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Postnatal dexamethasone exposure and lung function in adolescents born very prematurely

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Abstract

We previously demonstrated corticosteroid administration on the neonatal intensive care unit was associated with reduced lung function at 11 to 14 years of age in children born very prematurely. The objective of this observational study was to assess if lung function remained impaired at 16 to 19 years of age in those who had received postnatal corticosteroids and whether the trajectory of lung function with increasing age differed between those who had and had not received corticosteroids. One hundred and fifty-nine children born prior to 29 weeks of gestational age had comprehensive lung function measurements; 49 had received postnatal dexamethasone. Lung function outcomes were compared between those who had and had not received postnatal dexamethasone after adjustment for neonatal factors. Forced expiratory flow at 75%, 50%, 25% and 25–75% of the expired vital capacity, forced expiratory volume in one second, peak expiratory flow and forced vital capacity and lung volumes (total lung capacity and residual volume) were assessed. The majority of results were significantly lower in those who received dexamethasone (between 0.61 to 0.78 standard deviations). Lung function reduced as the number of courses of dexamethasone increased. Between 11 and 14 years and 16 to 19 years, lung function improved in the unexposed group, but forced expiratory flow at 75% of the expired vital capacity and forced expiratory volume in one second deteriorated in those who had received postnatal corticosteroids (p = 0.0006). These results suggest that prematurely born young people who received postnatal corticosteroids may be at risk of premature onset of chronic obstructive pulmonary disease.
Introduction

Corticosteroids are frequently given to prematurely born infants to try and reduce the development bronchopulmonary dysplasia (BPD) [1, 2]. Studies in animal models, however, have shown that postnatal corticosteroid administration can alter the lungs development, resulting in delayed alveolarisation and emphysematous lungs with fewer air spaces [3]. We have previously reported that within the United Kingdom Oscillation Study (UKOS) cohort [4], postnatal dexamethasone exposure was associated with poorer respiratory outcomes at two years of age [5] and poorer lung function at 11 to 14 years of age in a dose dependent manner [6].

During puberty there is a period of rapid growth of the airways and lung parenchyma [7]. It is possible that such changes might overcome those differences seen in lung function at 11–14 years. The aim of this study, therefore, was to determine if differences in lung function according to postnatal exposure to corticosteroids persisted at 16 to 19 years of age in very prematurely born young people. In addition, we wished to determine if any lung function changes between 11 to 14 years of age and 16 to 19 years of age differed according to those who did and did not receive postnatal corticosteroids.

Materials and methods

Children from UKOS were invited to attend for follow-up at 16 to 19 years of age at King’s College Hospital NHS Foundation Trust. Participants and parents gave informed, written consent to take part in the study and ethical approval for the study was given by The North East-Tyne and Wear South Research Ethics Committee.

Forced expiratory flow at 75% (FEF$_{75}$), forced expiratory flow at 50% (FEF$_{50}$), forced expiratory flow at 25% (FEF$_{25}$) and FEF$_{25-75}$, FEV$_1$, PEF and forced vital capacity (FVC) were assessed by spirometry. Lung volumes were assessed using a helium-dilution technique (functional residual capacity, FRC$_{He}$) and plethysmography ((FRC$_{pleth}$), total lung capacity (TLC) and residual volume (RV)). Respiratory resistance was measured by impulse oscillometry at 5Hz and 20Hz. The diffusing capacity of the lungs for carbon monoxide was measured using a single breath technique. All tests were done in accordance to guidance from the American Thoracic Society and the European Respiratory Society [8–14]. The results were converted into z-scores to adjust for age, sex, and height [15], except for PEF and respiratory resistance which were expressed as the percentage predicted for height and sex [16, 17]. Lung function was classified as obstructive if FEV$_1$/FVC was below the 5$^{th}$ percentile predicted, restrictive if the TLC and FVC were below the 5$^{th}$ percentile predicted, and mixed if the FEV$_1$/FVC and TCL were below the 5$^{th}$ percentile predicted [18].

Smoking was assessed by self report and salivary cotinine analysis. Cotinine levels of more than 15 ng/ml were interpreted as active smoking [19]. Pubertal status was ascertained when the participants were aged 11 to 14 years from participant-completed questionnaires using Tanner staging [20, 21].

Postnatal steroid exposure

Data for postnatal corticosteroid exposure were captured when the original UKOS study was undertaken in 1998 to 2001 [4]. Correspondence confirmed that dexamethasone was the corticosteroid used in the postnatal period in all units. The average course of dexamethasone was 0.25 mg twice daily for three days, followed by 0.15 mg twice daily for three days, followed by 0.05 mg twice daily for three days. In general, repeated courses were considered if the infant remained ventilated in high inspired oxygen concentrations or had been reintubated and weaning was difficult.
Statistical analysis

Baseline factors were compared between those who were and were not recruited at age 16 to 19 years and those who did and did not receive postnatal dexamethasone (see S1 File). Linear mixed effects models were used to examine the associations between postnatal dexamethasone use, lung function and subsequent exercise capacity. The mixed models allowed for clustering of data arising from multiple births [22] and for confounders. The final models adjusted for "neonatal" factors: sex, mother’s ethnic group, smoking in pregnancy, birthweight z-score, gestational age and oxygen dependency at 36 weeks postmenstrual age (corresponding to moderate to severe bronchopulmonary dysplasia [23]), Apgar score at five minutes, air leak, ventilation group and pulmonary haemorrhage and age at the time of assessment. Measures of dexamethasone use considered were a yes/no indicator and the number of courses of dexamethasone (none, one, two or three). Sensitivity analyses were conducted to explore the robustness of adjustment for confounders. The analyses used propensity score (PS) matching to compare outcomes in children who had and had not been exposed to dexamethasone. PS matching aims to match individuals according to baseline factors to replicate a randomised design. Full details of the PS methodology and the results are given in the supplement (S1 Table in S1 File). Further sensitivity analyses were done to allow for missing lung function data, using multiple imputation. A final sensitivity analysis was done adding antenatal corticosteroids and surfactant into the model. Differences in lung function according to exposure to postnatal corticosteroids, are reported as means and 95% confidence intervals and as proportions with abnormal lung function, below the fifth centile (z-score < -1.64), estimated using the distributional approach [24, 25] (see S1 File). Obstructive, restrictive and mixed abnormal lung function were defined based on z-score cut-offs of FEV\textsubscript{1}/FVC and TLC [15]: obstructive: FEV\textsubscript{1}/FVC z-score < -1.645; restrictive: TLC pleth z-score < -1.645 and a normal FEV\textsubscript{1}/VC (z-score > = -1.645) and mixed: FEV\textsubscript{1}/FVC z-score < -1.645 and TLC pleth z-score < -1.645.

To enable us to determine the trajectory of lung function with increasing age, adjusted linear mixed models were used for each lung function measure with a time-exposure interaction term added along with sex, mother’s ethnic group, smoking in pregnancy, birthweight z-score, gestational age and oxygen dependency at 36 weeks postmenstrual age, Apgar score at five minutes, age at the time of follow-up assessment, air leak, ventilation group, pulmonary haemorrhage and age at the time of assessment as covariates. Comparisons between exposed and non-exposed groups across two follow-up time points (11–14 years and 16–19 years) were carried out for the results of the following measurements: FEF\textsubscript{75}, FEF\textsubscript{50}, FEF\textsubscript{25}, FEV\textsubscript{1}, FVC, FEV\textsubscript{1}/FVC, DLCOc, FRC\textsubscript{pleth}, FRC\textsubscript{He} and Vcmax. The analyses used all available data between the two time points. Plots of the least squares means with 95% confidence intervals, along with adjusted p-values for the time x exposure interaction are included. Statistical modelling was done using R.

Results

Recruitment

Seven hundred and ninety-seven infants were recruited into UKOS from 25 centres; 22 were in England, Scotland or Wales and one in each of Australia, Ireland and Singapore. Three hundred and nineteen were followed up at age 11 to 14 years. Of these, 148 underwent lung function assessment at age 16 to 19 years. A further 11 children who were part of the original trial, but were not followed up at age 11 to 14 years, were followed up at age 16 to 19 years. In total, data from 159 children who completed the lung function assessments at 16–19 years were analysed (Fig 1).
Baseline characteristics

The participants who were assessed at age 16–19 years had higher mean birthweight and mean gestational age than those not recruited and their mothers were more likely to be white and not to have smoked in pregnancy. They were also more likely to have had a major cranial ultrasound abnormality and pulmonary haemorrhage (S1 Table in S1 File).

Mean follow up at 16 to 19 years was 5.5 years (SD = 0.6) after the 11 to 14 year follow up with no significant difference in the length of follow up between those who received or did not receive postnatal corticosteroids. When seen at 11 to 14 years of age, more than ninety percent of the children had reached at least Tanner stage two. The mean Tanner score for boys and
girls for genital or breast development respectively was three. Five percent of boys (3 of 62) and 6% of girls (4 of 69) had reached Tanner stage 5 and finished puberty.

Those who received compared to those who did not receive postnatal dexamethasone were more likely to be male, of lower mean birthweight and gestational age, have a lower Apgar score, have been oxygen dependent at 36 weeks postmenstrual age, more likely to have experienced an air leak or pulmonary haemorrhage and their mothers’ ethnic group was more likely to be white (Table 1).

|                                | No dexamethasone | Dexamethasone | P value |
|--------------------------------|------------------|---------------|---------|
| N                              | 110              | 49            |         |
| Age (years)                    | 17 (0.8)         | 18 (0.7)      | 0.281   |
| Time after 11–14 year follow up (years) | 5.44 (0.60)      | 5.54 (0.58)   | 0.409   |
| Major cranial ultrasound abnormality* | 8 (7)            | 6 (12)        | 0.472   |
| Male sex                       | 47 (43)          | 30 (61)       | 0.047   |
| Antenatal steroids             | 99 (90)          | 45 (94)       | 0.647   |
| Birthweight (g)                | 943.4 (217.9)    | 782.8 (173.1) | <0.001  |
| Birthweight z-score            | -0.6 (1.0)       | -0.6 (1.2)    | 0.679   |
| Gestational age, weeks         | 27.3 (1.3)       | 25.9 (1.3)    | <0.001  |
| Gestational group = 26–28 wk   | 87 (79)          | 24 (49)       | <0.001  |
| Multiple birth (%)             | 23 (21)          | 6 (12)        | 0.278   |
| Apgar score at 5 mins          | 8.5 (1.4)        | 7.3 (2.1)     | <0.001  |
| Surfactant given               | 107 (97)         | 47 (96)       | 0.644   |
| Mother smoked during pregnancy | 24 (23)          | 6 (13)        | 0.222   |
| Mothers ethnic group           |                 |               | 0.008   |
| White                          | 91 (83)          | 48 (98)       |         |
| Black                          | 15 (14)          | 0 (0)         |         |
| Other                          | 4 (4)            | 1 (2)         |         |
| Patent ductus arteriosus       | 25 (23)          | 19 (39)       | 0.063   |
| Pulmonary haemorrhage          | 2 (2)            | 5 (10)        | 0.052   |
| Air leak                       | 10 (9)           | 11 (22)       | 0.041   |
| Oxygen dependency at 36 weeks postmenstrual age | 45 (41)      | 41 (84)       | <0.001 |
| HFOV                           | 52 (47)          | 29 (59)       | 0.224   |
| Wheeze (%)                     | 16 (15)          | 6 (13)        | 0.949   |
| Antibiotics for chest problems (%) | 3 (3)           | 3 (6)         | 0.378   |
| Current asthma (%)             | 10 (9)           | 4 (9)         | >0.999  |
| Inhalers (%)                   | 9 (8)            | 4 (9)         | >0.999  |
| Type of admission (%)          |                 |               | 0.092   |
| Chest problems                 | 0 (0)            | 1 (2)         |         |
| Surgery                        | 6 (5)            | 6 (12)        |         |
| Other                          | 0 (0)            | 0 (0)         |         |
| None                           | 104 (95)         | 42 (86)       |         |
| Smoker (%)                     | 11 (10)          | 3 (6)         | 0.555   |

* This outcome was assessed in the early neonatal period, <14 days, as intraventricular haemorrhage with ventricular dilatation or any parenchymal haemorrhage or cystic changes.

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

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Lung function results

Those who received postnatal corticosteroids had lower mean FEF<sub>75</sub>, FEF<sub>50</sub>, FEF<sub>25</sub>, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FEF<sub>25-75</sub>, PEF, FRC<sub>pleth</sub> and RV<sub>pleth</sub> z-scores (Table 2). The percentage of children with an abnormal FEF<sub>75</sub> was 35% in the non-exposed and 60% in the exposed group. The other spirometry measures showed differences between the exposed and unexposed children ranging from 13 to 28 percentage points (Table 3). In the exposed group 60% had an obstructive abnormality compared to 27% in the unexposed group (difference exposed-unexposed 33%, 95% CI 15%, 49%), none of the exposed group had a restrictive abnormality and only 1% of the unexposed group (difference -1%, 95%CI -7%,-6%). There were no young people who had mixed lung function abnormalities.

Sensitivity analyses were performed on the lung function measurement results with missing outcome and baseline data imputed confirming significant differences between the two groups (S2 Table in S1 File). Propensity score matching on a 1:1 ratio, achieved balance in sex, birthweight, birthweight z-score, gestational age in weeks, smoking in pregnancy, multiple birth, ventilation group and Apgar score and gave effect sizes that were similar to the adjusted

Table 2. Lung function and postnatal dexamethasone exposure.

| Lung function | n | No dexamethasone exposure mean (sd) (n = 110) | Dexamethasone exposure mean (sd) (n = 49) | Unadjusted difference (95% CI) | P value | Differences adjusted for neonatal and maternal factors (95% CI)* | P value |
|---------------|----|---------------------------------|---------------------------------|-------------------------------|--------|---------------------------------------------------------------|--------|
| FEF<sub>75</sub> z-score | 150 | -0.70 (1.14) | -1.81 (1.24) | -1.06 (-1.49, -0.63) | <0.001 | -0.72 (-1.23, -0.22) | 0.006 |
| FEF<sub>50</sub> z-score | 150 | -0.72 (1.05) | -1.57 (0.90) | -0.83 (-1.20, -0.46) | <0.001 | -0.70 (-1.15, -0.26) | 0.003 |
| FEF<sub>25</sub> z-score | 148 | -0.35 (1.11) | -1.28 (0.94) | -0.87 (-1.27, -0.47) | <0.001 | -0.81 (-1.30, -0.33) | 0.001 |
| FEV<sub>1</sub> z-score | 150 | -0.72 (1.28) | -1.74 (1.14) | -0.98 (-1.44, -0.53) | <0.001 | -0.65 (-1.19, -0.10) | 0.023 |
| FVC z-score | 150 | -0.15 (1.36) | -0.46 (1.28) | -0.28 (-0.77,0.21) | 0.264 | -0.01 (-0.62,0.60) | 0.984 |
| FEF<sub>25-75</sub> z-score | 148 | -0.89 (1.10) | -1.83 (1.25) | -0.92 (-1.34, -0.50) | <0.001 | -0.80 (-1.32, -0.29) | 0.003 |
| PEF z-score | 150 | -1.12 (1.16) | -2.30 (1.22) | -1.13 (-1.56, -0.70) | <0.001 | -0.80 (-1.31, -0.29) | 0.003 |
| DLCOc z-score | 149 | -1.08 (1.34) | -1.56 (1.16) | -0.47 (-0.94,0.01) | 0.055 | 0.11 (-0.47,0.70) | 0.705 |
| DLCOc/VA | 149 | 1.59 (0.21) | 1.49 (0.20) | -0.09 (-0.16, -0.01) | 0.023 | -0.05 (-0.14,0.05) | 0.347 |
| TLC<sub>pleth</sub> z-score | 151 | 0.75 (1.14) | 1.13 (1.22) | 0.40 (-0.02,0.82) | 0.065 | 0.51 (-0.02,1.04) | 0.063 |
| FRC<sub>pleth</sub> z-score | 151 | 0.39 (1.28) | 1.24 (1.39) | 0.86 (0.39,1.32) | <0.001 | 0.78 (0.18,1.37) | 0.011 |
| FRC<sub>He</sub> z-score | 128 | 0.02 (1.34) | 0.16 (1.38) | 0.14 (-0.38,0.66) | 0.599 | 0.26 (-0.42,0.93) | 0.456 |
| RV<sub>pleth</sub> z-score | 150 | 0.81 (1.18) | 1.75 (1.57) | 0.94 (0.48,1.40) | <0.001 | 0.90 (0.32,1.48) | 0.003 |
| VC<sub>max</sub> | 148 | 3.88 (1.00) | 3.93 (1.13) | 0.07 (-0.31,0.45) | 0.715 | -0.10 (-0.46,0.25) | 0.572 |
| LCI | 124 | 9.08 (1.47) | 9.89 (1.90) | 0.80 (0.18,1.41) | 0.012 | 0.66 (-0.11,1.43) | 0.095 |
| R5Hz z-score | 155 | -0.14 (1.13) | 0.07 (1.24) | 0.21 (-0.20,0.61) | 0.314 | 0.33 (-0.17,0.83) | 0.195 |
| R20Hz z-score | 155 | 0.38 (1.00) | 0.29 (1.07) | -0.10 (-0.45,0.26) | 0.594 | 0.10 (-0.34,0.55) | 0.650 |

*adjusted for sex, mother’s ethnic group, birthweight, gestational age, oxygen dependency at 36wk and Apgar score at 5 mins, smoking in pregnancy, age at time of follow-up, air leak, ventilation group, and pulmonary haemorrhage.

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difference estimated using mixed models (S3 Table in S1 File). The final sensitivity analyses, with the addition of antenatal corticosteroids and surfactant also had similar effect sizes to the original adjusted model.

The mean lung function (FEF$_{75}$, FEV$_1$, FEV$_1$/FVC, PEF, FRC$_{pleth}$, RV$_{pleth}$) was lower in children who had received more courses of dexamethasone compared to no courses and this remained significant after adjustment (Table 4).

Comparison of the lung function measures at 11 to 14 years of age to those at 16 to 19 years of age showed an improvement over time in FEF$_{75}$ for those unexposed to postnatal dexamethasone and a deterioration for those exposed (p < 0.001) (Fig 2).

### Discussion

We have demonstrated that postnatal corticosteroid administration was associated with significantly poorer lung function in very prematurely born young people aged 16 to 19 years. Those differences remained significant after adjusting for neonatal factors. The differences were substantial, for example in FEF$_{75}$ being equivalent to a difference in 23 percentage points.

In addition, the greater the number of courses, the greater the adverse effect on lung function. Importantly, we demonstrate that with regard to FEF$_{75}$ and FEV$_1$, there were significant deteriorations in lung function between 11 to 14 years and 16 to 19 years in those who received corticosteroids rather than the improvements in lung function expected during puberty.

Prematurely born young people do not reach the same lung function in early adulthood as do those born at term [26]. Thus, even if their subsequent rate of decline in lung function mirrored that of those born at term, the threshold for respiratory symptoms will be crossed earlier [26]. Amongst children born at term, those who were in the lowest quartile of FEV$_1$/FVC at seven years of age were more likely to be at risk of asthma, chronic obstructive pulmonary disease (COPD) overlap syndrome at 45 years of age (odds ratio 16.3, 95% confidence intervals 4.7–55.9) and COPD (odds ratio 5.76, 95% CI 1.9–17.4) [27]. We have demonstrated both at 11 to 14 years [6] and at 16 to 19 years, those who received postnatal corticosteroids had significantly worse lung function than those who did not. We, thus, speculate the postnatal corticosteroid group may be at risk of premature development of COPD. It would, thus, be important

| Lung function | N | Mean differences adjusted for neonatal and maternal factors (95% CI) | Estimated adjusted percentage with abnormal lung function |
|---------------|---|---------------------------------------------------------------|----------------------------------------------------------|
|               |   | No dexamethasone exposure | Dexemethasone exposure | Difference (exposed-unexposed) (95% CI) |
| FEF$_{75}$ z-score | 150 | -0.72 (-1.23, -0.22) | 35% | 60% | 26% (13%, 38%) |
| FEF$_{50}$ z-score | 150 | -0.70 (-1.15, -0.26) | 37% | 65% | 28% (15%, 41%) |
| FEF$_{25}$ z-score | 148 | -0.81 (-1.30, -0.33) | 22% | 50% | 28% (15%, 40%) |
| FEV$_1$ z-score | 150 | -0.65 (-1.19, -0.10) | 29% | 50% | 20% (8%, 33%) |
| FEF$_1$:FVC z-score | 148 | -0.80 (-1.32, -0.29) | 43% | 70% | 28% (16%, 40%) |
| FEF$_{25-75}$ z-score | 150 | -0.80 (-1.31, -0.29) | 51% | 77% | 26% (15%, 37%) |
| PEF z-score | 151 | -0.73 (-1.21, -0.25) | 16% | 38% | 22% (11%, 34%) |
| FRC$_{pleth}$ z-score | 151 | 0.78 (0.18,1.37) | 8% | 21% | 13% (4%, 22%) |
| RV$_{pleth}$ z-score | 150 | 0.90 (0.32,1.48) | 23% | 49% | 26% (13%, 38%) |

* For FRC$_{pleth}$ z-score and RV$_{pleth}$ z-score, an abnormal value is above 5th centile (z > 1.645). For all other lung function measures presented here, an abnormal value is taken as below 5th centile (ie z < 1.645). The proportion with abnormal lung function was calculated using the distributional approach [25].

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to encourage smoking cessation and prevention, maintaining physical fitness, annual influenza immunisation and a general healthy lifestyle [26].

It is recognised that postnatal corticosteroids, particularly if given early i.e. in the first week after birth may increase the risk of neurodevelopmental problems at follow up [1]. We highlight adverse associations on pulmonary outcomes. The young people in this cohort received the commonly then used regimens of postnatal corticosteroids [28], variations of which are still used for infants with severe unresponsive respiratory failure. In view of the adverse effects of systemically administered corticosteroids, lower doses have been used [29] and in infants followed up for two years, no adverse effects were seen [30]. The authors of this study highlighted no definitive evidence of the effect of low dose steroids on morbidity at two years, but highlight that the study did not reach the targeted sample size and was stopped early.

Table 4. Lung function and number of postnatal dexamethasone courses.

| Lung function | Unadjusted | Differences adjusted* for neonatal and maternal factors |
|---------------|------------|------------------------------------------------------|
|               | Unadjust ed | Differences adjusted for neonatal and maternal factors |
|               | N = 110 | N = 37 | N = 10 | N = 2 | N = 110 | N = 37 | N = 10 | N = 2 |
| FEV\textsubscript{1}z-score | ref | -0.93 (-1.39,-0.46) | -1.58 (-2.49,-0.68) | -1.95 (-4.27,0.37) | <0.001 | -0.63 (-1.15,-0.11) | -1.24 (-2.37,-0.12) | -1.83 (-4.06,0.40) | 0.022 |
| FEV\textsubscript{20}z-score | ref | -0.72 (-1.12,-0.32) | -1.24 (-2.02,-0.47) | -1.64 (-3.63,0.35) | <0.001 | -0.63 (-1.09,-0.17) | -1.10 (-2.10,-0.10) | -1.77 (-3.75,0.21) | 0.012 |
| FEV\textsubscript{35}z-score | ref | -0.81 (-1.24,-0.38) | -1.06 (-1.95,-0.17) | -1.77 (-3.89,0.36) | <0.001 | -0.76 (-1.27,-0.25) | -0.94 (-2.10,0.21) | -1.89 (-4.05,0.27) | 0.011 |
| FEV\textsubscript{1}z-score | ref | -0.83 (-1.32,-0.34) | -1.41 (-2.36,-0.45) | -3.00 (-5.45,-0.55) | <0.001 | -0.54 (-1.11,0.02) | -1.01 (-2.23,0.21) | -2.60 (-5.01,-0.19) | 0.041 |
| FVC z-score | ref | -0.19 (-0.71,0.34) | -0.33 (-1.35,0.69) | -3.00 (-5.62,-0.37) | 0.137 | 0.08 (-0.55,0.70) | -0.03 (-1.39,1.32) | -2.49 (-5.17,0.19) | 0.328 |
| FEV\textsubscript{1}/FVC z-score | ref | -0.77 (-1.21,-0.32) | -1.76 (-2.69,-0.83) | -0.84 (-3.06,1.39) | <0.001 | -0.72 (-1.25,-0.20) | -1.71 (-2.95,-0.47) | -1.01 (-3.26,1.24) | 0.009 |
| FEF\textsubscript{25}z-score | ref | -0.56 (-0.95,-0.16) | -1.29 (-2.07,-0.52) | -2.14 (-3.55,-0.73) | <0.001 | -0.59 (-1.07,-0.11) | -1.29 (-2.32,-0.25) | -2.40 (-3.92,-0.89) | 0.002 |
| DLCOc z-score | ref | -0.37 (-0.89,0.15) | -0.86 (-1.81,0.09) | -0.64 (-3.23,1.96) | 0.013 | 0.13 (-0.48,0.74) | 0.08 (-1.13,1.30) | -0.57 (-3.33,2.19) | 0.941 |
| DLCOc/VF | ref | -0.07 (-0.15,0.02) | -0.15 (-0.30,0.00) | -0.31 (-0.72,0.10) | 0.063 | -0.04 (-0.14,0.06) | -0.06 (-0.26,0.14) | -0.31 (-0.77,0.14) | 0.513 |
| TLC\textsubscript{pleth} z-score | ref | 0.32 (-0.15,0.79) | 0.87 (0.01,1.72) | -0.12 (-1.78,1.53) | 0.161 | 0.46 (-0.09,1.01) | 1.09 (-0.01,2.19) | -0.07 (-1.79,1.66) | 0.158 |
| FRC\textsubscript{pleth} z-score | ref | 0.65 (0.14,1.16) | 1.53 (0.59,2.47) | 1.51 (-0.32,3.34) | 0.001 | 0.63 (0.02,1.25) | 1.48 (0.25,2.71) | 1.83 (-0.10,3.76) | 0.024 |
| FRC\textsubscript{He} z-score | ref | 0.14 (-0.45,0.71) | 0.27 (-0.86,1.39) | -0.59 (-3.27,2.10) | 0.894 | 0.27 (-0.43,0.97) | 0.48 (-0.95,1.90) | -0.57 (-3.33,2.18) | 0.795 |
| RV\textsubscript{pleth} z-score | ref | 0.64 (0.14,1.14) | 1.85 (0.93,2.76) | 2.27 (0.48,4.05) | <0.001 | 0.68 (0.08,1.27) | 1.99 (0.80,3.18) | 2.46 (0.60,4.32) | 0.001 |
| VC\textsubscript{max} z-score | ref | 0.17 (-0.24,0.58) | -0.02 (-0.77,0.73) | -1.16 (-2.61,0.30) | 0.354 | -0.06 (-0.42,0.31) | -0.25 (-0.97,0.48) | -0.63 (-1.77,0.51) | 0.68 |
| LCI | ref | 0.61 (-0.05,1.27) | 1.53 (0.36,2.69) | 0.92 (-0.33,2.17) | 0.016 | 0.52 (-0.27,1.32) | 1.41 (0.02,2.79) | 0.89 (-0.48,2.25) | 0.113 |
| R5Hz z-score | ref | 0.23 (-0.21,0.67) | 0.48 (-0.35,1.31) | -1.31 (-2.92,0.31) | 0.182 | 0.30 (-0.22,0.81) | 0.93 (-0.08,1.95) | -0.90 (-2.54,0.74) | 0.146 |
| R20Hz z-score | ref | -0.10 (-0.49,0.29) | 0.23 (-0.50,0.96) | -1.32 (-2.74,0.10) | 0.266 | 0.03 (-0.43,0.49) | 0.88 (-0.03,1.78) | -0.90 (-2.37,0.56) | 0.153 |

*adjusted for sex, mother’s ethnic group, birthweight, gestational age, oxygen dependency at 36wk and Apgar score at 5 mins, smoking in pregnancy, age at time of follow-up, air leak, ventilation group, and pulmonary haemorrhage.

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Corticosteroids have been also given by inhalation [31]. Although such regimens deliver a lower dose systemically, infants so treated have not been exposed to long term follow up, thus the safety of such regimens cannot be assumed. Research is urgently required to identify safe and effective therapies to prevent chronic oxygen dependency and long-term respiratory morbidity. Furthermore, there is a limited evidence base for treatments of prematurely born infants who remain ventilator and/or chronically oxygen dependent; this should be a further research priority.

Our study has strengths and some limitations. Our study population is similar to those currently receiving neonatal care in that over 90% were exposed to antenatal steroids and postnatal surfactant. They completed a comprehensive range of lung function tests. We attempted to account for confounding factors such as moderate to severe BPD as this has been associated with poorer lung function at follow up [32]. In addition, we do not report the results of a randomised trial, but analysed our data using statistical modelling to control for a variety of other confounders that is differences in neonatal factors including mode of ventilation. Furthermore the analyses for dexamethasone exposure as a binary outcome were also undertaken using propensity score matching, where cases were matched for their baseline characteristics (S1 Table in S1 File). This analysis also showed significant differences between the two groups. We did not assess pubertal stage at 16–19 years of age follow-up, but all of the children had been assessed at 11 to 14 years of age. The earliest signs of puberty occur at Tanner stage 2 with breast (girls) or genital (boys) development [20, 21]. More than ninety percent of the boys and girls seen at 11–14 years follow up of the UKOS cohort had reached Tanner stage 2. The average time to complete puberty is four to five years [33]. The young people were assessed five years later than their previous respiratory follow up at 11 to 14 years and hence would have been expected to have completed puberty [33]. The mother’s ethnic group was white in eighty seven percent of those who were recruited into this study. The Global Lung Institute reference ranges used in this study do, however, account for ethnicity and hence allow comparison of population derived z-scores across multiple ethnic groups. Twelve of our study population had received more than one course of postnatal steroids. A Cochrane review of late use of postnatal corticosteroids to facilitate extubation demonstrated infants in several studies had more than one course of an open label steroids after randomisation [2]. It is possible, however, that the ongoing severity of such infants’ respiratory problems resulted in their worse lung function at follow-up rather than dexamethasone per se.
In conclusion, we have demonstrated that infants born extremely prematurely who had received postnatal dexamethasone to enhance extubation and reduce the risk of chronic respiratory morbidity had poorer lung function at 16 to 19 years of age in a dose dependent manner. Furthermore, those young people who had received postnatal corticosteroids rather than experiencing the expected increase in lung function between 11 to 14 years of age and 16 to 19 years of age had a deterioration in FEF\(_{75}\) and FEV\(_1\). We suggest those young people may be at risk of premature development of chronic obstructive pulmonary disease. The association of postnatal corticosteroids use and poor lung function would suggest it will be essential to regularly follow them and others exposed to similar regimens worldwide to determine the speed of any subsequent deterioration in lung function and design appropriate interventions to improve their respiratory outcomes.

Supporting information
S1 File. (DOC)

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References
1. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017; 10: CD001146. https://doi.org/10.1002/14651858.CD001146.pub5 PMID: 29063585
2. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017; 10: CD001145. https://doi.org/10.1002/14651858.CD001145.pub4 PMID: 29063594
3. Tschanz SA, Damke BM, Burri PH. Influence of postnatally administered glucocorticoids on rat lung growth. Biol Neonate. 1995; 68: 229–245. https://doi.org/10.1159/000244241 PMID: 8580214
4. Johnson AH, Peacock JL, Greenough A, Marlow N, Limb ES, Marston L, et al; United Kingdom Oscillation Study Group. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med. 2002; 347: 637–642. https://doi.org/10.1056/NEJMoa020432 PMID: 12200550
5. Qin G, Lo JW, Marlow N, et al. Postnatal dexamethasone, respiratory and neurodevelopmental outcomes at two years in babies born extremely preterm. PLoS One 2017; 12:e0181176. https://doi.org/10.1371/journal.pone.0181176 PMID: 28723921
6. Harris C, Crichton S, Zivanovic S, Calvert SA, Greenough A, Peacock JL. Effect of dexamethasone exposure on the neonatal unit on the school age lung function of children born very prematurely. PLoS ONE. 2018; 13: e0200243. https://doi.org/10.1371/journal.pone.0200243 PMID: 29985964
7. Smith JR, Emerson SR, Kurti SP, Gandhi K, Harms CA. Lung volume and expiratory flow rates from pre- to post-puberty. Eur J Appl Physiol. 2015; 115: 1645–1652. https://doi.org/10.1007/s00421-015-3149-1 PMID: 25761732
8. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. Am J Respir Crit Care Med. 2017; 196: 1463–1472. https://doi.org/10.1164/rccm.201710-1981ST PMID: 29192835

9. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017; 49: 1600016. https://doi.org/10.1183/13993003.00016-2016 PMID: 28049168

10. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: Pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007; 175: 1304–1345. https://doi.org/10.1164/rccm.200605-462ST PMID: 17545458

11. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005; 26: 511–522. https://doi.org/10.1183/09031936.05.00390505 PMID: 16135736

12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005; 26: 319–338. https://doi.org/10.1183/09031936.05.0034805 PMID: 16055882

13. Miller MR, Crapo R, Hankinson J, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005; 26: 153–161. https://doi.org/10.1183/09031936.05.0034505 PMID: 15994402

14. Zivanovic S, Peacock J, Alcazar-Paris M, Lo JW, Lunt A, Marlow N, et al; United Kingdom Oscillation Study Group. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med. 2014; 370: 1121–1130. https://doi.org/10.1056/NEJMoa1309220 PMID: 24645944

15. Nowowiejska B, Tomalak W, Radlinski J, Siergiejko G, Latawiec W, Kaczmarski M. Transient reference values for impulse oscillometry for children aged 3–18 years. Pediatr Pulmonol. 2008; 43: 1193–1197. https://doi.org/10.1002/ppul.20926 PMID: 18988256

16. Peacock JL, Sauzet O, Viegi G, Brusasco V, Crapo RO, Burgos F, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26: 948–968. https://doi.org/10.1183/09031936.05.00320505 PMID: 16264058

17. Verifications SSoB. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002; 4: 149–159. https://doi.org/10.1080/1462200210123581 PMID: 12028847

18. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965 I. Arch Dis Child. 1966; 41: 454–471. https://doi.org/10.1136/adc.41.219.454 PMID: 5957718

19. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965 II. Arch Dis Child. 1966; 41: 613–635. https://doi.org/10.1136/adc.41.220.613 PMID: 5929718

20. Sauzet O, Wright K, Marston L, Brocklehurst P, Peacock JL. Modelling the hierarchical structure in data sets with very small clusters: a simulation study to explore the effect of the proportion of clusters when the outcome is continuous. Stats Med. 2013; 32: L1429–L1438.

21. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001; 163: 1723–1729. https://doi.org/10.1164/ajrccm.163.7.2011060 PMID: 11401896

22. Peacock JL, Sauzet O, Ewings SM, Kerry SM. Dichotomising continuous data when retaining statistical power using a distributional approach. Stat Med. 2012; 31: 3089–3103. https://doi.org/10.1002/sim.5354 PMID: 22865598

23. Sauzet O, Bonte T, Brenne S, David M, Razum O, et al. A distributional approach to obtain adjusted comparisons of proportions of a population at risk. Emerg Themes Epidemiol. 2016; 13: 8. https://doi.org/10.1186/s12982-016-0050-2 PMID: 27279891

24. Bolton CE, Bush A, Hurst JR, Kotecha S, Mcgarvey L. Lung consequences in adults born prematurely. Thorax 2015; 70: 574–480. https://doi.org/10.1136/thoraxjnl-2014-206590 PMID: 25825005

25. Bui DS, Burgess JA, Lowe AJ, Perret J, Bui MQ, Bowatte G, et al. Childhood lung function predicts adult chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap syndrome. Am J Respir Crit Care Med. 2017; 196: 39–46. https://doi.org/10.1164/rccm.201606-1272OC PMID: 28146643
28. Greenough A, Milner AD. Chronic lung disease. In: Rennie JM, Roberton NRC. Textbook of Neonatology 5th edition. Churchill Livingstone, Edinburgh 2011.

29. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB; DART Study Investigators. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: A multicenter, international, randomized, controlled trial. Pediatrics. 2006; 117: 75–83. https://doi.org/10.1542/peds.2004-2843 PMID: 16396863

30. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB; DART Study Investigators. Outcome at 2 years of age of infants from the DART study: a multicentre, international, randomized controlled trial of low dose dexamethasone. Pediatrics. 2007; 119: 716–721. https://doi.org/10.1542/peds.2006-2806 PMID: 17403842

31. Onland W, Offringa M, van Kaam A. Late (>7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017; 8: CD002311. https://doi.org/10.1002/14651858.CD002311.pub4 PMID: 28836266

32. Ali K, Greenough A. Long term respiratory outcome of babies born prematurely. Ther Adv Respir Dis. 2012; 6: 115–120. https://doi.org/10.1177/1753465812436803 PMID: 22323441

33. Marceau K, Ram N, Houts RM, Grimm KJ, Susman EJ. Individual differences in boys and girls timing and tempo of puberty: modelling development with nonlinear growth models. Dev Psychol. 2011; 47: 1389–1409. https://doi.org/10.1037/a0023838 PMID: 21639623