Preterm birth, early growth and adult metabolic health
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4 Preterm birth and body composition in adulthood:

different effects of intrauterine and infancy weight gain

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Abstract

Objectives:

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. Therefore, we studied the association between prenatal, early postnatal, and late infancy weight gain, and BMI, fat mass, and fat distribution in young adulthood.

Methods:

We included 403 men and women aged 19 years from a Dutch national prospective follow-up study who were born at a gestational age <32 weeks. BMI SD score (SDS), waist circumference SDS, and waist-to-hip ratio SDS, and subscapular-to-triceps ratio, percentage body fat, fat mass, and fat-free mass at age 19 years were studied in relation to birth weight SDS, weight gain from preterm birth until 3 months post-term (early postnatal weight gain), and from 3 months until 1 year post-term (late infancy weight gain).

Results:

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

Conclusions:

In individuals born very preterm, weight gain before 32 weeks 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 SDS and percentage body fat and more abdominal fat at age 19 years.

Introduction

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

Fetal life and the early postnatal period have been suggested to be important for the development of adult obesity (5;6). 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 (7;8). The association between birth weight, mainly an indicator of fetal growth during the third trimester, and adult obesity is equivocal (9). In several studies, a linear positive association has been found (10-12), whereas in others a J- or U-shape (13;14) or no association was observed (15). In these studies, obesity was expressed as BMI, 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 (16;17) and a lower BMI, mostly because of a lower lean body mass and not a lower fat mass (18-22). In addition, a rapid rate of weight gain during early infancy has been associated with both a higher BMI (23) and more fatness and a more central pattern of fat distribution in childhood (6). In certain specific populations, early growth has been positively associated with obesity and lean body mass in adulthood (24;25). However, the associations between birth weight and adult body composition have not been consistently found in all populations (26;27), and in various studies the associations became significant only after adjustment for adult BMI (16;17;21;22). 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 weeks of gestation, during the period from preterm birth until 3 months post-term (early postnatal weight gain), and from 3 months until 1 year post-term (late infancy weight gain) for BMI, fat distribution, and body composition at age 19 years.

Methods

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 <1,500 g, or both (28). The physical and psychosocial outcomes of the POPS cohort have been intensely studied over the years (28;29). In the current study, conducted when the subjects were 19 years of age, only those subjects with a gestational age <32 weeks were studied. Subjects with congenital malformations leading to changes in body proportions and body composition (e.g., 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.

Study protocol

Weight, length, and head circumference were measured at birth and expressed as SD score (SDS) to correct for gestational age and sex with the use of Swedish references for very preterm infants (30). At the ages of 3 months and 1 year post-term, weight and length were measured at the outpatient clinics of the participating centers by trained physicians and nurses. These measurements were expressed as SDS using Dutch reference values (31). Weight gain between birth and the age of 3 months post-term (early postnatal weight gain), and between the ages of 3 months and 1 year post-term (late infancy weight gain) were computed as delta-SDS.

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 years. All assessors had received extensive training before the start of the study; during the study, retraining and standardization were carried out at 2-months intervals to maximize interobserver reliability. 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^2 in cm (2). Waist circumference was measured at the level midway between the lower costal margin and the iliac crest after gentle 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 thicknesses were taken in duplicate with a calibrated skinfold calliper on the left side of the body at the triceps, biceps, subscapular, and iliacal regions, according to guidelines of the World Health Organisation (biceps and subscapular) (32), and Falkner and Tanner (triceps and iliacal) (33). 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 (34). Fat mass and the corresponding fat-free mass were computed by using the equations of Durnin and Rahaman (35). All outcome measures at age 19 years, except for the derived outcomes, were expressed as SDS according to recent Dutch references (31;36;37).

Statistical analysis

Multivariate linear regression analyses were performed in SPSS 11.0 software (SPSS Inc, Chicago, USA) to assess associations between prenatal, early postnatal, and late infancy weight gain and the outcome measures at age 19 years. 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 SDS and early postnatal weight gain and late infancy weight gain, respectively, was introduced to assess whether the effect of early postnatal and late infancy weight gain on outcome measures at age 19 years was different for those individuals with low birth weights compared to 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 SDS 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 years as outcomes were also adjusted for variations in adult body size by adjusting for current height SDS. The analyses with height SDS at age 19 years as outcome measure were adjusted for target height SDS, which was computed as: midparental height + 6.5 cm (-6.5 cm for females) + 4.5 cm (estimated secular trend per generation). All analyses were repeated with adjustment for the possible confounders race (white versus non-white), socio-economic 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, 1,012 infants who were born before 32 weeks of gestation were included in the POPS cohort; 669 without congenital malformations were still alive at age 19 years. 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 anthropometry was performed at age 19 years.

Characteristics of the subjects are given in Table 1. Non-response was higher among males, non-whites, and those with a mother with a low educational level. Birth weight SDS and gestational age did not differ significantly between responders and non-responders.

Table 1. Perinatal characteristics of participants and non-responders.

Characteristic	Participants	Non-responders
N	403	254
General		
Sex (% male)	46.4[b]	65.7
Race (% white)	87.7[c]	80.2
Low educational level mother (%)	38.9[b]	56.5
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 intoxication (%)[a]	52.0	52.0
Elective delivery (%)	19.4[c]	13.4
Birth		
Gestational age (weeks)	29.7±1.5	29.8±1.5
Birth weight		
- g	1,316±336	1,347±274
- SDS	-0.13±1.0	-0.09±0.9
Birth length		
- cm	39.1±3.4[c]	39.6±2.9
- SDS	-0.12±1.2	-0.06±1.1
Head circumference at birth		
- cm	27.4±2.1	27.6±1.9
- SDS	0.03±1.2	-0.09±1.0
Postnatal		
Weight at 3 mo		
- kg	5.1±0.90	5.3±0.88
- SDS	-0.94±1.3	-0.90±1.4
Weight at 1 yr		
- kg	8.9±1.2	9.1±1.4
- SDS	-0.98±1.2	-0.94±1.4

Values represent mean±SD or percent. Continuous variables were compared with the unpaired t test. Dichotomous variables were compared by the χ^2 test.

[a] Smoking, drinking alcohol, or using soft drugs, hard drugs or methadone during pregnancy.

[b] P <0.001 between participants and non-reponders.

[c] P <0.05 between participants and non-responders.

The anthropometric characteristics of the response group are provided in Table 2 as absolute values and SDSs. 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-year-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.

The associations between prenatal, early postnatal, and late infancy weight gain and the anthropometric outcomes at age 19 years are shown in Table 3. Birth weight SDS was positively associated with adult height SDS, weight SDS, BMI SDS, and waist circumference SDS, although the 95% CIs for the latter 2 variables almost included 0. There was also a positive association between birth weight SDS and both fat mass and fat-free mass but not between birth weight SDS and percentage body fat at age 19 years. When adjusted for current height SDS, the association between birth weight SDS and waist circumference SDS disappeared. The regression coefficient of the association between birth weight SDS and fat-free mass decreased, and the association between birth weight SDS and fat mass became non-significant after correction for current height SDS. No significant associations were found between birth weight SDS and the waist-to-hip ratio SDS, the sum of 4 skinfold thicknesses SDS, and the subscapular-to-triceps ratio at age 19 years.

Early postnatal weight gain and late infancy weight gain were both positively associated with height SDS, weight SDS, BMI SDS, waist circumference SDS, fat mass, fat-free mass, and percentage body fat at age 19 years. Late infancy weight gain was also positively associated with the adult sum of 4 skinfold thicknesses SDS. The coefficients of waist circumference SDS, fat mass, and fat-free mass in relation to early postnatal and late infancy weight gain diminished after correction for current height SDS but remained significant. When adjusted for target height SDS, the associations between prenatal, early postnatal, and late infancy weight gain and adult height SDS 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 SDS or subscapular-to-triceps ratio in young adulthood.

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

For the anthropometric outcomes at age 19 years 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 SDS, 37.5% of variance was explained by target height SDS. Birth weight SDS explained 6.2% of the variance in current height SDS not explained by target height SDS, whereas early postnatal weight gain explained another 4.5% of current height SDS variance not explained by target height SDS or birth weight SDS. Late infancy weight gain explained 3.3% of the variance of current height SDS not explained by the abovementioned variables. So, for current height SDS adjusted for target height SDS, the largest change in R^2 values was observed for the effect of birth weight SDS.

For adult weight SDS, the effect of birth weight SDS on R^2 change equalled the effect of early postnatal weight gain. For BMI SDS, waist circumference SDS, fat mass, fat-free mass, and percentage body fat, the largest increase in R^2 – apart from adjustments for sex and current height SDS – 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.

Table 2. Characteristics of participants at age 19 years by sex.

Characteristic	Men	Women	P
N	187	216	
Height			
- cm	179.4±7.9	166.4±7.1	0.001
- SDS	-0.55±1.1	-0.60±1.1	0.633
Weight			
- kg	69.9±12.1	60.5±10.6	0.001
- SDS	-0.41±1.2	-0.48±1.4	0.583
BMI			
- kg/m²	21.7±3.1	21.8±3.4	0.659
- SDS	-0.10±1.2	-0.17±1.2	0.569
Waist circumference			
- cm	80.2±8.9	76.6±7.9	0.001
- SDS	0.24±1.1	0.73±0.92	0.001
Hip circumference			
- cm	92.1±8.1	94.2±9.4	0.017
- SDS	-0.22±1.2	0.03±1.1	0.037
Waist-to-hip ratio			
- cm/cm	0.87±0.054	0.82±0.063	0.001
- SDS	0.72±0.92	0.90±0.93	0.055
Sum of 4 skinfold thicknesses			
- mm	41.3±20.6	62.6±22.4	0.001
- SDS	1.7±2.8	1.1±1.6	0.012

Values represent mean±SD. Variables were compared with the unpaired t test.

Discussion

This study describes the results of a large-scale prospective study on the relation between birth weight, postnatal weight gain, and anthropometric parameters at the age of 19 years 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 (i.e., 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 weeks 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 SDS 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 non-response groups. Some subjects had missing data on weight at 3 months or 1 year, but these missing data were not related to any of the outcome measures.

We found some differences between anthropometric characteristics at age 19 years between the male and the female participants. Whereas the differences in absolute values were expec-

Table 3. Regression analyses of birth weight SDS and infancy weight gain on size and body composition at age 19 years.

Outcome	Birth weight SDS			Early postnatal weight gain			Late infancy weight gain		
	N	ß	95% CI	N	ß	95% CI	N	ß	95% CI
Height SDS	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 SDS adjusted for target height SDS	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 SDS	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 SDS	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 SDS	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 SDS adjusted for current height SDS	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 SDS	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 SDS adjusted for current height SDS	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 SDS	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)[a]	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 current height SDS[a]	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)[a]	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 current height SDS[a]	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 (%)[a]	390	0.176	-0.329 to 0.682	361	0.479	0.022 to 0.936	340	0.651	0.033 to 1.269

Waist-to-hip ratio SDS, subscapular-to-triceps ratio, and the interaction terms between birth weight and infancy weight gain were not significant and thus were not reported.

[a] Adjusted for sex.

ted, the different SDSs 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 inter-observer variation (38). However, although skinfold-thickness measurements tend to overestimate fat mass somewhat compared with a direct method such as dual-energy X-ray absorptiometry, Fewtrell et al (39) concluded from their study on prematurity and body fatness at age 8 to 12 years 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 (40). 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 intra-observer reliability (intraclass correlation coefficient >0.99). Because the birth weights of participants did not substantially differ between centers, this relatively low inter-observer reliability will have only attenuated the associations between birth weight and body composition at age 19 years.

We found that birth weight was positively associated with weight, height, and BMI at age 19 years. These findings are consistent with those of studies in populations born at term (11;12). Our study indicates that the positive association between birth weight and adult BMI is determined as early as in 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 (7;8). Our study does not confirm the J- or U-shape relationship between birth weight and adult BMI found in some studies (13;41;42),

Table 4. Explained variance (R^2) and change in explained variance (R^2 change) for the anthropometric variables at age 19 years.

Outcome	N	R^2 change						Total R^2
		Target height SDS	Adult height SDS	Sex	Birth weight SDS	Early postnatal weight gain	Late infancy weight gain	
Height SDS	351	37.5[a]	-	-	6.2[a]	4.5[a]	3.3[a]	51.6
Weight SDS	351	-	-	-	9.6[a]	9.6[a]	8.8[a]	28.1
BMI SDS	351	-	-	-	2.7[a]	4.9[a]	2.5[a]	10.1
Waist circumference SDS	347	-	8.8[a]	-	0.0	2.3[a]	1.1[a]	12.2
Sum of 4 skinfold thicknesses SDS	340	-	-	-	0.1	1.5	1.5[a]	3.1
Fat mass (kg)	340	-	5.4[a]	25.2[a]	0.2	1.8[a]	1.4[a]	34.1
Fat-free mass (kg)	340	-	18.1[a]	60.1[a]	0.7[a]	1.0[a]	0.9[a]	80.9
Percentage body fat (%)	340	-	-	64.7[a]	0.0	0.7[a]	0.4[a]	65.8

Values represent percent.
[a] Significant R^2 change ($P < 0.05$).

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 (18) 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 years. 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 (13;43). 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 relationship 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 (6) and Stettler et al (24) between early catch-up growth and fatness in childhood persist into young adulthood. This is in accordance with a study by Li et al (25) 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 SDS. Fetal weight gain was also positively associated with waist circumference SDS, but after adjustment for current body height SDS, 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 found. This finding agrees with the results of Fall et al (13) and Li et al (25). In some studies, low birth weight and early growth have been associated with a more truncal and abdominal fat pattern (13;16;17) 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 (44). However, we think it is theoretically not correct 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, and late infancy weight gain, and adult BMI and body composition might be explained by perinatal programming (45). 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.

Conclusions

In conclusion, in individuals born very preterm both gestation, the period from birth until 3 months post-term, and the period from 3 months until 1 year post-term seem to be important predictors of body size and body mass in young adulthood. Greater weight gain during these periods is associated with higher height, weight, BMI, and fat-free mass at age 19 years. Birth weight in infants born very preterm is not associated with fat distribution. However, early post-natal 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 months post-term on adult fat mass and fat distribution is more pronounced than is the effect of weight gain from 3 months until 1 year post-term.

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