to -0.2)	<0.001	-0.2 (-0.3 to 0.0)	0.06
1 year - 5 years	0.0 (-0.1 to 0.1)	0.43	-0.1 (-0.3 to 0.0)	0.10	0.0 (-0.1 to 0.2)	0.78
5 years - 19 years	0.8 (0.6 to 0.9)	<0.001	0.5 (0.3 to 0.7)	<0.001	0.9 (0.8 to 1.1)	<0.001
<b>HC</b>						
Birth - 5 years	0.0 (-0.2 to 0.1)	0.66	0.0 (-0.2 to 0.2)	0.99	1.4 (1.2 to 1.5)	<0.001
Birth - 3 months	0.2 (0.0 to 0.3)	0.02	0.3 (0.1 to 0.5)	<0.001	1.2 (1.1 to 1.4)	<0.001
3 months - 1 year	-0.3 (-0.4 to -0.2)	<0.001	-0.4 (-0.5 to -0.3)	<0.001	0.0 (-0.1 to 0.0)	0.32
1 year - 5 years	0.1 (0.0 to 0.2)	0.04	0.1 (0.0 to 0.2)	0.16	0.2 (0.1 to 0.3)	<0.001

Values represent beta (95%CI), as compared with the GEE

VP: very preterm; VLBW: very low birth weight; BMI: body mass index; HC: head circumference

BMI in the VP+/VLBW- group was significantly higher at all ages compared with the VP+/VLBW+ and VP-/VLBW+ groups, except for age 19 (Figure 3C). The BMI in the VP+/VLBW+ and VP-/VLBW+ groups was significantly different at ages 1, 2 and 5.

HC was significantly different between groups at all ages (Figure 3D). The VP+/VLBW- group consistently had the largest HC, whereas the VP-/VLBW+ group had the smallest.

Table 3 shows the changes in SDS within the groups over time. Between birth and age 19, length/height SDS significantly increased in the VP-/VLBW+ group, while the VP+/VLBW+ and VP+/VLBW- groups showed a decrease in length/height SDS. A similar pattern was observed for weight SDS between birth and age 19. The greatest changes in SDS took place between birth and 3 months of corrected age, and between ages 5 and 19. BMI did not change in the VP+/VLBW- group between 3 months and age 19, but there was a significant increase in SDS in the VP+/VLBW+ and VP-/VLBW+ groups

between ages 5 and 19. Between birth and age 5, HC SDS increased significantly in the VP-/VLBW+ group, whereas there was no change in SDS in the VP+/VLBW+ and the VP+/VLBW- groups. The greatest SDS change took place between birth and 3 months.

## DISCUSSION

In this study, we found significantly different growth patterns for length/height, weight, BMI, and HC between VP+/VLBW+, VP+/VLBW- and VP-/VLBW+ infants. This indicates that the terms VP and VLBW describe two different entities, which impact differently on growth.

We observed that VP-/VLBW+ infants were severely growth restricted at birth, as evidenced by an SGA rate of 79.4%, and exhibited rapid catch-up growth postnatally. However, they remained shorter and lighter, and with a smaller HC, as compared with the other two groups. In contrast, the VP+/VLBW+ and VP+/VLBW- groups showed sharp decreases in length/height SDS and weight SDS between birth and 3 months, which could most likely be attributed to the greater percentage of children with neonatal illnesses or to inadequate nutritional support for their degree of illness, although this was not measured in our study.<sup>19</sup> In a recent systematic review, poor early postnatal growth after preterm birth was associated with adverse neurodevelopment.<sup>20</sup> Conversely, yet another study found that rapid early postnatal growth in subjects born SGA was associated with cardiometabolic disease propensity.<sup>21</sup> HC SDS did not change for both groups. Nevertheless, despite this parallelism in growth patterns, the VP+/VLBW+ group remained below the means of the norm population for length/height, weight and HC. In contrast, the length/height, weight and HC of the VP+/VLBW- group remained close to the population reference mean.

At age 19 years, all three groups had a BMI that was comparable to the norm population, with significant increases in BMI SDS for the VP+/VLBW+ and VP-/VLBW+ groups between ages 5 and 19. This pattern has previously been associated with an increased risk of coronary events later in life.<sup>22</sup>

A previous study found significantly different early neonatal outcomes between VP and VLBW infants.<sup>13</sup> This was replicated in our study, in which we observed a greater percentage of neonatal morbidities in the VP+/VLBW+ and VP+/VLBW- groups. VP-/VLBW+ infants, in turn, were more often born SGA. In addition, they were more often born to mothers who had (pre-existent) hypertension or who smoked during pregnancy, which are known risk factors for IUGR.<sup>23</sup> This suggests that short-term outcomes are significantly different depending on the classification that is used. Our current findings indicate that the differences between these groups could be extended with growth up until adulthood, with the VP-/VLBW+ group, and to a lesser extent the VP+/VLBW+ group,

showing a growth pattern that has previously been associated with cardiometabolic disease.<sup>21</sup>

Because of the different neonatal outcomes and growth patterns found in our study between children born VP and/or with a VLBW, we argue that these terms cannot be used interchangeably. Therefore, findings from studies in children born with VLBW cannot be automatically extrapolated to children born VP, and vice versa.

For future studies on preterm infants, we suggest that researchers strive to use the same inclusion criteria, enabling comparisons between different cohorts. Notably, it is desirable to use inclusion criteria that result in representative samples of preterm infants. The definition of prematurity is based on pregnancy duration and not on birth weight, and with current technologies, pregnancy dating can be determined very accurately, especially in the first trimester.<sup>24,25</sup> Therefore, we would strongly recommend that, at least for industrialized countries, the inclusion of preterm subjects is based on gestational age rather than on birth weight.

Our study has several strengths and limitations. The major strengths of our study are its large sample size, long-term follow-up and completeness of data, including growth parameters.

Our study also has some limitations. First, the follow-up rate between ages 5 and 19 dropped substantially. A non-response analysis (Table 2) showed that non-response was associated with male gender, non-Caucasian ethnicity and a lower SES. However, aside from gender, these factors were not significantly different between the three study groups. Moreover, responders had a 0.2 SD higher target height SDS and their mothers were more often hypertensive compared with non-responders. However, perinatal characteristics, including SGA status, did not differ between response groups. Moreover, the distribution of subjects among the three study groups was not different between responders and non-responders. Therefore, although small differences were present, we think that our results at age 19 are not subject to attrition bias. Second, subjects in this cohort were born in 1983. Therefore, our data are not representative for the current generation of preterm infants,<sup>26</sup> as neonatal care has advanced significantly in the past three decades. However, preterm infants still show EUGR despite improved neonatal care,<sup>27</sup> and VP and/or VLBW subjects can therefore still be expected to have different growth patterns. Nevertheless, these growth patterns will presumably be more favorable than the growth patterns observed in this study. As IUGR pregnancies are nowadays strictly monitored and labor is induced if necessary<sup>23</sup>, infants will be less likely severely growth restricted at birth, leading to lower numbers being VLBW but not VP. Moreover, because of improved nutritional strategies, which include earlier introduction and rapid increases in protein intake<sup>28,29</sup>, as well as an increased awareness of the benefits of human breast milk<sup>30</sup>, VP+/VLBW+ and VP+/VLBW- infants will likely show a smaller decrease in SDS, whereas VP-/VLBW+ infants will show improved catch-up growth. Third, although post-

natal growth charts have been designed specifically for preterm infants, we did not use these reference data, as they apply to the current generation of NICU-treated infants. Instead, we have used reference charts that are applicable to Dutch children born in the 1980s.<sup>16,17</sup> Although these charts were not designed specifically for preterm infants, they do allow comparison between the study groups. Finally, the observed growth patterns, especially those of the VP-/VLBW+ group, could also be partly ascribed to regression to the mean. However, this phenomenon is difficult to quantify and to separate from catch-up growth. Nonetheless, despite possible regression to the mean, the three groups still show significantly different growth at age 19.

In conclusion, infants born VP+/VLBW+, VP+/VLBW- or VP-/VLBW+ appear to have significantly different growth patterns, and, therefore, the terms VP and VLBW cannot be used interchangeably. Because pregnancy dating can be reliably assessed nowadays, we recommend, at least for industrialized countries, to use gestational age instead of birth weight as the inclusion criterion for future studies in preterm infants.

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