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Longitudinal changes in lung function in very prematurely born young people receiving high-frequency oscillation or conventional ventilation from birth

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Abstract

Objective: To examine changes in lung function over time in extremely prematurely born adolescents.

Working Hypothesis: Changes in lung function during adolescence would vary by ventilation mode immediately after birth.

Study Design: Longitudinal follow-up study.

Patient Subject Selection: Participants from the United Kingdom Oscillation Study who were randomized at birth to high-frequency oscillation (HFO) or conventional ventilation (CV) were assessed at 11–14 years ($n = 319$) and at 16–19 years ($n = 159$).

Methodology: Forced expiratory flow (FEF), forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and lung volumes including functional residual capacity (FRC) were reported as z-scores. The diffusion capacity of the lungs for carbon monoxide (DLCO) was measured. Lung function trajectories were compared by mode of ventilation using mixed models. Changes in z-scores were scaled to 5-year average follow-up.

Results: There were significant changes in the mean FEF75, FEF50, FEF25, FEV1, FVC, and DLCO z-scores within the CV and HFO cohorts, but no significant differences in the changes between the two groups. The mean FRC z-score increased in both groups, with an average change of greater than one z-score. The mean FEV1/FVC z-score increased significantly in the CV group, but not in the HFO group (difference in slopes: $p = 0.02$). Across the population, deterioration in lung function was associated with male sex, white ethnicity, lower gestational age at birth, postnatal corticosteroids, oxygen dependency at 36 weeks postmenstrual age, and lower birth weight, but not ventilation mode.

Conclusions: There was little evidence that the mode of ventilation affected changes in lung function over time.

KEYWORDS
prematurity, ventilation mode, longitudinal changes, lung function

1 | INTRODUCTION

Infants born extremely prematurely, that is before 29 weeks of gestation, suffer chronic respiratory morbidity[1] that persists into adult life.[2-4] The respiratory support these infants receive can be lifesaving but may be associated with lung damage leading to long-term respiratory problems.[5] Bronchopulmonary dysplasia (BPD), birth weight z-score, and sex are known predictors of future respiratory morbidity in preterm infants, but the reported effects are variable.[3,6-8] Few studies have presented longitudinal data pre and postpuberty on lung function changes within neonatal populations routinely exposed to antenatal steroids and postnatal surfactant. Earlier studies are conflicting as to whether conventional or high-frequency oscillation are associated with better lung function at follow-up.[9-13]

The United Kingdom Oscillation Study (UKOS) found no significant difference in the risk of death or prevalence of BPD in infants born before 29 weeks of gestation who received HFO or conventional ventilation (CV) within 1 h of birth.[14] There were, however, beneficial effects of HFO on respiratory outcomes at 11–14 years of age,[15] which were not apparent at 16–19 years of age.[1] It is unclear whether these results were explained by catch up growth between 11 and 14 years and 16–19 years in those who had received CV, or whether the HFOV group's lung function had not improved as expected during puberty.

Our aims were to describe trends in lung function in UKOS participants between 11 and 14 years and 16–19 years and to determine which factors were associated with changes in lung function over time. In particular, we compared trends according to the allocated neonatal ventilation mode.

2 | MATERIALS AND METHODS

Comprehensive lung function assessment was undertaken when the UKOS participants were 11–14 and 16–19 years of age. Full details of the respiratory assessments are reported elsewhere.[1,15] In brief, airway function was assessed by spirometry—forced expiratory flow at 75%, 50%, or 25% vital capacity (FEF$_{75}$, FEF$_{50}$, and FEF$_{25}$, respectively), and forced expiratory flow at one second (FEV$_1$) and lung volumes were assessed by measurements of functional residual capacity using the helium dilution technique and plethysmograph (FRC$_{He}$ and FRC$_{pleth}$, respectively) and forced volume vital capacity (FVC). The gas transfer was assessed by testing for the diffusing capacity of the lung for carbon monoxide (DLCO). All measurements are analyzed as z-scores using published standards.[16-19] The same reference ranges were used at both time points and for the same individuals. The GLI Quanjer equations were used where available, however, the Rosenthal equations were used for FEF25 and FEF50 as Quanjer did not give reference equations for those values. Pubertal status was assessed by questionnaire when the participants were between 11 and 14 years of age.[15] Ethnic background was assessed by a self-reported questionnaire and included the following options; white (British, Irish, Other), mixed (White and Black Caribbean, White and Black African, White and Asian, and Other), Asian (Indian, Pakistani, Bangladeshi, and Other), Black or Black British (Caribbean, African, and Other), and Chinese. These options were identical at each study point.

The original UKOS trial was granted ethical approval by the South Thames Multicentre Research Ethics Committee. Subsequent follow-up studies at 11–14 years and 16–19 years were approved by South West London National Research Ethics Service Committee and by The North East-Tyne and Wear South Research Ethics Committee, respectively. Participants were invited to attend by letter, email, and phone call, and gave written consent to take part in this study.

2.1 | Analysis

To investigate trends in lung function over time, we used random-effects regression models ("mixed-effects model") as these allow for the longitudinal lung function measurements over time and also allow for the nonindependence among participants from multiple births.[20] These regression models allowed for incomplete follow-up with the assumption that missing data points are "missing at random." an assumption which was tested in sensitivity analyses described below. Ventilation group, age of young person at assessment, and the interaction between group and age were included in the model in the first instance as part of the unadjusted analyses. The adjusted analysis added in the young person's birth weight, gestational age, and whether surfactant was given as these were found to differ significantly between the two modes of ventilation at the 11–14-year follow-up.[21] The interaction terms in the unadjusted and adjusted analyses were assessed to determine if the trajectories of lung function differed between ventilation groups. Estimates of the yearly change in lung function with 95% confidence intervals (CIs) were calculated, along with the difference in rates of change. In keeping with the previous studies, we used FEF$_{75}$ as the predefined primary outcome and have regarded the other lung function measures as secondary outcomes thus we have not adjusted these for multiple testing.

Maternal and child characteristics were compared for each lung function outcome where the child deteriorated versus maintained or improved in their lung function score over time. T tests, χ^2, or Fisher's exact tests were used to identify the characteristics associated with lung function deterioration.

The representativeness of those assessed at 16–19 years was determined by comparing the neonatal and maternal characteristics of participants with those not evaluated. Sensitivity analyses were undertaken where the model was further adjusted for factors that differed between participants and dropouts. The main model was fitted (i) using all participants and (ii) using only those with complete data to confirm validity of the "missing at random" assumption used in the statistical models. Analysis was conducted using the lme4 package in R (R Core Team, 2019).

3 | RESULTS

3.1 | Characteristics of the study sample

Three hundred and nineteen young people born before 29 completed weeks of gestational age had comprehensive lung function measurements at ages 11–4 years (160 received HFO); 159 were seen at 16–19 years (81 received HFO) (Figure 1). One hundred and forty-eight young people were assessed at both time points (74 received HFO). At 11–14 years, the mean Tanner score for breast and genital development was three, and 5% of boys and 6% of girls had reached Tanner Stage 5 and complete puberty.

At the 11–14 year follow-up, there were significant differences between CV and HFO groups in mean birth weight, gestational age at birth, and whether surfactant was given (Table 1), therefore those factors were used in the adjusted model in keeping with our previous study.[21] There were no other significant differences between the two ventilation groups in baseline maternal and neonatal characteristics or the characteristics of the children assessed at 16–19 years of age (Tables 1–2). Participants differed from dropouts in terms of the mother's ethnic group, mean birthweight, gestational age, and whether the mother smoked during pregnancy (E-Table S1), thus in a second sensitivity analysis, we included ethnic group and smoking during pregnancy as additional variables in the adjusted model. Further adjustment resulted in similar effect sizes and confidence intervals to the original model (E-Table S2).

3.2 | Change in lung function z-score over time

The plots of lung function over time (Figures 2 and SE1) and the adjusted model (Table 3) show the mean rates of changes in the FEF, FEV_1, FVC, DLCO, and FRC results, which were similar in the two ventilation groups. There was no evidence for a change in FEF_{75} z-score (primary outcome in the 11–14 year follow-up) with age in either group nor was their evidence for a difference between the groups (Table 3). Results were virtually identical when only participants with complete data were included (E-Table S3). The mean FEF_{50} and FEF_{25} z-scores improved with age in both ventilation groups with FEF_{50} increasing by 0.04 z-scores per additional year of age for both groups and FEF_{25} increasing by 0.07 z-scores per year in the CV group and 0.06 z-scores in the HFO group. The mean forced expiratory flow z-scores were below expected reference values with mean values at 19 years of age at −0.8 or lower for both groups (Figure 2, Tables 2 and 4).
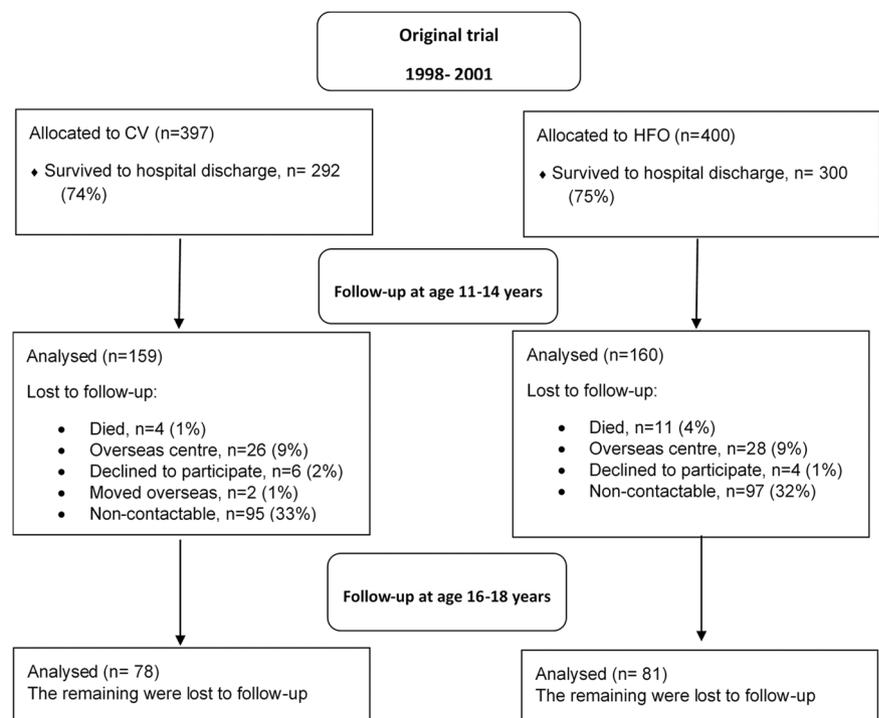

FIGURE 1 United Kingdom Oscillation Study CONSORT flow diagram. CV, conventional ventilation; high-frequency oscillation

TABLE 1 Maternal and neonatal characteristics of the children according to ventilation group.

	11–14 years			16–19 years		
	CV	HFOV	p Value	CV	HFO	p Value
N	159	160		78	81	
Male (%)	85 (53)	77 (48)	0.409	38 (49)	39 (48)	>0.999
Mother's ethnic group (%) = white	142 (90)	143 (89)	0.920	68 (87)	71 (88)	0.329
Black	11 (7)	10 (6)		9 (12)	6 (7)	
Other	5 (3)	7 (4)		1 (1)	4 (5)	
Birthweight (g) (mean (SD))	923.1 (206.0)	866.5 (208.9)	0.016	921.3 (226.2)	867.5 (207.1)	0.119
Birthweight z-score (mean (SD))	−0.6 (1.0)	−0.6 (1.0)	0.521	−0.6 (1.1)	−0.6 (1.0)	0.740
Gestational age, weeks (mean (SD))	27.0 (1.2)	26.7 (1.4)	0.014	27.1 (1.3)	26.7 (1.5)	0.079
Gestational group = 26-28 week (%)	129 (81)	108 (68)	0.008	60 (77)	51 (63)	0.081
Multiple birth (%)	39 (25)	37 (23)	0.871	13 (17)	16 (20)	0.765
Surfactant given (%)	158 (99)	152 (95)	0.036	78 (100)	76 (94)	0.059
Mother smoked during pregnancy (%)	31 (21)	38 (26)	0.408	16 (22)	14 (18)	0.743
Systemic steroids given before extubation (%)	36 (23)	48 (31)	0.161	20 (26)	29 (36)	0.224
Oxygen dependency at 36 weeks postmenstrual age (%)	95 (60)	88 (55)	0.457	42 (54)	44 (54)	>0.999
Oxygen dependency at 28 days (%)	131 (82)	131 (82)	>0.999	59 (76)	63 (78)	0.896
Oxygen-dependent at discharge (%)	34 (22)	37 (23)	0.858	18 (24)	19 (23)	>0.999

Note: The data are presented as the mean (SD) or number (%) unless specified.

Abbreviation: CV, conventional ventilation; HFO, high-frequency oscillation; SD, standard deviation.

TABLE 2 Characteristics of the children according to ventilation group and time.

	CV	HFO	p Value	CV	HFO	p Value
n	159	160		78	81	
Age (years)	12.5 (0.6)	12.5 (0.6)	0.660	17.9 (0.8)	17.9 (0.7)	0.936
Weight (kg)	44.4 (12.5)	44.9 (11.5)	0.709	63.6 (16.4)	62.0 (15.7)	0.535
Height (cm)	152.7 (9.2)	151.5 (8.2)	0.264	167.8 (8.6)	166.3 (9.4)	0.302
BMI	18.8 (3.7)	19.4 (3.8)	0.190	22.4 (4.7)	22.3 (4.8)	0.881

Note: The data are presented as the mean (SD) or number (%) unless specified.

Abbreviation: CV, conventional ventilation; HFO, high-frequency oscillation; SD, standard deviation.
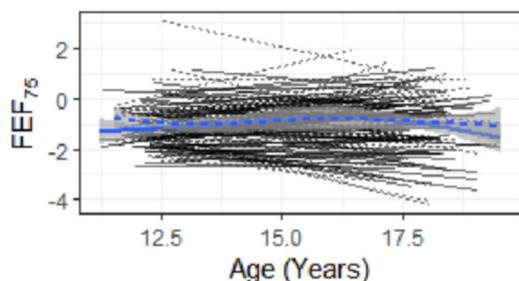

FIGURE 2 Individual trajectories for FEV_{75} by mode of ventilation. FEV, forced expiratory volume [Color figure can be viewed at wileyonlinelibrary.com]

Mean FRC increased with age for both groups; the CV group had a mean increase of 0.12 z-score per year regarding FRC_{pleth} and 0.13 z-score regarding FRCHe, while in the HFO group FRC_{pleth} increased by 0.15 z-score and FRC_{He} by 0.17 z-score (Table 3). This is equivalent to a predicted increase in mean z-score of between 0.95 and 1.37 from 11 to 19 years of age for both groups (Table 4).

The slope of the mean trajectory for FEV_1/FVC z-score with increasing age differed significantly by mode of ventilation (interaction test: $p = 0.02$; Table 3). The mean ratio increased by 0.08 z-score per year for the CV group compared to a decrease of −0.01 z score per year in the HFO group. Despite the changes in slopes, the mean z-scores in both groups remained low with predicted values less than −1.7 z-scores at 19 years of age (Table 4).

TABLE 3 the mean change in lung function per year (slope)[a] by ventilation group, along with the difference in slopes (with 95% CI).

	Unadjusted analyses				Adjusted for child's birthweight, gestational age, and surfactant given			
	CV	HFO	Difference HFO-CV	p Value for the difference	CV	HFO	Difference HFO-CV	p Value for the difference
FEF$_{75}$ z-score	0.02	0.00	0.02 (−0.04 to 0.08)	0.56	0.01	0.00	0.02 (−0.04 to 0.08)	0.59
FEF$_{50}$ z-score	0.04	0.04	0.01 (−0.04 to 0.06)	0.72	0.04	0.04	0.01 (−0.04 to 0.05)	0.76
FEF$_{25}$ z-score	0.07	0.06	0.01 (−0.04 to 0.07)	0.57	0.07	0.06	0.01 (−0.04 to 0.06)	0.61
FEV$_1$ z-score	−0.02	−0.04	0.02 (−0.04 to 0.07)	0.48	−0.03	−0.04	0.02 (−0.04 to 0.07)	0.53
FVC z-score	0.03	0.05	−0.01 (−0.07 to 0.05)	0.68	0.03	0.04	−0.01 (−0.07 to 0.04)	0.65
FEV$_1$/FVC z-score	0.09	−0.02	0.10 (0.02–0.18)	0.02	0.08	−0.01	0.10 (0.02–0.18)	0.02
DLCO z-score	−0.02	−0.05	0.02 (−0.04 to 0.09)	0.49	−0.02	−0.04	0.02 (−0.05 to 0.09)	0.57
FRC$_{pleth}$ z-score	0.12	0.15	−0.04 (−0.10 to 0.03)	0.26	0.12	0.15	−0.03 (−0.10 to 0.03)	0.32
FRC$_{He}$ z-score	0.13	0.17	−0.04 (−0.12 to 0.04)	0.30	0.13	0.17	−0.04 (−0.12 to 0.04)	0.30

Abbreviations: CI, confidence interval; CV, conventional ventilation; DLCO, diffusion capacity of the lungs for carbon monoxide; FEF, forced expiratory flow; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; HFO, high-frequency oscillation.

[a]Mean change per year in lung function z-score is expressed as the number of standard deviations from the random effects regression model using all available data (319 at age 11–14 and 159 at age 16–19 years).

TABLE 4 Predicted mean values[a] of lung function from 11 to 19 years of age.

	CV			HFO		
	11 years	19 years	Difference (19–11 years)	11 years	19 years	Difference (19–11 years)
FEF$_{75}$ z-score	−1.53	−1.41	0.12	−1.25	−1.26	−0.01
FEF$_{50}$ z-score	−1.78	−1.44	0.34	−1.48	−1.20	0.28
FEF$_{25}$ z-score	−1.52	−0.95	0.57	−1.27	−0.80	0.47
FEV$_1$ z-score	−1.23	−1.44	−0.21	−0.91	−1.26	−0.35
FVC z-score	−0.45	−0.20	0.25	−0.37	−0.01	0.36
FEV$_1$/FVC z-score	−2.43	−1.77	0.66	−1.73	−1.85	−0.12
DLCO z-score	−1.32	−1.52	−0.20	−1.02	−1.38	−0.36
FRC$_{pleth}$ z-score	−0.43	0.52	0.95	−0.61	0.61	1.21
FRC$_{He}$ z-score	−0.56	0.48	1.04	−0.75	0.62	1.37

Abbreviations: CI, confidence interval; CV, conventional ventilation; DLCO, diffusion capacity of the lungs for carbon monoxide; FEF, forced expiratory flow; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; HFO, high-frequency oscillation.

[a]Adjusted for child's birthweight, gestational age, and surfactant given from the random effects regression model using all available data (319 at age 11–14 and 159 at age 16–19 years).

3.3 | Factors associated with deterioration in lung function

Those whose lung function scores decreased from 11 to 14 to 16–19 years of age tended to be male (FEF$_{75}$), born to mothers of white ethnicity (FEF$_{75}$, FEV$_1$, FVC, and DLCO), have lower mean gestational age (FEF$_{50}$), lower mean birthweight (FEF$_{50}$, FEV$_1$, and FRC$_{pleth}$), received postnatal corticosteroids (FEF$_{75}$ and FEV$_1$), and were oxygen dependent at 36 weeks postmenstrual age (FEV$_1$; E-Table S4). Mode of ventilation was not associated with deterioration in lung function with the exception of FEV$_1$/FVC

(0.10; 95% CI 0.02–0.18, p = 0.02) favoring those conventionally ventilated.

4 | DISCUSSION

We demonstrated overall no significant difference in the change in lung function between 11 and 14 and 16–19 years according to neonatal mode of ventilation. Only the FEV$_1$/FVC results showed significantly different trajectories for CV and HFO, with the HFO group's mean z-scores remaining similar over time, whereas the CV

group's mean z-scores increased by 0.08 z-scores per year. The CV group had similar mean FEV_1/FVC results to the HFO group at 16–19 years, this may be an indication of "catch up growth."

There was a decrease in small airway lung function, which is consistent with the deterioration previously reported in a subsample of UKOS young people measured at 1 year and 11–14 years.[22] Small airway function was measured by spirometry and impulse oscillometry. Forced expiratory flow at 75% of the FVC (FEF75) has been suggested to be a noneffort dependent, sensitive marker of small airway disease.[23,24] Airways resistance at 5 Hz has been shown to be nonvolitional marker of small airways.[25]

FEF_{75} was pre-specified as the primary outcome in the UKOS trial follow-up at ages 11–14 and 16–19 years as described in our primary publications at those time points.[1,15] Hence we followed that plan for these analyses for consistency. FEF_{75} has been suggested to be a noneffort dependent, a sensitive marker of small airway disease [23,24] and the small airways are an area of concern in prematurity-related lung disease. It is accepted that the new Quanjer reference values for FEV_1 have to some extent, negated the need for additional measurements of small airways disease within a symptomatic population (those with cystic fibrosis and asthma) beyond FEV_1,[26] however, it remains an accurate measure of small airways disease. We felt it was important to maintain consistency and report our primary outcome, but do report all spirometry results (including FEV_1) using the most up-to-date reference ranges.

There have been three recent longitudinal studies reporting lung function in adults born prematurely.[3,27,28] All three showed a mismatch in lung function trajectories concerning airways and lung volumes, in concordance with our reported data. Furthermore, airways (FEV_1) were affected to a larger degree. In one study,[27] however, the mean FEV_1/FVC was shown to fall in contrast to the results of our study. In that study, only 40% of infants received postnatal surfactant compared to 90% in our study population. It should also be noted however that in our study, only those who were conventionally ventilated showed an improvement in mean FEV_1/FVC.

Pubertal status was assessed at 11–14 years and 90% of participants had reached Tanner Stage 2 suggesting they had entered puberty.[29,30] It usually takes 4–5 years to complete puberty once they pass Tanner Stage 2.[31] We reassessed the young people on average when they were 5 years older, anticipating the majority of participants would have completed puberty. Puberty is a period of lung development characterized by rapid growth of the airways and lung volumes.[32,33] This growth occurs dysnaptically, that is at different times.[32–34] In our study population, mean FEV_1 decreased by up to 0.35 z-scores between the two-time points, while mean FVC increased. This would suggest that the airway growth in our population was affected to a higher degree than the lung volume growth, which was conserved. Given that the pubertal growth phase of the lungs is the last positive effector of lung function, it is possible that prematurely born infants would be at risk of adult lung disease due to this disruption. This mismatch in the growth of the airways and lung volumes was seen in a study of 297 infants born before

29 weeks compared to 260 infants born at term.[4] In that study, whilst mean FEV_1 and mean FVC z-scores decreased in those born preterm, the changes in mean FEV_1 were more statistically significant. The effect was more pronounced in those who had developed BPD compared with those had not. The poorer lung function overall in that study may reflect that only 73% of the infants were exposed to antenatal steroids and 40% received surfactant. In contrast in the UK and Ireland EPICure study of individuals born before 26 weeks of gestation between 11 and 19 years, mean FEV_1 values decreased over time but were similar in those with and without neonatal BPD and term-born controls.[3] The disparity in lung development was, however, not shown in a smaller study of 35 preterm infants assessed at 10 s and 18 years, which highlighted that airway and lung volume z-scores tracked through puberty.[35] In that study, however, in addition to lower rates of antenatal steroid exposure (44%) and postnatal surfactant (49%), the young people were born at a later gestational age that is up to 31 weeks of gestation.

We observed an association between a deterioration in FEF_{75} and male sex, white ethnicity, and postnatal corticosteroid use. Male sex and postnatal corticosteroid use are known to be associated with poor respiratory outcomes.[36–38] Caution is needed when interpreting the ethnicity results as, although this could represent survivor bias as other studies have highlighted,[39,40] the majority of UKOS participants were white.

Our study has strengths and some limitations. We believe it is the first to quantify the effects of HFO versus CV on lung growth trajectories of young people born extremely prematurely. There was incomplete follow-up and so we compared baseline and neonatal characteristics in those included with those not and adjusted statistically for the few differences observed. We also compared the analyses using all participants assuming data were missing at random with those with complete data and found no differences in effect sizes and p values. These comparisons provided assurance of the robustness of our findings. While factors other than the "neonatal" mode of ventilation could exert influences on respiratory outcomes, we accounted for this by using multivariable analyses and by using z-scores standardized for height, age, and sex. Since the completion of the study, further reference ranges have been suggested by the GLI for lung volumes and DLCO. For consistency, we have continued to use the reference equations used in other publications relating to the UKOS cohort.[1,15]

In conclusion, there was little evidence that the mode of ventilation affected changes in lung function over time in these young people born very prematurely. Despite some improvements in the mean FEF, FEV_1/FVC, and FRC over time, "normal" respiratory function was not achieved, which may result in an increased susceptibility to COPD.

AUTHOR CONTRIBUTIONS

writing—review & editing (equal). **Sanja Zivanovic**: Investigation (equal); writing—review & editing (equal). **Neil Marlow**: Funding acquisition (equal); writing—review & editing (equal). **Sandy Calvert**: Funding acquisition (equal); writing—review & editing (equal). **Anne Greenough**: Conceptualization (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (equal); writing—review & editing (equal). **Janet L Peacock**: Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (equal); writing—review & editing (equal).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data will be made available on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.