Growth to early adulthood following extremely preterm birth: the EPICure study

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What is already known on this topic?

- Poor growth attainment in early childhood and early adolescence has been reported for extremely preterm survivors.
- Growth data beyond adolescence are scarce in such populations.

What this study adds?

- EP participants remained shorter and lighter and had smaller head circumferences than reference data or term-born controls in adulthood, despite catch-up growth.
- Trajectories in height and head circumference were similar in EP and control participants, but weight, and therefore BMI, rose faster among EP individuals.
- Birth characteristics and neonatal feeding practices were related to growth over childhood to 19 years.

Abstract

Objective: To investigate growth trajectories from age 2.5 to 19 years in individuals born before 26 weeks of gestation (extremely preterm; EP) compared with term-born controls.

Methods: Multilevel modelling of growth data from the EPICure Study, a prospective 1995 birth cohort of 315 participants born in the UK and Ireland and 160 term-born controls recruited at school age. Height, weight, head circumference and body mass index (BMI) z-scores were derived from UK standards at age 2.5, 6, 11 and 19 years.

Results: 129 (42%) EP children were assessed at 19 years. EP individuals were on average 4.0 cm shorter and 6.8kg lighter with a 1.5 cm smaller head circumference relative to controls at 19 years. Relative to controls, EP participants grew faster in weight by 0.06 SD per year (95% CI 0.05 to 0.07), in head circumference by 0.04 SD (0.03 to 0.05), but with no catch-up in height. For the EP group, because of weight catch up between 6 and 19 years, BMI was significantly elevated at 19 years to +0.32 SD; 23.4% had BMI>25 kg/m^2 and 6.3% >30 kg/m^2 but these proportions were similar to those in control subjects. EP and control participants showed similar pubertal development in early adolescence, which was not associated with height at 19y in either study group. Growth through childhood was related to birth characteristics and to neonatal feeding practices.

Conclusions: EP participants remained shorter and lighter and had smaller head circumferences than reference data or controls in adulthood but had elevated BMI.

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Poor growth attainment in early childhood and early adolescence has been reported for extremely preterm survivors (EP; <26 weeks of gestation)[1-3]. Growth data beyond adolescence are scarce in such populations. Several studies have reported growth outcomes in young adulthood for very low birth weight (VLBW; <1500 g) or extremely low birth weight (ELBW; <1000 g) children[4-8]. However, the findings were in populations defined by birth weight rather than gestational age, which may introduce bias because more mature children with intrauterine growth restriction were included[9]. Additionally, these studies only included individuals born in the 1970s-1980s. Advances in perinatal and neonatal care in the 1990s markedly improved the survival rates of EP infants, which may impact long term growth.

We conducted a longitudinal analysis of growth from infancy to early adulthood for individuals evaluated in the EPICure study, a large prospective, population-based cohort of EP births. At 2.5y and 6y, all main growth parameters were significantly below population norms[2,3]. The main objective of this paper was to investigate growth trajectories in EP children to 19 years compared with those of a term-born comparison group. Our secondary objectives were to explore the impact of neonatal variables and important childhood outcomes, and to examine pubertal development in early adolescence and its association with growth attainment in adulthood. We hypothesised that EP children would demonstrate poorer growth than controls in young adulthood, but that this might be offset by delayed puberty and catch up growth.

Methods

Participants. The EPICure cohort comprised all babies born at 25 completed weeks of gestation or less in all 276 maternity units in the UK and Ireland from March to December 1995. Recruitment of the cohort has been described in detail previously[10-12]; 315 survived to discharge and were followed at age 2.5, 6, 11 and 19 years. Nine deaths occurred between discharge and the 19-year assessment, at which 129 (42%) of EP participants were assessed. A flow chart detailing dropout and recruitment of controls has been published previously[13]. Written informed consent was obtained from parents up to 11 years and from individual participants at 19 years. Ethical approval was obtained for each follow up assessment. The study at 19 years was approved by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514).

Measures. Participants were invited for a comprehensive evaluation at 11 and 19 years, which included physical assessment of growth by a paediatrician or paediatric nurse. Assessors were not informed of the child's group status. Weight, height and occipito-frontal head circumference were measured. Measurement at age 2.5 and 6 years has been described in detail previously[2,3]. At 11 and 19 years, height was measured using a portable height measure; length or arm span was used in participants unable to stand. Weight was measured using standard paediatric metric scales and head circumference using a non-distensible LASS-O tape. All parents and children were asked to complete an anonymised questionnaire about pubertal development at 11 years based on Tanner staging[14-16]. Self-assessment can be validly used for large epidemiologic studies for evaluating sexual maturation in children, although studies of outcomes that are strongly dependent on precise staging of pubertal development must ensure correct assessment by standardized clinical examination[17,18]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Standard deviation scores (z-scores) for height, weight, BMI and head circumference were calculated at each age based on UK population norms[19]. Overweight and obesity were defined using internationally accepted cut-offs of 25 and 30 kg/m^2 respectively[19].

Neonatal variables were obtained from the main study database, including gestational age, birth weight for gestational age (a measure of intrauterine growth), ethnicity (white vs other), neonatal brain injury (defined as moderate/severe injury: ventricular size >4mm over 97th centile/hemorrhage/cysts/ cystic leukomalacia or any unilateral/bilateral parenchymal problem[13]), enteral feeding begun before day 7 (yes vs no), and the number of weeks of steroid therapy for chronic lung disease. Cognitive outcomes have been reported previously[11-13,20].

Statistical analysis. Data were analysed using Stata 15.1. Multilevel modelling was used to investigate growth trajectories from infancy to adulthood. It treats the data as having a hierarchical structure with observations at each time point nested within each individual, which allows adjustment for missing observations where the individual was not assessed. When comparing the EP and control groups, age was fitted as a random effect. This allows both the average level and the change in z-scores to vary between individuals. A group term was added as a fixed covariate to test for a difference in intercept between the EP and control groups. An interaction term between age and group was then added to test whether the EP and control groups differed in slope. The effects of sex were examined by adding them separately to the model as a fixed covariate and then as interactions with group. For a parameter to be retained in the model, it was required to have a p value <0.05. Similar analyses were then conducted within the EP group to test effects of neonatal variables. Analyses were first conducted in all participants with data available at any time point, and then restricted to those with complete longitudinal data only. Relationships between puberty and growth trajectories were also explored using multilevel modelling.

As previously we had observed an association between cognitive scores and head circumference[2], relationships of head size with cognition/attainment at different ages were analysed using multiple linear regression models. We adjusted for neonatal brain injury, gestational age and sex for EP participants, and sex for controls.

Results

Participants and attrition: Characteristics of EP participants and term-born controls by age of assessment are shown in **table 1**. Progressive loss to follow up occurred for the EPICure cohort over the period of 19 years, and similar attrition occurred in the control group. EP completers (no missing growth assessments) were more likely than non-completers (one or more missing assessments) to be from multiple births and to have parents with a non-manual occupation, and were less likely to have severe motor disability at 2.5 years (online supplementary **table S1**) but in other respects the cohort included in this analysis were representative of the total original cohort.

Growth trajectories: Mean z-scores for growth measures in EP participants were significantly below zero from age 2.5 to 19 years; at 19 years, height was -0.98 SD, weight -0.25 SD and head circumference -0.84 SD; because of discrepant catch up in weight rather than height, BMI z scores increased faster from 6 to 19 years to be on average 0.32 SD greater than population means (**table 1**). In the EP group the trajectory of weight (and therefore BMI) z-scores showed a greater relative increase between 6 and 11 years, with a subsequent similar trajectory to controls over adolescence to 19 years (**figure 1**). Trajectories in height and head circumference were similar in EP and control participants. Similar findings were present when compared to controls: at 19 years, on average EP individuals were 4.0 cm shorter and 6.8kg lighter with a 1.5 cm smaller head circumference relative to controls; mean BMI in EP individuals was 23.3 kg/m^2 (95% CI 22.6 to 24.1); 23.4% (30/128) met criteria for overweight and 6.3% (8/128) for obese, and were not significantly different from controls in whom mean BMI was 24.7 kg/m^2 (95% CI 23.3 to 26.1). There were no sex differences in either group. At 11 years, 13.8% (30/217) of EP children met criteria for overweight and 0.9% (2/217) for obese, lower than controls (overweight: 17.1%; obese: 4.0%), but the differences were not statistically significant *(p=0.089)*. EP participants who were overweight or obese at 11 years were at higher risk of being overweight or obese at 19 years (RR [95% CI]: 3.16 [1.97, 5.07], $p<0.001$).

From age 2.5 to 19 years, using multilevel modelling z scores for height were on average 0.83 SD lower in EP participants compared to controls, weight 0.94 SD lower, and head circumference 1.22 SD lower (all $p<0.001$; **table 2**). Using multilevel modelling, EP participants on average showed catch-up gain in weight by 0.06 SD per year (0.05 to 0.07), BMI by 0.08 SD (0.07 to 0.10), and head circumference by 0.04 SD (0.03 to 0.05; all $p<0.001$), but no evidence of catch-up in height. There were no significant differences between z scores of males and females for all four growth measures in either group at each age (**table 2 & figure S1a**).

Impact of neonatal variables – We evaluated the influence of neonatal factors on growth over 19 years within EP participants using multilevel models (**Table 3**). Birthweight for gestational age was related to height and head circumference trajectories (all $p<0.001$) and white ethnicity to height and weight at age 2.5, 6 and 11 years but not at 19 years (**figure S1b**). Gestational age, despite the narrow range among this group (23-25 weeks), was significantly related to head growth ($p<0.001$). The variable "enteral feeds begun before day 7" was positively related to all outcomes except for height at 19 years (**figure S1c**), but other neonatal variables, including neonatal brain injury and the use of long courses of postnatal steroid (commonly used in 1995), were not related to growth in this model. All analyses were repeated among participants who were examined at each age with essentially similar findings (**tables S2 and S3)**. Some significances were reduced but the direction and magnitude of effects were similar.

Puberty and growth in adulthood: EP boys and girls at age 11 reported similar pubertal development compared with term-born boys and girls. Proportions who had entered puberty were 15% for boys in both groups, 40% for EP girls. This compared to 32% for term-born girls ($p=0.301$; **table S4**). At 11 years, EP and term-born girls (but not boys) who have entered puberty were significantly taller than prepubescent peers. In contrast, by 19 years, height did not differ with pubertal status at 11 years in either boys or girls for both groups (**figure 2**; **table S5**).

Head size and cognition/attainment: In the EP group, reduced head circumference z-scores were positively correlated with lower IQ and attainment scores at each age, which remained significant after adjustment for neonatal brain injury, sex and gestational age, and after excluding participants with severe motor disability (coefficients ranging 1.98-5.67; **table S6**).

Discussion

We report growth trajectories from infancy to early adulthood in EP survivors born in 1995. Growth patterns in height and head circumference were similar in EP participants and term-born controls, but EP participants remained shorter and lighter and had smaller head circumferences than reference data or controls. With the exception of height, multilevel modelling shows evidence of catch-up growth in the EP group throughout childhood and adolescence, for weight by 0.06 SD per year and head circumference by 0.04 SD. In this clinical cohort, catch up was greatest in weight, and therefore BMI, between 6 and 11 years but similar proportions of EP and control participants were considered overweight or obese at 19 years. We evaluated a range of possible influences on growth to 19 years. Pubertal status at 11y was not associated with final height but in the group that commenced enteral feeds in the first week, better childhood and adolescent growth was found. Head size was associated with IQ score at 19 years.

It is hard to make direct comparisons with other studies of growth attainment in adulthood in preterm children, as they have focused on VLBW/ELBW survivors, which included children born at higher gestations who were small for gestational age and had a higher mean birthweight and gestational age[4-6,8]. This report supports findings from the Canadian cohort of 147 ELBW children[6]. In contrast, among 42 ELBW participants from Victoria, Australia average weight was attained by early adulthood[4]. A further study conducted in Cleveland, Ohio reported complete catch-up in weight among VLBW females in young adulthood, but not among males[5]. The authors argue that this might be related to the lesser neonatal and early childhood morbidity among VLBW females[5]. We did not find significant differences between males and females in any growth measure in either EP or control groups.

Both groups showed similar pubertal development in early adolescence, in agreement with previous studies[7,21,22]. Pubertal status at 11 years was unrelated to final height in both groups, again in support of previous findings[23,24]. Early sexual maturity has been reported in low-birth-weight (LBW)/VLBW girls [25,26], but this was not demonstrated in our study. We did not collect information on parental height or determine bone age, but final height is dependent on mid-parental height [4,21], although in very low birthweight children advanced bone age in adolescence may contribute to shorter height in adulthood[22].

Irrespective of size at birth, mean BMI in the EP group and controls at age 19 was significantly above the 1990 UK population standards, indicating that they were relatively heavy for their height. In previous cohorts it normalised but was not significantly different from population norms[4,6]. We show greater relative catch-up in BMI among EP participants than among term-born controls over time, consistent with the Swedish cohort[1]. The rates of overweight (23%) and obesity (6%) for EP participants in young adulthood are much higher than those reported in the 1990 UK population at age 18 – around 10% for overweight and 1% for obesity[19], but the findings are consistent with those among controls and may reflect secular trends. There is accumulating evidence that low birth weight together with rapid growth in weight or BMI in childhood is associated with increased risk for cardiovascular diseases in adult life[27-30]. We also show that EP participants being overweight/obese at 11 years were at increased risk of being overweight/obese at 19 years. Early interventions can help to prevent obesity among young people.

Associations of subnormal head size with poor developmental outcomes have been reported for VLBW children at school age[22,31]. We show that the positive relationship between head size and cognitive outcomes persists into early adulthood, despite improved growth velocity in head circumference. Consistent with our previous reports[2,3], head size in the EP cohort at 11 and 19 years continued to be significantly associated with birth characteristics, being smaller for babies born at lower gestational ages (0.46 SD per week) and those with low birthweight for gestation (0.38 SD per birthweight SD).

Within the EP cohort, birth weight for gestational age predicted height and head size at all ages, indicating that intrauterine growth has an important effect on growth into adulthood. In adulthood, head size was smaller in EP participants receiving long courses of postnatal steroid. Short-term detrimental effects of long courses of postnatal steroid on growth have been reported in premature children[2,3,32,33]. EP children appeared to have better growth in weight and BMI in early adulthood following early introduction of enteral feeding. Nutritional practices varied greatly among neonatal intensive care units, reflecting both lack of evidence and strong local traditions[34]. Our findings show an association but randomised trials are needed to show causation and this may reflect a group of individuals with less severe neonatal illness.

The strength of this study lies in the longitudinal design with data collected at multiple ages. Other strengths are the inclusion of a comparison group and the use of multilevel modelling to partially account for attrition, and the validation analysis of individuals with complete follow-up. The major weakness is that the number of participants lost to follow-up increased over time and dropout was associated with markers of social disadvantage and disability. However, our findings were strengthened by the analysis of individuals with complete follow-up which corroborated the main results, and there were no significant differences in growth measures between participants with complete and incomplete data. Growth trajectories from participants with complete data were similar compared to all participants (figure S2). Controls were recruited at age 6 years, and thus we did not have measures in early childhood for comparison.

In conclusion, impaired growth over the postnatal period among extremely preterm births, related to birth characteristics and feeding patterns, was reflected in lower linear growth and smaller head circumferences, associated with lower cognitive attainment over childhood to 19 years. In contrast, rapid increase in weight relative to height between 6 and 11 years led to elevated average BMI values in this group.

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Ethics approval The study at 19 years was approved by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514).

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

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Table 1 Characteristics in extremely preterm (EP) participants and term-born controls by age of assessment

Variables		Whole cohort EP (n=315)		Age 2.5 years⁺	Age 6 years		Age 11 years		Age 19 years	
		At birth	EDD	EP (n=283)	EP (n=241)	Control (n=160)	EP (n=219)	Control (n=153)	EP (n=129)	Control (n=65)
Age (years)	Mean (range)	-	-	2.5 (2.3-3.3)	6.3 (5.2-7.3)	6.1 (5.1-7.2)	10.9 (10.1-12.1)	10.9 (9.8-12.3)	19.3 (18.4-20.5)	19.2 (18.1-20.3)
Male Sex	% (n)	49% (155)	49% (155)	48% (135)	51% (122)	44% (71)	46% (101)	42% (64)	47% (61)	38% (25)
Gestational age	Mean (SD)	24.9 (0.7)	24.9 (0.7)	24.9 (0.7)	24.9 (0.7)	-	24.9 (0.7)	-	24.9 (0.8)	-
<=23 weeks	% (n)	9% (29)	9% (29)	9% (26)	10% (24)	-	11% (23)	-	11% (15)	-
24 weeks	% (n)	32% (100)	32% (100)	32% (90)	30% (73)		32% (70)		29% (37)	
25 weeks	% (n)	59% (186)	59% (186)	59% (167)	60% (144)	-	57% (126)	-	60% (77)	-
Neonatal Brain injury	% (n/N)	23% (71/314)	23% (71/314)	22% (63/283)	22% (54/241)	-	22% (49/218)	-	17% (22/128)	-
Growth parameters										
Height (cm)	Mean (95%CI)	-	-	88.6 (88.1, 89.1) [n=258]	112.7 (111.9,113.5) [n=237]	116.2 (115.2,117.2) [n=159]	139.7 (138.7,140.6) [n=218]	144.5 (143.3,145.8) [n=153]	163.7 (162.0,165.3) [n=129]	167.7 (165.6,169.7) [n=65]
Difference in means	(95%CI)	-	-	-	-3.5 (-4.8, -2.3)		-4.9 (-6.4, -3.3)		-4.0 (-6.8, -1.3)	
Height z-score	Mean (95%CI)	-	-	-0.70 (-0.84, -0.55) [n=258]	-0.95 (-1.09, -0.81) [n=237]	-0.00 (-0.17, 0.17) [n=159]	-0.55 (-0.69, -0.41) [n=218]	0.15 (-0.01, 0.32) [n=153]	-0.98 (-1.19, -0.78) [n=129]	-0.18 (-0.42, 0.06) [n=65]
Difference in means	(95%CI)	-	-	-	-0.95 (-1.16, -0.73)		-0.71 (-0.92, -0.50)		-0.81 (-1.14, -0.47)	
Weight (kg)	Mean (95%CI)	0.75 (0.73, 0.76) [n=315]	2.57 (2.51, 2.62) [n=306]	11.9 (11.7, 12.1) [n=271]	18.8 (18.3, 19.3) [n=241]	21.6 (21.0, 22.3) [n=159]	34.1 (33.0, 35.2) [n=217]	38.4 (36.8, 40.0) [n=152]	62.8 (60.4, 65.2) [n=128]	69.6 (65.2, 74.1) [n=65]
Difference in means	(95%CI)	-	-	-	-2.8 (-3.6, -2.0)		-4.3 (-6.1, -2.4)		-6.8 (-11.4, -2.3)	
Weight z-score	Mean (95%CI)	-0.18 (-0.26, -0.09) [n=312]	-1.69 (-1.81, -1.57) [n=299]	-1.19 (-1.35, -1.03) [n=271]	-1.18 (-1.35, -1.01) [n=241]	0.07 (-0.12, 0.25) [n=159]	-0.42 (-0.59, -0.25) [n=217]	0.21 (0.02, 0.39) [n=152]	-0.25 (-0.51, -0.00) [n=128]	0.54 (0.18, 0.89) [n=65]
Difference in means	(95%CI)	-	-	-	-1.25 (-1.51, -0.99)		-0.62 (-0.88, -0.37)		-0.79 (-1.22, -0.36)	
BMI (kg/m2)	Mean (95%CI)	-	-	15.1 (14.9, 15.3) [n=253]	14.6 (14.4, 14.8) [n=237]	15.9 (15.6, 16.2) [n=158]	17.3 (16.9, 17.7) [n=217]	18.2 (17.6, 18.7) [n=152]	23.3 (22.6, 24.1) [n=128]	24.7 (23.3, 26.1) [n=65]
Difference in means	(95%CI)	-	-	-	-1.3 (-1.7, -1.0)		-0.9 (-1.5, -0.2)		-1.3 (-2.8, 0.1)	
BMI z-score	Mean (95%CI)	-	-	-1.00 (-1.17, -0.83) [n=253]	-0.87 (-1.03, -0.70) [n=237]	0.11 (-0.07, 0.29) [n=158]	-0.22 (-0.40, -0.03) [n=217]	0.17 (-0.03, 0.37) [n=152]	0.32 (0.08, 0.56) [n=128]	0.69 (0.36, 1.02) [n=65]
Difference in means	(95%CI)	-	-	-	-0.98 (-1.23, -0.73)		-0.39 (-0.66, -0.11)		-0.37 (-0.78, 0.04)	
Head circumference (cm)	Mean (95%CI)	23.3 (23.1, 23.5) [n=209]	33.3 (33.1, 33.6) [n=293]	48.3 (48.1, 48.6) [n=278]	50.6 (50.3, 50.8) [n=239]	52.2 (52.0, 52.4) [n=160]	52.5 (52.3, 52.8) [n=217]	54.3 (54.1, 54.5) [n=152]	55.0 (54.7, 55.4) [n=125]	56.6 (56.1, 57.0) [n=63]
Difference in means	(95%CI)	-	-	-	-1.6 (-2.0, -1.3)		-1.8 (-2.1, -1.4)		-1.5(-2.1, -0.9)	
Head circumference z-score	Mean (95%CI)	-0.24 (-0.42, -0.06) [n=207]	-0.88 (-1.06, -0.70) [n=287]	-1.56 (-1.74, -1.39) [n=278]	-1.63 (-1.79, -1.46) [n=239]	-0.33 (-0.49, -0.17) [n=160]	-1.27 (-1.44, -1.10) [n=217]	-0.01 (-0.17, 0.14) [n=152]	-0.84 (-1.07, -0.61) [n=125]	0.29 (0.02, 0.55) [n=63]
Difference in means	(95%CI)	-	-	-	-1.30 (-1.54, -1.06)		-1.26 (-1.50, -1.02)		-1.13 (-1.50, -0.75)	

⁺Growth measures corrected for prematurity at 2.5 years

Table 2 Estimated mean differences and 95% confidence intervals in z-scores for growth parameters from multilevel modelling analyses in extremely preterm (EP) participants and term-born controls [a]

(a)				
Parameter	**Height z-score**	**Weight z-score**	**BMI z-score**	**Head circumference z-score**
	Unadjusted model [b] (n=489) Estimate (95% CI)	Unadjusted model [b] (n=491) Estimate (95% CI)	Unadjusted model [b] (n=486) Estimate (95% CI)	Unadjusted model [b] (n=493) Estimate (95% CI)
EP (ref.=controls) [c]	**-0.83 (-1.01, -0.64)**	**-0.94 (-1.15, -0.73)**	**-0.78 (-1.00, -0.56)**	**-1.22 (-1.43, -1.02)**
Age at assessment [d]	-0.00 (-0.01, 0.00)	**0.06 (0.05, 0.07)**	**0.05 (0.02, 0.07)**	**0.04 (0.03, 0.05)**
EP*Age	-	-	**0.04 (0.01, 0.07)**	-
(b)				
	Adjusted for sex [e] (n=489) Estimate (95% CI)	Adjusted for sex [e] (n=491) Estimate (95% CI)	Adjusted for sex [e] (n=486) Estimate (95% CI)	Adjusted for sex [e] (n=493) Estimate (95% CI)
EP (ref.=controls) [c]	**-0.82 (-1.01, -0.64)**	**-0.94 (-1.15, -0.73)**	**-0.78 (-1.00, -0.56)**	**-1.22 (-1.43, -1.02)**
Age at assessment [d]	-0.00 (-0.01, 0.00)	**0.06 (0.05, 0.07)**	**0.05 (0.02, 0.07)**	**0.04 (0.03, 0.05)**
EP*Age	-	-	**0.04 (0.01, 0.07)**	-
Male (ref.=female)	-0.05 (-0.23, 0.13)	0.02 (-0.18, 0.23)	0.06 (-0.14, 0.26)	-0.00 (-0.20, 0.20)

[a] For all models, age was centred at 6 years to make intercept coefficients more meaningful.

[b] Variables in the model: group status (EP participants or controls), age at assessment and group*age interaction. Interactions were only shown if significant. Trajectories of height, weight and head circumference z-scores were similar in the EP and control groups. The group*age interaction was significant for BMI z-scores, indicating that the trajectory of BMI z-scores was different in the two groups.

[c] Estimates represent mean differences in growth measure z-scores between EP participants and controls.

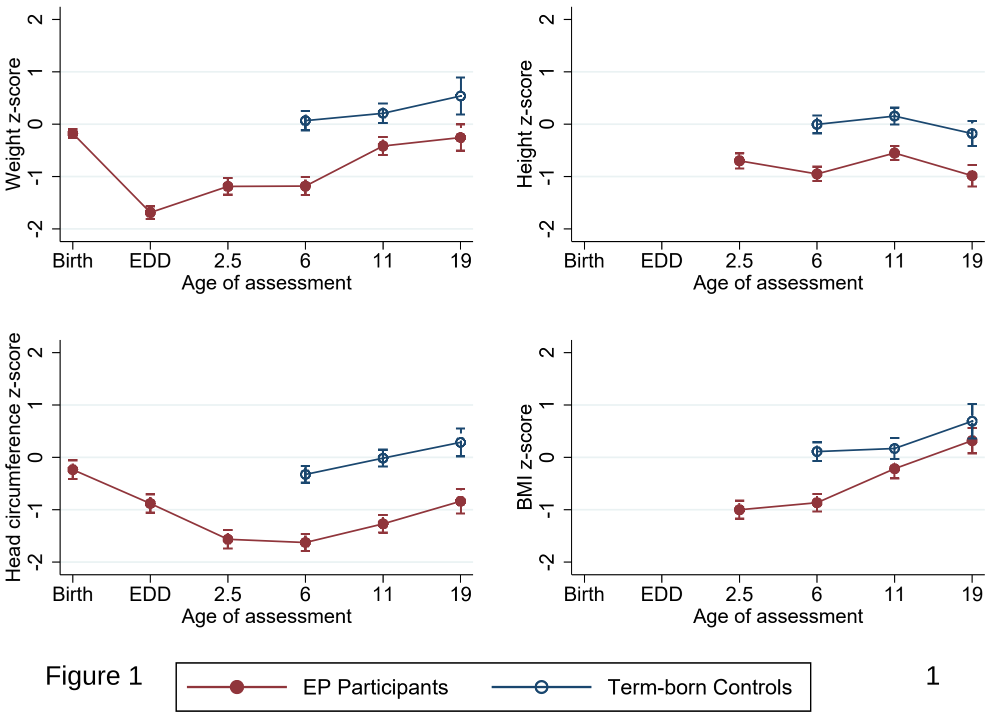
[d] Estimates represent estimated average changes in growth measure z-scores over time: for instance, on average, weight increased by 0.06 SD per year and head circumference increased by 0.04 SD per year.

[e] Sex was further adjusted for to examine whether it would affect growth trajectories in the two groups. The group*sex interactions were insignificant (not shown), which indicates similar trajectories between females and males in both groups.

Table 3 Multi-level modelling: factors associated with growth trajectories within EP participants [a]

Variables	Height z-score (Unadjusted)		Height z-score (Adjusted [b]) (n=277)	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
Gestational age (per week)	0.05 (-0.11,0.21) [n=287]	0.546	-	-
Moderate-severe brain injury (ref.=minor/none)	-0.26 (-0.54,0.02) [n=286]	0.068	-	-
Birthweight z-score (per SD)	0.28 (0.13,0.43) [n=284]	<0.001	0.27 (0.13,0.41)	<0.001
White ethnicity (ref.=other ethnicities)	-0.65 (-0.94,-0.37) [n=287]	<0.001	-0.65 (-0.92,-0.38)	<0.001
Ethnicity*Age[c]	0.02 (0.00,0.05) [n=287]	0.041	0.03 (0.01,0.05)	0.007
Enteral feeding begun before day 7 (ref.=no)	0.33 (0.09,0.56) [n=279]	0.006	0.35 (0.13,0.57)	0.002
Enteral feeding*Age[c]	-0.02 (-0.04,-0.00) [n=279]	0.017	-0.02 (-0.04,-0.00)	0.011
Steroids for chronic lung disease (per week)	-0.03 (-0.07,0.01) [n=282]	0.133	-	-
	Weight z-score (Unadjusted)		**Weight z-score (Adjusted [b]) (n=280)**	
	Estimate (95% CI)	***p***	**Estimate (95% CI)**	***p***
Gestational age (per week)	-0.01 (-0.20,0.18) [n=290]	0.919	-	-
Moderate-severe brain injury (ref.=minor/none)	-0.15 (-0.47,0.17) [n=289]	0.363	-	-
Birthweight z-score (per SD)	0.29 (0.12,0.17) [n=287]	0.001	0.28 (0.11,0.45)	0.001
Birthweight z-score*Age[c]	-0.03 (-0.04,-0.01) [n=287]	0.005	-0.03 (-0.05,-0.01)	0.003
White ethnicity (ref.= other ethnicities)	-0.63 (-0.95,-0.30) [n=290]	<0.001	-0.63 (-0.95,-0.32)	<0.001
Ethnicity*Age[c]	0.04 (0.00,0.07) [n=290]	0.030	0.04 (0.01,0.08)	0.015
Enteral feeding begun before day 7 (ref.=no)	0.42 (0.15,0.68) [n=282]	0.002	0.45 (0.19,0.70)	0.001
Steroids for chronic lung disease (per week)	-0.03 (-0.07,0.01) [n=285]	0.141	-	-
	BMI z-score (Unadjusted)		**BMI z-score (Adjusted [b]) (n=276)**	
	Estimate (95% CI)	***p***	**Estimate (95% CI)**	***p***
Gestational age (per week)	-0.02 (-0.20,0.16) [n=286]	0.813	-	-
Moderate-severe brain injury (ref.=minor/none)	-0.01 (-0.32,0.31) [n=285]	0.970	-	-
Birthweight z-score (per SD)	0.13 (-0.04,0.30) [n=283]	0.144	0.13 (-0.04,0.31)	0.133
Birthweight z-score*Age[c]	-0.02 (-0.04,-0.00) [n=283]	0.017	-0.03 (-0.05,-0.01)	0.014
White ethnicity (ref.= other ethnicities)	-0.13 (-0.44,0.19) [n=286]	0.432	-	-
Enteral feeding begun before day 7 (ref.=no)	0.30 (0.03,0.56) [n=278]	0.026	0.29 (0.03,0.56)	0.028
Steroids for chronic lung disease (per week)	-0.01 (-0.05,0.03) [n=281]	0.708	-	-
	Head circumference z-score (Unadjusted)		**Head circumference z-score (Adjusted [b]) (n=276)**	
	Estimate (95% CI)	***p***	**Estimate (95% CI)**	***p***
Gestational age (per week)	0.25 (0.05,0.44) [n=290]	0.013	0.46 (0.25,0.67)	<0.001
Moderate-severe brain injury (ref.=minor/none)	-0.19 (-0.53,0.16) [n=289]	0.289	-	-
Birthweight z-score (per SD)	0.31 (0.13,0.49) [n=287]	0.001	0.38 (0.19,0.56)	<0.001
White ethnicity (ref.= other ethnicities)	0.13 (-0.22,0.48) [n=290]	0.467	-	-
Enteral feeding begun before day 7 (ref.=no)	0.38 (0.09,0.66) [n=282]	0.009	0.30 (0.02,0.57)	0.033
Steroids for chronic lung disease (per week)	-0.05 (-0.10,-0.01) [n=285]	0.020	-0.04 (-0.08,0.00)	0.079

[a] For all models, age was centred at 6 years to make intercept coefficients more meaningful. One variable each time in the unadjusted models. For continuous variables (e.g., birthweight z-score), estimate refers to estimated change in growth measure z-scores for per unit change in the predictor. For categorical variables, it refers to estimated difference in means relative to the reference group.
[b] Adjusted for age and variables with a p value <0.05 in the unadjusted models.
[c] Interactions with age at assessment were shown if significant. Significant interactions indicate that the impact of the predictor on the growth outcomes differed with age at assessment.



Weight z-score
Height z-score
Head circumference z-score
BMI z-score
2
1
0
-1
-2
Birth
EDD
2.5
6
11
19
Age of assessment
EP Participants
Term-born Controls

Figure 1

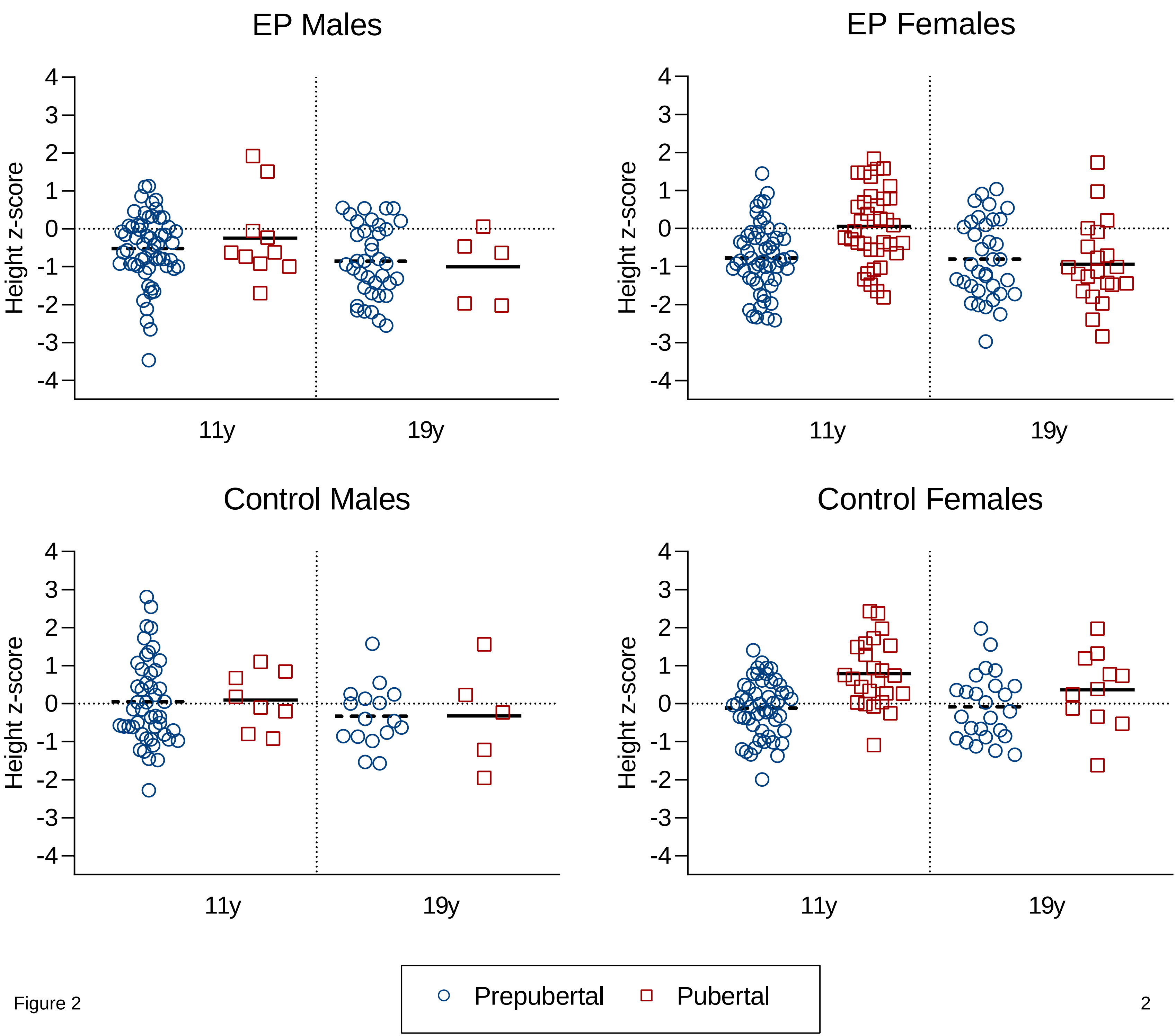

EP Males
EP Females
Control Males
Control Females
Height z-score
4
3
2
1
0
-1
-2
-3
-4
11y
19y
Prepubertal
Pubertal

Figure 2