Size at birth, growth trajectory in early life and cardiovascular and metabolic risk in early adulthood: the EPICure study

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What is already known on this topic?

- Low birth weight and rapid catch-up in infancy and early childhood are associated with increased cardiovascular risk in later life in general populations.
- Evidence is limited and mixed on the long-term health effects of the growth trajectory from birth to full-term age in preterm infants.
- Greater catch-up in weight in childhood is shown in populations born preterm, but whether this put them at increased cardiometabolic risk deserves more research.

What this study adds?

- No associations of size at extremely preterm birth with the presence of metabolic syndrome, BMI or central SBP in early adulthood were found.
- An inverse relationship between size at extremely preterm birth and BMI in early adulthood was found in the lower socioeconomic status group.
- Increased catch-up in weight from 2.5-6 years (not in preterm period nor in infancy) was associated with BMI and central SBP in early adulthood.

Abstract

Objectives: To investigate whether size at birth and growth trajectories in infancy and childhood are associated with determinants of cardiovascular and metabolic risk in young adults born extremely preterm (EP; <26 weeks of gestation).

Methods: We used longitudinal data from the EPICure study of 129 EP survivors up to 19 years in the UK and Ireland in 1995. Determinants of cardiovascular and metabolic risk at 19 years included the presence of metabolic syndrome, BMI, and systolic blood pressure (SBP). Predictors were birth weight for gestation and gain in weight z-scores in the following periods: birth to 40 weeks postmenstrual age (term), infancy (term to 2.5 years), early childhood (2.5-6 years) and late childhood (6-11 years).

Results: Metabolic syndrome was present in 8.7% of EP participants at 19 years. Compared to subjects without, those with metabolic syndrome tended to have a smaller size at birth (difference in means: -0.55 SD, 95% CI: -1.10 to 0.01, *p*=0.053) and a greater increase in weight z-scores from term to 2.5 years (difference in means: 1.00 SD (-0.17 to 2.17), *p*=0.094). BMI at 19 years was positively related to growth from 2.5-6 years (β: 1.03 (0.31, 1.75), *p*=0.006)**;** an inverse association with birthweight z-scores was found in the lower SES group (β: -1.79 (-3.41, -0.17), *p*=0.031). Central SBP was positively related to growth from 2.5-6 years (β: 1.75 (0.48 to 3.02), *p*=0.007).

Conclusions: Size at EP birth and increased catch-up in weight from 2.5-6 years were associated with BMI and central SBP in early adulthood.

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INTRODUCTION

The relationships between low weight at birth and increased risk in later life of adiposity, cardiovascular disease and type 2 diabetes (T2DM) are well established in general populations [1-8]. Higher risk is thought to be a consequence of persisting physiological and metabolic changes that accompany slow intrauterine growth. However, many of the early epidemiological studies had very limited data on gestational age. In the general population, low weight at birth can result from both fetal growth restriction and preterm birth. Advances in perinatal and neonatal care in the 1990s were associated with greatly improved survival of very preterm babies, which, together with enhanced accuracy in gestational age estimation, have made it possible to examine influences on childhood growth and cardiometabolic risk in early adult life.

We have previously shown that, compared to birth at term, fetal growth in extremely preterm survivors (EP; <26 weeks of gestation) has a slower trajectory from birth to full-term age, leading to an appreciable decrease in weight z-scores. Catch-up in weight only commences after reaching term age[9]. This is in line with reports from other cohort studies in the UK, Sweden and the Netherlands[10-13]. Evidence has been limited and mixed on the long-term health effects of this growth trajectory in preterm infants. Some studies indicate that a greater weight gain during the period from birth to term age/discharge has adverse effects on later body composition, obesity and cardiovascular health[11,13], whilst others reported no effects on the markers of the metabolic syndrome[12,14-17].

We have previously shown greater catch-up in weight in childhood among EP participants than term-born children[18]. Weight at birth is lower for preterm births than that expected from fetal growth data. There is increased concern that pronounced fetal and postnatal growth restriction, with accelerated catch-up growth in childhood, may put these children at increased risk of metabolic and cardiovascular morbidity in later life. Repeatedly in babies born at full term, rapid catch-up in infancy and early childhood has been associated with increased risk for obesity, hypertension, cardiovascular disease and T2DM in adulthood[19-25]. Evidence linking such factors in populations born preterm is less extensive, but data suggest that weight gain in infancy after term age is positively related to BMI[26], fat mass or percentage body fat[11,26], insulin level[27] and serum levels of total cholesterol and low-density lipoprotein (LDL) cholesterol[11], and borderline related to high-density lipoprotein (HDL) cholesterol level [11]. There is also some evidence showing accelerated postnatal growth during the first months after birth did not affect systolic blood pressure (SBP) at 19 years in individuals who were born preterm, but those who showed increased postnatal weight gain and BMI after 5 years had higher SBP[28].

We used longitudinal data from the EPICure study of 129 EP survivors up to 19 years to investigate whether size at birth and growth trajectories in preterm period (birth to term age defined as 40 weeks postmenstrual age), infancy (term-2.5 years), early childhood (2.5-6 years) and late childhood (6-11 years) were associated with determinants of metabolic and cardiovascular risk at age 19 years. We hypothesised that following EP birth, size at birth and growth in infancy and childhood, but not growth in the preterm period, would be associated with determinants of cardiovascular and metabolic risk in early adult life.

METHODS

Subjects

The EPICure study comprised 315 infants born at 25 completed weeks of gestation or less in all 276 maternity units in the UK and Ireland from March to December 1995 who were discharged alive from neonatal intensive care units. Recruitment of the cohort has been described in detail previously[29-31]. The survivors were followed longitudinally at age 2.5, 6, 11 and 19 years. A flow chart detailing dropout has been published previously[32]. Nine deaths occurred between discharge and the 19-year assessment, at which 129 (42%) of EP participants were assessed. At 6 years, 160 term-born classmates (≥37 weeks of gestation) were recruited for 204 children attending mainstream schools. They were matched on age, sex and ethnicity. At 11 years, 110 of them were re-assessed and 43 new controls were recruited. At 19 years, 65 of those attending at 11 years were re-assessed. Each follow up assessment was approved by the ethics committee. Written informed consent was provided by parents up to 11 years and by individual participants at 19 years. The assessment at 19 years was approved by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514).

Measures

Growth, cardiovascular evaluations and other risk factors at age 19 years have been described previously (Hurst et al. 2020, in press). The prevalence of metabolic syndrome was calculated, based on the criteria defined by the International Diabetes Federation as having central obesity measured by waist circumference or BMI, together with any two of the following components: (1) raised triglycerides; (2) reduced HDL cholesterol; (3) raised blood pressure; and (4) raised fasting plasma glucose[33].

Explanatory variables of interest included birth weight and changes in (Δ) weight z-scores during the following periods: birth to term, infancy (term-2.5 years), early childhood (2.5-6 years), and late childhood (6-11 years). Growth data were collected at each age, which have been described in detail previously [9,15]. Only weight was collected at birth and term age. Standard deviation scores (z-scores)

for weight were calculated at each age based on UK population norms[34]. Birthweight z-scores (birth weight for gestation) were derived from the complete birth population[29].

Data on confounding factors were obtained from the main study. These included sex (males vs females), gestational age, multiple births (yes vs no), ethnicity (white vs non-white), maternal age, maternal education (A level or above vs GCSE or below), maternal smoking during pregnancy (yes vs no) and socioeconomic status (SES), which was based on parental occupational status at 2.5 years and dichotomised as (1) higher: non-manual employment; (2) lower: including those in manual employment or unemployed.

Statistical Analyses

Factors related to the presence of metabolic syndrome (yes vs no) at 19 years were explored using two sample t-tests or chi-square tests. Multivariate linear regression was used to examine associations of birthweight z-score with BMI and central SBP at age 19 years (two determinants of cardiovascular and metabolic risk). Univariate linear regression was used to screen for confounders. For a potential confounder to be retained in the final models, it was required to have a *p* value <0.10. Interactions of birthweight z-score and confounders were tested. Confounding factors in the final models included sex, maternal age and maternal smoking during pregnancy. Similar strategies were followed when examining the impacts of growth patterns in infancy and childhood. All analyses were performed using STATA 15.1. Correction for multiple comparisons was applied using the Benjamini-Hochberg procedure to control for the false discovery rate [35]. There was a small amount of missing data in BMI (0.01%) and central SBP (0.03%) measured at 19 years and they were excluded from the analysis. This is unlikely to influence the results due to small numbers.

RESULTS

Participants. The mean birth weight (range) for the whole cohort of 315 EP survivors was 747g (423-1040); 41% were 24 weeks of gestational age or less; 49.2% were males and 25.2% were multiple births. Birthweight z-score were derived from the complete birth population[29] and were available for 312 infants (mean -0.18 SD; table 1); among them, 49 (15.7%) had z-scores < -1 SD. Progressive loss to follow up occurred for the EPICure study over the period of 19 years, and similar attrition occurred in the control group. The cohort included in this analysis were representative of the total original cohort in relation to sex, birth weight and gestational age. EP participants at 19 years were more likely to be from a multiple pregnancy, have mothers who were older, of white ethnicity and with higher educational attainment, and have parents with higher SES (**table S1**), which has been

reported previously[32]. The anthropometric and clinical characteristics of the participants are shown in **table 1**.

Early growth and cardiovascular and metabolic risk at 19 years. The prevalence of metabolic syndrome was 8.7% for EP participants and 3.7% for controls (*p*=0.240; **table 1**). Similar results were shown for the five metabolic syndrome components (**table 1**). EP participants with metabolic syndrome tended to have a smaller size at birth (difference in means: -0.55 SD, 95% confidence interval: -1.10 to 0.01, *p*=0.053; **table 2**) and a higher increase in weight z-scores from term to 2.5y (difference in means: 1.00 SD, 95% CI: -0.17 to 2.17, *p*=0.094).

Change in (Δ) weight z-scores in early childhood from 2.5-6 years was positively related to BMI at 19 years (β: 1.03 (0.31, 1.75), *p*=0.006; **table 3**): an average increase of 1.03 kg/m^2 in BMI for per SD increase in Δ weight z-scores from 2.5-6 years; this relationship was independent of size at birth. Young adults with BMI >30 kg/m^2 had a mean of 1.87 SD in Δ weight z-scores from 2.5-6 years, significantly higher than those with lower BMI (difference in means: 1.54 (0.76, 2.32)). A significant interaction was found between SES and birthweight z-score (β: 2.06 (0.01, 4.12), *p*=0.049). Birthweight z-score was not associated with BMI at 19 years (**table 3**), but after adjusting for the interaction between SES and birthweight z-score, the association became significant (β: -1.90 (-3.35, -0.45), *p*=0.011; **figure 1**). Subgroup analysis showed an inverse association in the lower SES group, and this remained significant after adjusting for sex, maternal age and maternal smoking during pregnancy (β: -1.79 (-3.41, -0.17), *p*=0.031), which was not found in the higher SES group (**figure S1**). Growth in other periods was not significantly associated with BMI at 19 years (**table 3**). Central SBP at 19 years was positively associated with Δ weight z-scores from 2.5-6 years (β: 1.75 (0.48 to 3.02), *p*=0.007; **figure 2**), but unrelated to size at birth and growth in other periods (**table 3**). Significant findings remained unchanged after adjustment for multiple comparisons.

DISCUSSION

Using data from EP survivors born before 26 weeks of gestation in 1995, we show that firstly, 8.7% met the criteria for metabolic syndrome and 3.7% of term-born controls. This is similar to a pooled analysis reporting a range of 4.8-7.0% in healthy adults aged 18-30 years[36]. Secondly, we found that size at EP birth was not associated with the presence of metabolic syndrome, BMI or central SBP in early adulthood, although an inverse relationship with BMI was found in the lower SES group. Thirdly, growth during the preterm period from birth to term equivalent age, which is a period where growth velocity is frequently poor, was not related to early adult outcomes, in line with most previous studies in preterm children[12,14-17]. In contrast, after term equivalent age, increased weight gain from 2.5-6 years was associated with BMI and SBP in early adulthood.

Previous studies have reported either no or variable associations between birth weight and determinants of cardiovascular and metabolic risk in populations born preterm[12,17,26-28]. Here in young adults born EP, we did not find that size at birth was associated with cardiovascular and metabolic risk. This is not consistent with previous studies in adults born at term[37,38] and fails to support the fetal origins hypothesis[39]. Interestingly, an inverse relationship between birth weight for gestation and BMI at 19 years was found in the lower SES group. The underlying mechanism is unknown. Previous research suggests that low SES, measured by occupational status, was associated with increased risk of obesity in women[40] and that maternal weight/BMI before pregnancy explains the association between birth weight and adult BMI[41]. We therefore speculate that pre-pregnancy weight might mediate this relationship.

Loss to follow-up was higher among participants with lower SES, so the question arises whether the observed association was biased by selective response. Lower SES was neither related to birth weight nor outcomes in our study but was associated with greater weight gain from birth to term-age. Adjusting for confounders and subsequent growth did not change the relationships, which makes this less likely. In comparison to birthweight, gestational age was unrelated to any outcome (data not shown), indicating that it may not be a good marker for cardiovascular and metabolic risk in this group.

Our data show that EP participants with metabolic syndrome at 19 years tended to have smaller size at birth and a higher increase in weight z-scores from term-2.5 years. Previous research has shown that weight gain in infancy after term age is positively related to BMI[26], fat mass or percentage body fat[11,26], insulin level[27] and serum levels of total cholesterol and LDL cholesterol[11]. We also show positive associations of growth from 2.5-6 years with BMI and central SBP in young adults born EP. Despite a lack of evidence from other preterm populations, a Swedish birth cohort study of healthy singletons showed rapid weight gain in early childhood (3-6 years) predicted adiposity at 17 years [22], but not metabolic syndrome risk [23]. We found no relationship between growth from 6-11 years and determinants of cardiovascular and metabolic risk, failing to support our hypothesis and in contrast to a previous study suggesting that increased postnatal weight gain after age 5 years was a predictor for systolic blood pressure at 19 years[28].

The strength of this study lies in the longitudinal design with a long duration of follow-up from birth to early adulthood and detailed assessment on cardiovascular and metabolic risk. It allows us to explore the effects of size at birth and growth in both early life and throughout childhood in relation to determinants of cardiovascular and metabolic risk in early adulthood. Other strengths are

adjusting for potential confounders and controlling for the false discovery rate using the Benjamini–Hochberg procedure to decrease the risk of type I error.

The study also has limitations. First, although the original cohort encompassed the entire population of extremely preterm infants in the UK and Ireland in 1995 who had been discharged alive after neonatal intensive care, the number of participants lost to follow-up increased over time and dropout was associated with markers of social disadvantage. However, those who participated did not differ from the original cohort on baseline characteristics (sex, gestational age and birth weight). Second, we have to be cautious to generalise our findings to other populations and they need to be confirmed in cohorts from different socioeconomic and cultural settings. We also have to be cautious in inferring causality as in any observational study. Lastly, it is possible that some weak associations would have reached significance in a larger sample, for instance, the associations of birth weight for gestation and the increase in weight z-scores from term-2.5 years with the presence of metabolic syndrome at 19 years.

In conclusion, following EP birth, an inverse relationship between size at birth and BMI in early adulthood was only found in the lower SES group, measured by parental occupational status. Increased catch-up in weight from 2.5-6 years (not in preterm period nor in infancy) was associated with BMI and central SBP in early adulthood, which suggests an opportunity for targeted interventions in early childhood to prevent the development of cardiovascular and metabolic risk in later life.

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Competing interests None declared.

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Data sharing statement Data are available subject to the EPICure Data Sharing Policy (www.epicure.ac.uk).

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Table 1 Characteristics of extremely preterm and control participants

Variables		Whole cohort N=315	Controls
Perinatal variables			
Male Sex	% (n)	49.2% (155)	38.5% (25) [+]
Gestational age			
<=23 weeks	% (n)	9.2% (29)	-
24 weeks	% (n)	31.7% (100)	-
25 weeks	% (n)	59.0% (186)	-
Multiple births	% (n/N)	25.2% (79/314)	-
White ethnicity	% (n)	76.5% (241)	-
Maternal age	Mean (SD)	28.5 (5.9) [n=313]	-
Maternal smoking during pregnancy	% (n/N)	32.9% (93/283)	-
Maternal education (A level or above) [a]	% (n/N)	25.9% (68/263)	-
Higher SES [a]	% (n/N)	31.0% (84/271)	-
Birth weight (kg)	Mean (SD)	0.75 (0.11) [n=315]	-
Birthweight z-score	Mean (SD)	-0.18 (0.76) [n=312]	-
Early growth [b]			
Weight gain from birth to term (kg)	Mean (SD)	1.82 (0.49) [n=284]	-
Change in (Δ) z-score from birth to term	Mean (SD)	-1.50 (1.05) [n=275]	-
Weight gain from term to 2.5y (kg)	Mean (SD)	9.3 (1.7) [n=264]	-
Δ z-score from term to 2.5y	Mean (SD)	0.07 (1.42) [n=258]	-
Weight gain from 2.5y to 6y (kg)	Mean (SD)	6.8 (2.7) [n=226]	-
Δ z-score from 2.5y to 6y	Mean (SD)	0.37(1.03) [n=226]	-
Weight gain from 6y to 11y (kg)	Mean (SD)	15.6 (6.2) [n=201]	17.4 (7.5) [n=110]
Δ z-score from 6y to 11y	Mean (SD)	0.84 (0.86) [n=201]	0.25 (0.75) [n=110]
Continuous outcomes at 19 years			
BMI (kg/m^2)	Mean (SD)	23.3 (4.4) [n=128]	24.7 (5.7) [n=65]
Waist circumference (cm)	Mean (SD)	82.7 (11.4) [n=103]	82.3 (12.8) [n=52]
Waist-hip ratio	Mean (SD)	85.3 (6.3) [n=103]	81.3 (5.5) [n=52]
Seated brachial Systolic BP (mmHg)	Mean (SD)	119.5 (10.1) [n=127]	117.9 (9.8) [n=64]
Seated brachial Diastolic BP (mmHg)	Mean (SD)	73.2 (7.9) [n=127]	71.6 (6.0) [n=64]
Supine brachial Systolic BP (mmHg)	Mean (SD)	119.1 (10.0) [n=127]	116.1 (10.0) [n=64]
Supine brachial Diastolic BP (mmHg)	Mean (SD)	69.4 (7.4) [n=127]	65.9 (5.8) [n=64]
Central Systolic BP (mmHg)	Mean (SD)	101.2 (8.0) [n=126]	96.7 (7.8) [n=64]
Central Diastolic BP (mmHg)	Mean (SD)	70.6 (7.6) [n=126]	66.9 (5.9) [n=64]
Aortic Augmentation Index (%)	Mean (SD)	6.6 (9.0) [n=126]	0.4 (8.2) [n=64]
Triglycerides (mmol/l)	Mean (SD)	0.9 (0.5) [n=109]	0.9 (0.4) [n=61]
HDL (mmol/l)	Mean (SD)	1.5 (0.4) [n=109]	1.6 (0.4) [n=61]
LDL (mmol/l)	Mean (SD)	2.3 (0.8) [n=109]	2.4 (0.7) [n=61]
Fasting glucose (mmol/l)	Mean (SD)	4.9 (0.7) [n=111]	4.9 (0.4) [n=60]
Metabolic syndrome at 19 years [c]	% (n/N)	8.7% (9/103)	3.7% (2/54)
Central obesity [c]	% (n/N)	35.6% (37/104)	35.2% (19/54)
Raised triglycerides [c] (>=1.7mmol/l)	% (n/N)	9.2% (10/109)	6.6% (4/61)
Raised HDL [c]	% (n/N)	17.4% (19/109)	11.5% (7/61)
Raised blood pressure [c]	% (n/N)	18.1% (23/127)	9.4% (6/64)
Raised glucose [c] (>=5.6mmol/l)	% (n/N)	7.2% (8/111)	3.3% (2/60)

[+] Data reported for controls at 19 years. [a] Maternal education and socioeconomic status (SES) were collected using parent questionnaire at age 2.5 years; SES was based on using parent occupation: (1) higher: non-manual employment; (2) lower: including those in manual employment or unemployed. [b] Growth data at 2.5 years: uncorrected for prematurity. [c] Metabolic syndrome was defined by the International Diabetes Federation as having central obesity measured by waist circumference or BMI, together with any two of the following components: (1) raised triglycerides; (2) reduced HDL cholesterol; (3) raised blood pressure; and (4) raised fasting plasma glucose.

Table 2 Factors related to the presence of metabolic syndrome at 19 years in young adults born extremely preterm[+]

	Metabolic syndrome [a]			
	No	Yes	Yes vs No	*p*
	mean (SD)	mean (SD)	Difference in means (95% CI)	
Maternal age	29.58 (5.18) [n=92]	27.89 (5.25) [n=9]	-1.69 (-5.28, 1.91)	0.354
Gestational age	24.95 (0.78) [n=94]	24.76 (1.21) [n=9]	-0.19 (-0.76, 0.37)	0.500
Birthweight z-score	-0.15 (0.77) [n=92]	-0.70 (0.55) [n=8]	-0.55 (-1.10, 0.01)	0.053
Change in (Δ) weight z-score from birth to term	-1.59 (1.05) [n=88]	-1.51 (1.28) [n=6]	0.08 (-0.81, 0.97)	0.853
Δ weight z-score from term to 2.5y [b]	0.11 (1.50) [n=86]	1.11 (1.48) [n=7]	1.00 (-0.17, 2.17)	0.094
Δ weight z-score from 2.5y to 6y [b]	0.38 (1.06) [n=87]	0.70 (1.25) [n=9]	0.32 (-0.43, 1.06)	0.403
Δ weight z-score from 6y to 11y	0.72 (0.82) [n=88]	0.90 (0.68) [n=8]	0.17 (-0.42, 0.77)	0.561
	Metabolic syndrome [a]			
	No	Yes		
	%(n/N)	%(n/N)		*p*
Sex				
Female	92.7% (51/55)	7.3% (4/55)	-	0.573
Male	89.6% (43/48)	10.4% (5/48)	-	
Gestational age				
<=23 weeks	83.3% (10/12)	16.7% (2/12)	-	0.325
24 weeks	96.8% (30/31)	3.2% (1/31)	-	
25 weeks	90.0% (54/60)	10.0% (6/60)	-	
Multiple births				
Yes	88.2% (30/34)	11.8% (4/34)	-	0.459
No	92.6% (63/68)	7.4% (5/68)	-	
White ethnicity				
Yes	92.9% (79/85)	7.1% (6/85)	-	0.190
No	83.3% (15/18)	16.7% (3/18)	-	
Maternal smoking during pregnancy				
Yes	78.6% (22/28)	21.4% (6/28)	-	0.005*
No	96.0% (72/75)	4.0% (3/75)	-	
Higher SES [c]				
Yes	95.5% (42/44)	4.5% (2/44)	-	0.227
No	88.7% (47/53)	11.3% (6/53)	-	
Maternal education (A level or above) [c]				
Yes	96.2% (25/26)	3.8% (1/26)	-	0.340
No	90.1% (64/71)	9.9% (7/71)		

[+] *p* values were calculated using two sample t-tests or chi-square tests. *Correction for multiple comparisons was applied using the Benjamini-Hochberg procedure and a false discovery rate of 0.05 was chosen. Adjusted *p* value: 0.070 for maternal smoking during pregnancy. [a] Metabolic syndrome was defined by the International Diabetes Federation as having central obesity measured by waist circumference or BMI, together with any two of the following components: (1) raised triglycerides; (2) reduced HDL cholesterol; (3) raised blood pressure; and (4) raised fasting plasma glucose. [b] Growth data at 2.5 years: uncorrected for prematurity. [c] Maternal education and socioeconomic status (SES) were collected using parent questionnaire at age 2.5 years; SES was based on using parent occupation: (1) higher: non-manual employment; (2) lower: including those in manual employment or unemployed.

Table 3 Multivariate linear regression: BMI and central systolic blood pressure (SBP) at 19 years as dependent variables in young adults born extremely preterm [+]

	BMI (kg/m^2)		Central SBP (mmHg)	
	β (95%CI) [ך]	*p*	β (95%CI) [ך]	*P*
Birthweight z-score (SD)	-0.54 (-1.58, 0.50)	0.305	-0.69 (-2.49, 1.11)	0.448
Δ weight z-score from birth to term-age (SD)	0.30 (-0.46, 1.06)	0.438	0.08 (-1.28, 1.44)	0.907
Δ weight z-score from term-age to 2.5y (SD)	0.18 (-0.33, 0.69)	0.482	0.19 (-0.74, 1.12)	0.687
Δ weight z-score from 2.5y to 6y (SD)	1.03 (0.31, 1.75)	0.006*	1.75 (0.48, 3.02)	0.007*
Δ weight z-score from 6y to 11y (SD)	0.98 (0.02, 1.93)	0.046	0.13 (-1.60, 1.86)	0.882

[+]Adjusted for sex, maternal age, and maternal smoking during pregnancy. [ך] β presents the average change in BMI and central SBP for per SD change in birth weight z-scores or in Δ weight z-scores in different periods. *Correction for multiple comparisons was applied using the Benjamini-Hochberg procedure and a false discovery rate of 0.05 was chosen. Adjusted *p* values: 0.030 for BMI and 0.035 for central SBP.

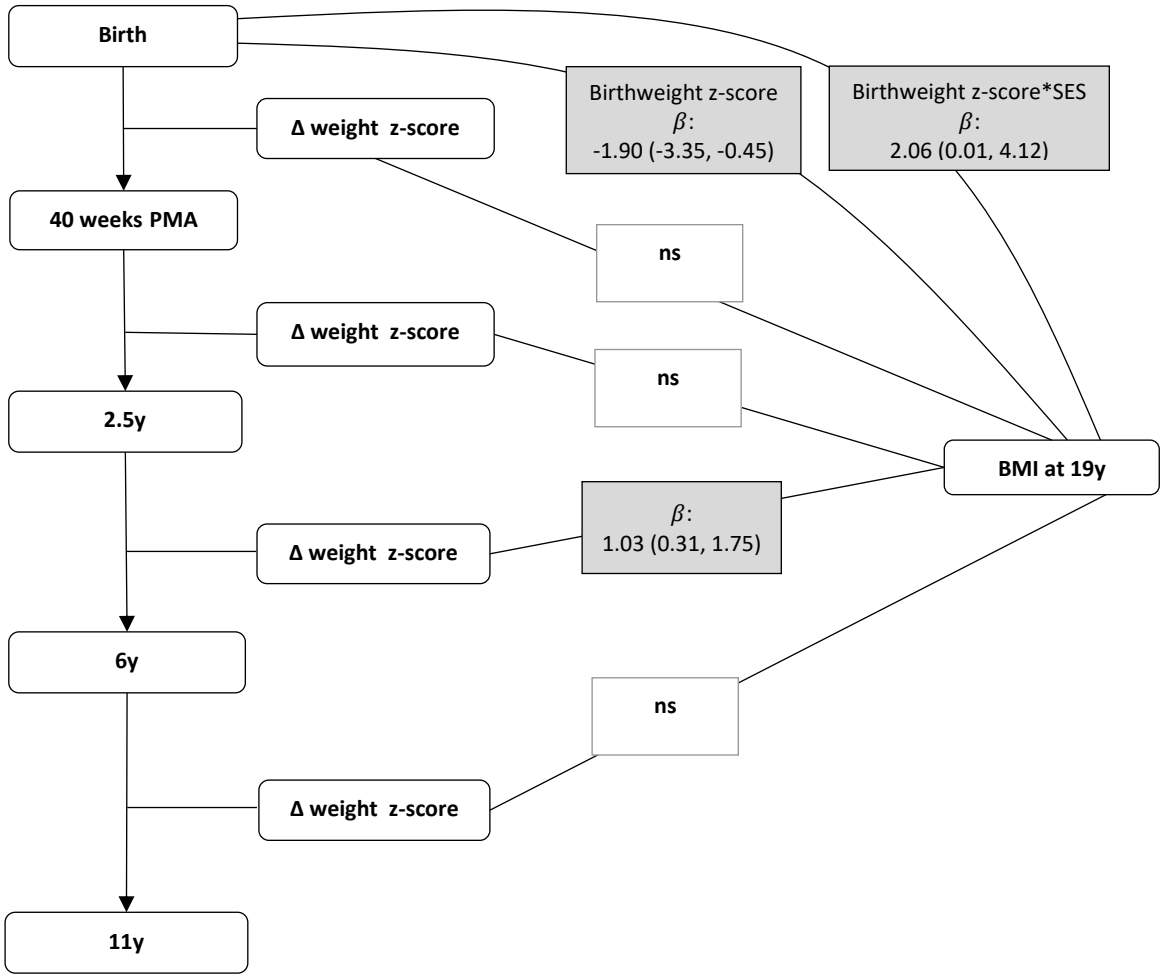

Figure 1 Size at birth, growth trajectory in early life and BMI in early adulthood

Note: ns represents not significant; birthweight z-scores were derived from the complete birth population[29]. Socioeconomic status (SES) was collected using parent questionnaire at age 2.5 years and was based on using parent occupation: (1) higher: non-manual employment; (2) lower: including those in manual employment or unemployed.

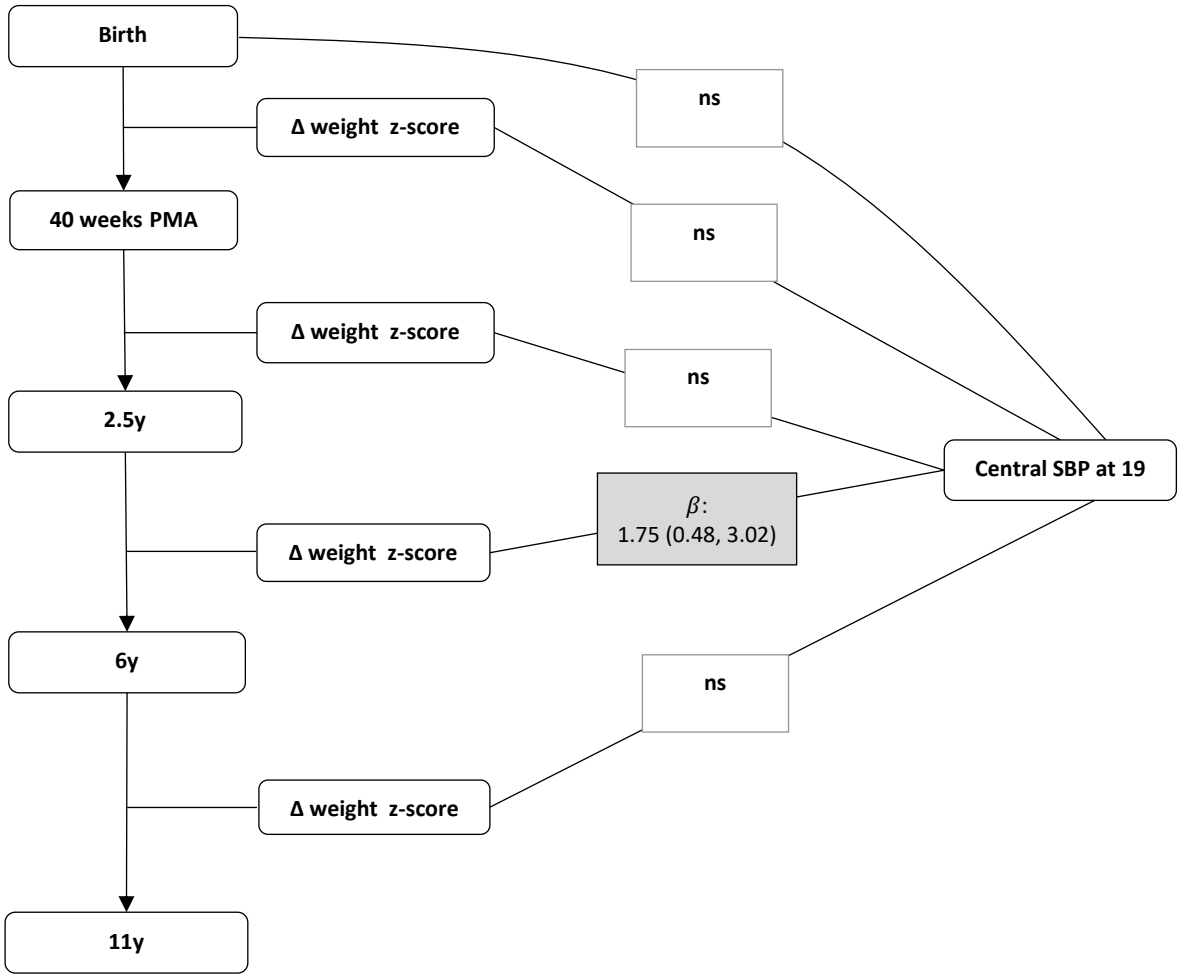

Figure 2 Size at birth, growth trajectory in early life and central SBP in early adulthood

Note: ns represents not significant; SBP represents systolic blood pressure.

Table S1 Characteristics of extremely preterm participants assessed at each age

Variables		Whole cohort N=315	Assessed at 2.5 years N=283	Assessed at 6 years N=241	Assessed at 11 years N=219	Assessed at 19 years N=129
Male Sex	% (n)	49.2% (155)	47.7% (135)	50.6% (122)	46.1% (101)	47.3% (61)
Gestational age						
<=23 weeks	% (n)	9.2% (29)	9.2% (26)	10.0% (24)	10.5% (23)	11.6% (15)
24 weeks	% (n)	31.7% (100)	31.8% (90)	30.3% (73)	32.0% (70)	28.7% (37)
25 weeks	% (n)	59.0% (186)	59.0% (167)	59.8% (144)	57.5% (126)	59.7% (77)
Multiple births	% (n/N)	25.2% (79/314)	26.9% (76/283)	26.1% (63/241)	28.0% (61/218)	31.3% (40/128)
White ethnicity	% (n)	76.5% (241)	78.8% (223)	78.4% (189)	82.2% (180)	80.6% (104)
Maternal age	Mean (SD)	28.5 (5.9) [n=313]	28.59 (5.83) [n=282]	28.97 (5.69) [n=240]	28.79 (5.75) [n=217]	29.2 (5.6) [n=127]
Maternal smoking during pregnancy	% (n/N)	32.9% (93/283)	33.2% (93/280)	32.3% (76/235)	33.8% (72/213)	25.6% (33/129)
Maternal education (A level or above)[+]	% (n/N)	25.9% (68/263)	25.9% (68/263)	23.6% (52/220)	24.0% (48/200)	27.3% (33/121)
Higher SES[+]	% (n/N)	31.0% (84/271)	31.0% (84/271)	32.2% (73/227)	32.9% (68/207)	44.3% (54/122)
Birth weight (kg)	Mean (SD)	0.75 (0.11) [n=315]	0.75 (0.11) [n=283]	0.75 (0.12) [n=241]	0.74 (0.12) [n=219]	0.74 (0.12) [n=129]
Birthweight z-score	Mean (SD)	-0.18 (0.76) [n=312]	-0.18 (0.77) [n=281]	-0.18 (0.75) [n=239]	-0.15 (0.79) [n=216]	-0.22 (0.76) [n=126]

[+] Maternal education and SES were collected using parent questionnaire at age 2.5 years. Socioeconomic status (SES) was based on using parent occupation: (1) higher: non-manual employment; (2) lower: including those in manual employment or unemployed.

Figure S1 Birth weight for gestational age and BMI stratified by socioeconomic status (SES)