Lung function and respiratory symptoms at 11 years in extremely preterm children: The EPICure Study

Joseph Fawke, Sooky Lum, Jane Kirkby, Enid Hennessy, Neil Marlow, Victoria Rowell, Sue Thomas, Janet Stocks

On-line supplement

Additional Results

For reasons of space the following information could not be presented in the main manuscript. The mean birthweight for all live admissions $<25^{+6}$ w GA to neonatal intensive care units in the UK in 1995 (n = 811) was 700g, and the mean birthweight for those who survived to discharge (n=314) was 744g. Mean birthweight of the cohort in whom spirometry was assessed was 750g (table E1) and hence representative of all EP babies surviving to discharge.

As commonly undertaken in such studies, extreme factors that could affect lung growth and development such as TB, whooping cough, pneumonia or hospitalisation for respiratory illness were exclusion criteria for controls. However, in practice no potential controls required exclusion from the study.

Table E1: Perinatal data in children born EP in whom spirometry was obtained at 11 years in comparison with those in whom it was not

	EP seen at 11y N = 219		EP not seen N = 88	Spiro – no spiro	Spiro- not seen
	Spirometry N = 182	No Spiro N = 37			
	mean (SD)	mean(SD)	mean (SD)	Δ (95% CI)	Δ (95% CI)
Gestation Age, GA (w)	25.0 (0.7)	24.6 (0.8)	25.0 (0.6)	**0.4 (0.1; 0.7)** [†]	-0.1 (-0.2; 0.1)
Birth weight (kg)	0.75 (0.12)	0.71(0.10)	0.75 (0.11)	0.04 (-0.0;0.08)	0.00 (-0.03; 0.03)
Birthweight z-score[§]	-0.15 (0.76)	-0.17(0.99)	-0.22 (0.70)	0.02 (-0.27; 0.31)	0.09 (-0.10; 0.27)
Maternal Age (yrs)	29.0 (5.4)	28.0 (7.1)	27.7 (6.2)	1.0 (-1.1; 3.0)	1.2 (-0.2;2.7)
	n (%)	**n (%)**	**n (%)**	**Δ (95% CI)**	**Δ (95% CI)**
BPD	129 (71%)	31 (84%)	65 (74%)	-13% (-26; 1%)	-3% (-14; 8%)
GA <25 weeks	68 (37%)	24 (65%)	33 (38%)	-28% (-44;-11%)	-0% (-13; 12)
Male	79 (43%)	22 (59%)	48 (55%)	-16% (-33; 1%)	-11% (-24; 2.0)
White mother	151 (83%)	28 (76%)	57 (65%)	8% (7; 23%)	**19% (7;30%)** [‡]
Multiple Births	52 (29%)	9 (24%)	18 (20%)	5% (11; 20%)	9% (-1; 20%)
Antenatal steroids	148 (82%)	30 (81%)	66 (75%)	1% (-13, 15%)	7% (-3; 18%)
Maternal Smoking [‖]	63(35%)	9 (28%)	21 (30%)	7% (-24, 10%)	5% (-8; 18%)
Maternal PET	5 (3%)	2 (5%)	1 (1%)	-3% (-10; 5%)	2% (-2; 5%)
Maternal APH	34 (19%)	15 (41%)	25 (29%)	**-22%(-38; -5%)** [†]	-9% (-20; 2%)
Received surfactant	153 (85%)	33 (89%)	76 (86%)	-5% (-16; 5%)	-2% (-11; 7%)
Chorioamnionitis	41 (23%)	6 (16%)	29 (33%)	7% (-7; 20%)	-9% (-22; 2%)
PROM (>24 hr)	47 (26%)	10 (27%)	28 (32%)	-1% (-16; 15%)	-6 (-17; 6%)
Postnatal steroids	125 (69%)	33 (89%)	64 (73%)	**-20% (-32; -8%)***	-4% (-15; 8%)
SupplO$_2$ at discharge	50 (28%)	16 (47%)	28 (41%)	**-19% (-37; -1%)***	**-13% (-27; 0%)***

Δ (95% CI) = differences in means or proportions between groups with 95% confidence intervals

≤ 4 cases with missing data for each variable;   * p<0.05,   [†] p<0.01,   [‡] p<0.001

§ Child Growth Foundation (1). ‖maternal smoking in pregnancy;

Abbreviations: PET = pre-eclamptic toxemia; APH: ante-partum hemorrhage; PROM:

premature rupture of membranes > 24h prior to delivery

Table E2: Group characteristics and respiratory morbidity in EP children with and without spirometry results

	EP seen at 11y N = 219		
	Spirometry	**No Spiro**	**Spiro – No Spiro Δ (95% CI)**
N	182	37	
% boys	43%	59%	-17% (-32; 1%)
Age (yrs)	10.9 (0.4)	10.9 (0.4)	-0.0 (-0.2; 0.1)
N (%) in special school	8 (4%)	21 (57%)	**-52% (-67; -36%)[‡]**
Height z-score	-0.48 (0.99)	-0.93 (1.10)	**0.45 (0.09; 0.81)***
Weight z-score	-0.41 (1.29)	-0.47 (1.21)	0.07 (-0.40; 0.53)
BMI z-score	-0.27 (1.4)	0.04 (1.2)	-0.30 (-0.8; 0.20)
[§]Physical examination			
• **Chest asymmetry**	6 (3.3%)	1 (3%)	1% (-5%; 7%)
• **Harrison's sulci**	16 (9%)	3 (8%)	1% (-9%; 10%)
• **Pectus excavatum**	29 (17%)	6 (17%)	0 (-14%; 13%)
• **Pectus carinatum**	2 (1%)	1 (3%)	-2% (-7%; 4%)
[‖]Resp morbidity in past 12m			
Wheeze	35 (21%)	4 (18%)	3% (-14%; 20%)
Number of wheeze attacks over past 12m			
• 1 - 3	19 (11%)	1 (5%)	
• 4 - 12	12 (7%)	2 (9%)	p=0.86 **
• > 12	4 (2%)	1 (5%)	
Sleep disturbed by wheeze			
• < 1 night / week	11 (7%)	1 (5%)	
• ≥ 1 night / week	7 (4%)	2 (9%)	p=0.66 **
Speech limited by wheezing	8 (5%)	1 (5%)	0% (-17; 6%)
Exercise induced wheeze	34 (21%)	1 (5%)	0% (-9%, 10%)
Nocturnal Cough	33 (20%)	7 (32%)	-12% (-32%; 8%)
Seen by respiratory specialist	14 (8%)	1 (5%)	4% (-6%; 14%)
Asthma medication	41 (25%)	4 (17%)	7 (-10%; 23%)
Current asthma[††]	42 (25%)	4 (17%)	12% (-9%; 24%)

Data presented as Mean (SD) or n (%) as indicated. * p < 0.05;   [†] p<0.01,   [‡] p<0.001

[§]Clinical examination in 181 EP and 160 classmates

5

Prematurity & lung function at 11y_OLS

ǁ Amongst those with successful spirometry, the respiratory questionnaire was returned by 168 EP children (116 with BPD, 52 no BPD) and 148 classmates. Of those with no spirometry, 22 returned their questionnaire.

** p-value calculated from non parametric test for trend

†† Current asthma defined as either: a) doctor-diagnosis of asthma (at any time) and *either* respiratory symptoms *or* asthma medication in the last 12 months, or b) asthma medication and respiratory symptoms in the past twelve months even if no recall of doctor diagnosis.

Table E3: Univariable models of all associated perinatal and current factors for FEV_1, FEV_1/FVC and FEF_{25-75} z-scores in children born EP

Perinatal factors	‖zFEV₁	‖zFEV₁/FVC	‖zFEF₂₅₋₇₅
Gestational age per wk	0.10 (-0.16, 0.35)	0.04 (-0.23, 0.31)	0.04 (-0.23, 0.31)
§zBirthweight	0.11 (-0.12, 0.35)	-0.02 (-0.27, 0.23)	0.01 (-0.24, 0.26)
White mother	**0.71 (0.24, 1.17)** †	-0.10 (-0.61, 0.41)	0.24 (-0.27, 0.75)
Postnatal steroids per wk	**-0.07 (-0.13, -0.02)** †	0.03 (-0.03, 0.09)	-0.02 (-0.08, 0.04)
BPD	**-0.86 (-1.23, -0.49)** ‡	**-0.45 (-0.86, -0.03)***	**-0.72 (-1.13, -0.32)** ‡
Maternal smoking in pregnancy	-0.09 (-0.47, 0.28)	0.12 (-0.28, 0.52)	-0.04 (-0.45, 0.36)
Current factors			
§zWeight at 11y	0.07 (-0.07, 0.21)	0.05 (-0.09, 0.20)	0.12 (-0.03, 0.27)
§zHeight at 11y	0.03 (-0.15, 0.21)	0.13 (-0.06, 0.32)	0.17 (-0.02, 0.36)
Asthma ever	**-0.44 (-0.82, -0.06)***	**-0.51 (-0.91, -0.10)***	**-0.53 (-0.94, -0.13)** †
Current asthma	**-0.72 (-1.14, -0.30)** ‡	**-0.50 (-0.96, -0.05)***	**-0.66 (-1.12, -0.20)** †
Steroid treatment past 12m	**-0.66 (-1.15, -0.17)** †	**-0.64 (-1.17, -0.12)***	**-0.69 (-1.21, -0.17)** †
B-Agonists treatment past 12m	**-0.76 (-1.20, -0.32)** ‡	**-0.49 (-0.97, -0.01)***	**-0.64 (-1.12, -0.17)** †
Passive tobacco smoke exposure	-0.08 (-0.47, 0.31)	-0.15 (-0.56, 0.26)	-0.09 (-0.51, 0.33)
Sleep disturbed by wheeze	**-0.46 (-0.86, -0.06)***	-0.18 (-0.62, 0.26)	-0.31 (-0.74, 0.13)
Wheeze on exercise	**-0.66 (-1.12, -0.20)** †	-0.26 (-0.76, 0.24)	-0.44 (-0.94, 0.06)

Data presented as Mean (95% CI); **significant differences shown in bold; * $p < 0.05$; † $p<0.01$, ‡ $p<0.001$**
§Results expressed as z-scores (1) which adjust for sex and age
‖Results expressed as z-scores (2) which adjust for sex, height and age.

Table E4: Association between diagnostic groups, bronchodilator responsiveness, medication and lung function

	EP & BPD		EP noBPD		Classmate	
	Asthma (n=32)	No Asthma (n=82)	Asthma (n=10)	No Asthma (n=42)	Asthma (n=20)	No Asthma (n=131)
BDR positive, no Medication, normal LF	0	1 (2%)	0	0	0	5 (4%)
BDR positive + Asthma Medication + abnormal LF	13 (41%)	1 (2%)	3 (30%)	0	1 (5%)	0
BDR positive, no Medication, abnormal LF	0	19 (23%)	0	1 (2%)	1 (5%)	2 (2%)

Data presented as n (%) from available questionnaire data only.

Abbreviations: BDR = bronchodilator response; LF = Lung function

Of the 33/124 (27%) EP&BPD with both positive BDR and abnormal LF, 19 (58%) had not received any treatment over the past 12 months. Only 4/52 (8%) EP without prior BPD had a positive BDR and abnormal LF, and all but one of these were receiving treatment. An abnormal LF with a positive BDR was only found in 4/151 (3%) classmates, 3 of whom were not being treated.

Figure E1: **Pre and post bronchodilator responsiveness according to birth status and current asthma**

A. FEV_1: Baseline

B. FEV_1: Post bronchodilator

C. FEV_1: % change

EP&BPD   EP noBPD   Classmates
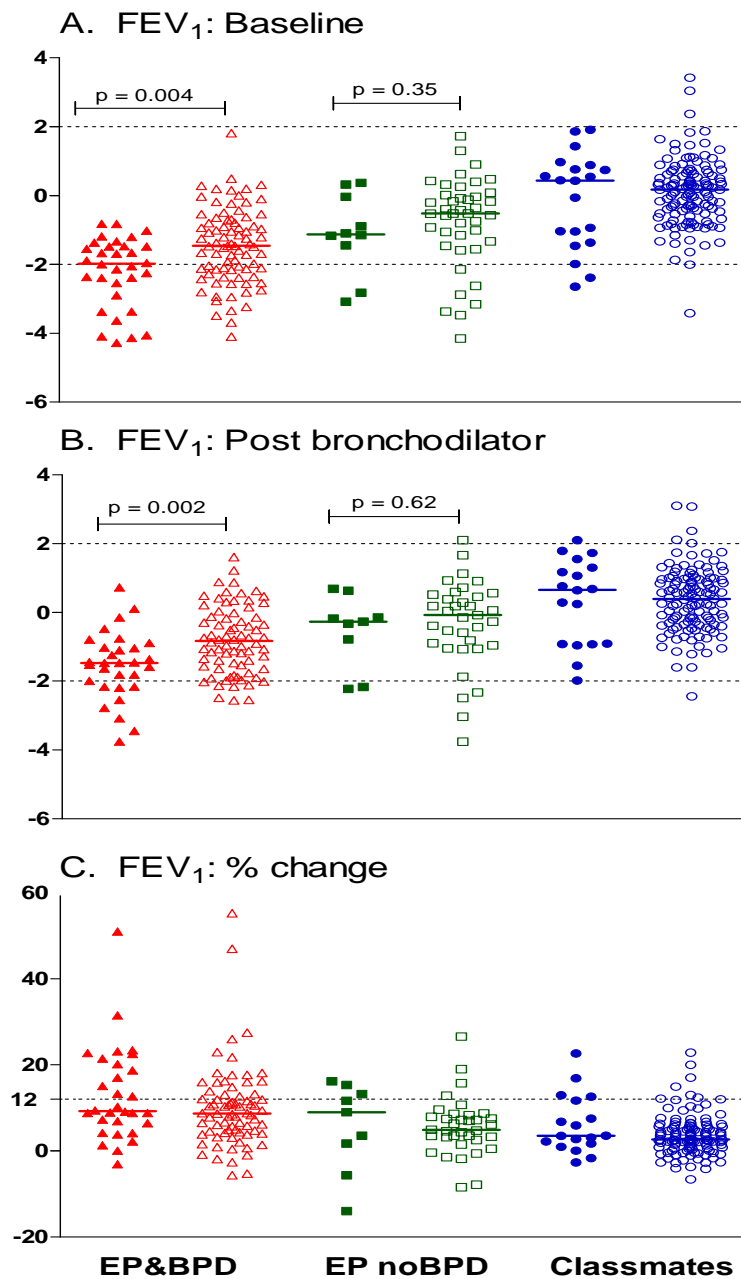
Footnote: open symbols represents those with no asthma and closed symbols those with current asthma. When data were examined *within* diagnostic groups, pre and post bronchodilator FEV_1 were significantly lower in those with asthma only if they had been born EP and had had prior BPD. (Figure E1A and E1B). More reversibility of airway obstruction was observed in children born EP (with or without BPD) than classmates (Fig E1C and Table 3, main MS). Within the sub-groups there was no difference in the degree of reversibility according to asthma diagnosis among either the BPD group or classmates. Similar changes were observed for forced expired flows.

Figure E2:   Associations between lung function and current asthma medication (last 12 m) in children born extremely preterm
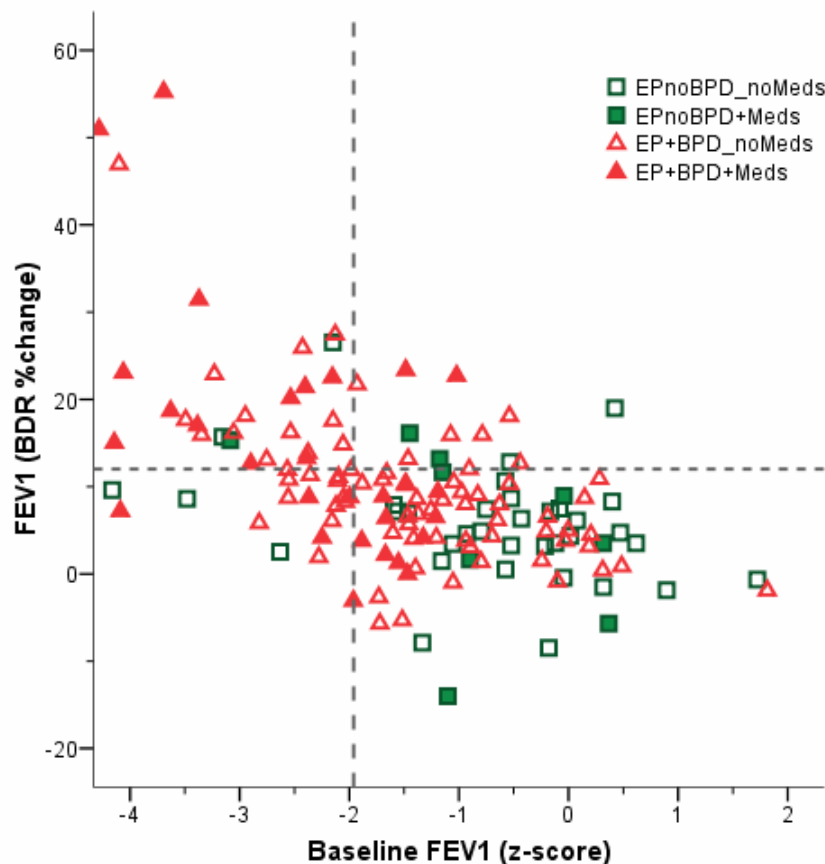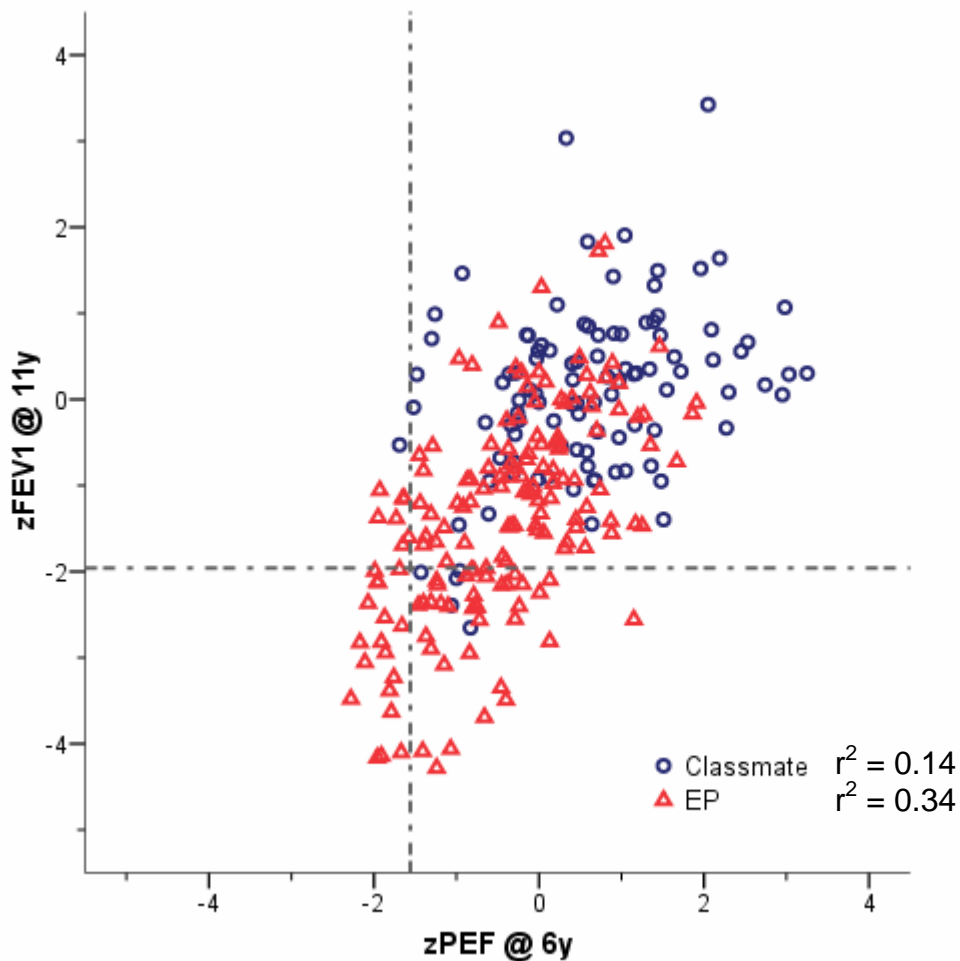

Legend: This scatter plot shows % change in FEV_1 following administration of a bronchodilator (Salbutamol) vs. baseline FEV_1 (expressed as a z score which adjusts for height, sex and age) according to diagnostic group (with or without BPD) and medication use in the last 12 months. The vertical dashed line denotes the lower limit of normal for FEV_1 (-1.96 z-score) i.e. the datapoints to the left of this line were classified as abnormal FEV_1. The horizontal dashed line denotes the threshold for a positive bronchodilator response (+12%); i.e. those with datapoints above the horizontal line were classified as having a positive bronchodilator response, while those below the line had normal BDR. As can be seen, many of the children in the upper left quadrant were not receiving medication, despite abnormal FEV_1 and a positive BDR (see also Table E4).

Figure E3   Associations between bronchodilator responsiveness and baseline FEV_1 in EP

children (with and without BPD) and respiratory symptoms in the last 12 months
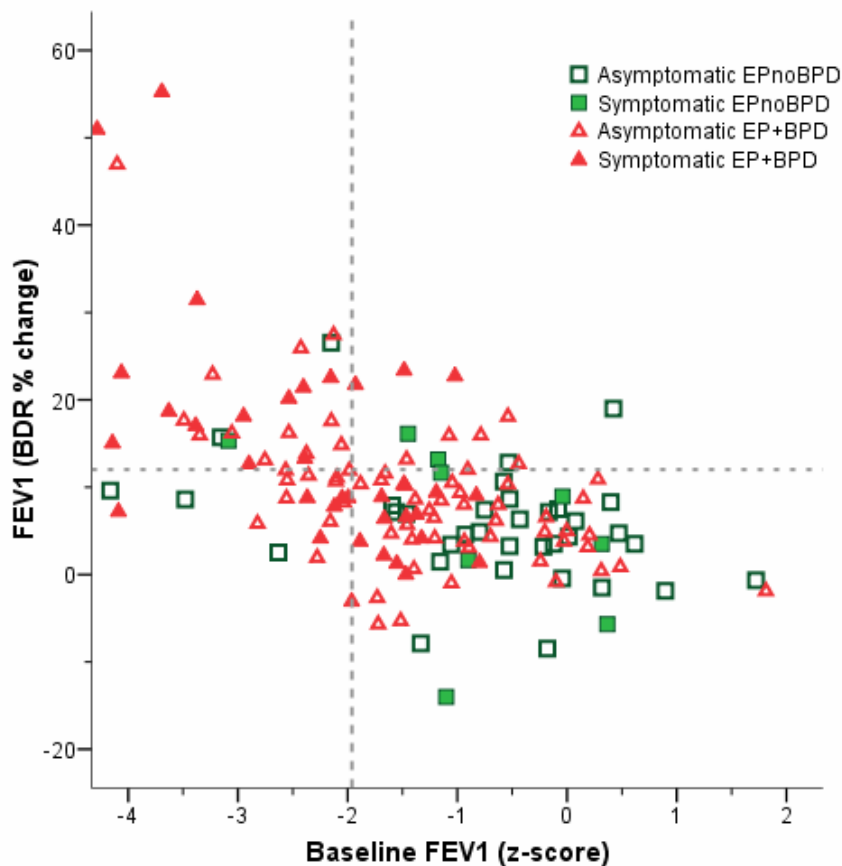
Legend: This scatter plot has an identical layout to Fig E2 but shows % change in FEV_1 following administration of a bronchodilator (Salbutamol) vs. baseline FEV_1 z-score and respiratory symptoms during the last 12 months. Of the 48 EP children reporting current symptoms, 8(17%) had not received any recent asthma medication all of whom had had prior BPD. As can be seen from the plot, many children were asymptomatic despite marked decrements in lung function and increased airway responsiveness.

Fig E4 Association between PEF at 6y and FEV_1 at 11y.

Legend: This scatter plot shows FEV_1 z-score at 11 years vs. peak expiratory flow (PEF) z-score (www.growinglungs.org.uk) at the 6 year follow-up according to diagnostic groups. The horizontal dashed line represents the lower limit of normal for FEV_1 and the vertical dashed/dotted line represents the lower limit of normal for PEF. The latter is set at -1.2 z-scores, which represents the 2.5[th] centile from the classmates in this study. Despite considerable scatter, there was a significant correlation between PEF at 6y and FEV_1 at 11y particularly in those born EP (r^2 =0.34 for EP [p< 0.001], r^2 =0.14 for classmates [p< 0.001]). As a group, the PEF z-score was significantly lower in the EP children (mean (SD): -0.44 (0.99)) than in classmates (0.60 [.10]; 95% CI difference: -1.28; 0.79; p < 0.0001)

Reference List

1. Cole TJ, Freeman JV, and Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat.Med* 1998;17:407-429.

2. Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, Hall GL, Welsh L, Kirkby J, Nystad W, Badier M, Davis S, Turner S, Piccioni P, Vilozni D, Eigen H, Vlachos-Mayer H, Zheng J, Tomalak W, Jones M, Hankinson JL, and Stocks J. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. *Am J Respir Crit Care Med* 2009;180:547-552.