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Lung function at 16–19 years in males and females born very prematurely

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Abstract

Objectives: To determine if there were differences in lung function at 16–19 years of age between males and females born very prematurely.

Working Hypothesis: Females compared with males would have superior lung function and exercise capacity.

Study Design: Cohort study.

Patient-Subject Selection: Those born at less than 29 weeks of gestational age.

Methodology: Lung function testing (spirometry, oscillometry, diffusion capacity, lung clearance index, and plethysmography), a shuttle sprint test for exercise capacity, and a respiratory symptoms questionnaire.

Results: Amongst 150 participants, males had poorer lung function compared with females with mean *z* score differences (95% CI [confidence interval]) after adjustment: forced expiratory flow at 75% (FEF_{75}) (−0.60 [−0.97,−0.24]), forced expiratory flow at 50% (FEF_{50}) (−0.39 [−0.72,−0.07]), forced expiratory flow at 25%–75% (FEF_{25-75}) (−0.62 [−0.98,−0.26]), the ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs (FEV_1:FVC ratio) (−0.71 [−1.09,−0.34]), diffusing capacity of the lungs for carbon monoxide (DLCO) (−0.41 [−0.78,−0.03]), diffusing capacity of the lung for carbon monoxide divided by alveolar volume (DLCO/VA) (−0.57 [−0.86,−0.28]).

Exercise capacity and self-reported exercise were both significantly better in males than females (46% males achieving between 1250 and 1500 m shuttle sprint distance vs. 4.8% females) and 74% males versus 67% females undertaking some exercise. There were no significant differences by sex in the prevalence of either wheeze or current asthma.

Conclusions: Males had poorer lung function than females at age 16–19 years, but their exercise capacity was superior to females.

KEYWORDS

biological sex, exercise capacity, preterm

Janet Peacock and Anne Greenough are joint senior authors.

1 | INTRODUCTION

Male compared with female infants have structurally different lungs at birth.[1,2] Androgen receptors have been demonstrated throughout the fetal lung[1] and murine studies have shown that exposure of lung tissue to dihydrotestosterone changes the amount of terminal lung buds.[2] Amniotic fluid sampling in humans have highlighted that male fetuses reach surfactant maturity approximately 1.5 weeks after females.[3] Males have greater respiratory morbidity in infancy[4] and childhood.[5] Furthermore, at 11–14 years of age, mean airway function forced expiratory volume in the first one second (FEV_1) in males was poorer than in females[6] and males were more likely to have a clinically abnormal FEV_1 (*z* score below the 5th centile).[6] Studies in adults, however, have suggested that females may be more adversely affected by premature birth. Nineteen-year-old women born before 32 weeks of gestation with a birth weight below 1.5 kg, had a higher incidence of shortness of breath during exercise compared with their male peers.[7] In addition, females born at less than 35 weeks of gestation between 1925 and 1949 and studied between 1987 and 2006 had a higher lifetime incidence of chronic obstructive airways disease (COPD) and asthma.[8]

During puberty, the last positive effector on lung function,[9] there is rapid growth of the parenchyma and airways.[10] This growth results in flow and volume differences between boys and girls, particularly in late adolescence[11] and may explain the superior outcomes of male compared with female adults born prematurely.[7,8] Both studies, however, were undertaken in populations that were not routinely exposed to antenatal corticosteroids or postnatal surfactant. Chronic respiratory problems such as COPD can be predicted by poor lung function postpuberty.[12] It is, therefore, important to determine if the differences in lung function between males and females routinely exposed to antenatal corticosteroids and postnatal surfactant persist postpuberty and are associated with reduced exercise capacity and the aim of this study.

2 | MATERIALS AND METHODS

Young people who had been recruited into the United Kingdom Oscillation Study (UKOS)[13] were invited to King's College Hospital NHS Foundation Trust to undergo lung function and exercise testing and complete a health questionnaire[14] when they were aged between 16 and 19 years of age. Ethical approval for UKOS was granted by the Thames Multicentre Research Ethics Committee[13] and for this follow-up study by the North-East–Tyne & Wear South Research Ethics Committee.

Spirometry forced expiratory flow at 75%, forced expiratory flow at 50%, forced expiratory flow at 25%, forced expiratory flow at 25-75%, forced vital capacity of the lungs, peak expiratory flow (FEF_{75}, FEF_{50}, FEF_{25}, FEF_{25-75}, FEV_1, FVC, PEF), lung volumes by plethysmography funtional residual capacity measured by plethsmogprahy, totallung capacity measured by plethsmography, residual volume measured by plethsmography (FRC_{pleth}, TLC_{pleth}, RV_{pleth}), lung volumes by helium dilution (FRC_{He}), impulse oscillometry at 5 and 20 Hz, diffusion capacity of the lungs to carbon monoxide (DLCO and DLCO/VA) and lung clearance index were performed according to American Thoracic Society/European Respiratory Society standards.[15–20] Spirometry, plethysmography, impulse oscillometry, DLCO, and FRC by helium dilution were measured using Vyair lung function equipment. Lung clearance index was calculated using the SF6 (Innocor). Lung function results were converted to *z* scores using global lung initiative (GLI) reference equations or appropriate reference equations for those lung measurements not included in the GLI reference equations.[19–23] Abnormal lung function was defined as lung function below the 5th centile for normal as reported previously.[24] A shuttle sprint[25] test was used to assess exercise capacity in meters.

Participants completed a questionnaire regarding their respiratory symptoms, a current diagnosis of asthma, and exercise undertaken on a weekly basis. Smoking status of the participants was set at "yes" if either they were a self-reported smoker or had a salivary cotinine level greater than 15 ng/mL. Puberty was previously assessed when the participants were 11–14 years of age.[26] More than 90% of children were found to be of Tanner stage 2.[27,28]

2.1 | Analysis

FEF_{75} was the primary outcome of this study to maintain consistency as the primary outcome of other studies of this cohort.[14,26] Demographic factors, lung function, exercise and respiratory symptoms were compared by sex with analyses adjusted for the nonindependence of multiple births using mixed effects multiple linear regression where the participant was the random effect (continuous outcomes)[29] or using logistic regression with robust standard errors (categorical outcomes).[30] The effects of sex on lung function used the same models as described above with adjustment for the following confounders: antenatal steroids (yes/no), birthweight, gestational age at birth, oxygen dependency at 36 weeks corrected (yes/no), administration of postnatal corticosteroids (dexamethasone, yes/no), maternal smoking in pregnancy (yes/no), and the participant's age at assessment.

The percentage of participants with abnormal lung function was calculated for all lung function measures and reported as *z* scores (all except lung clearance index [LCI]), using the distributional approach [31] and using $z < -1.64$ as the cut-off for "abnormal" for lung function measures where a smaller value indicates poorer function and $z > 1.64$ for measures where a larger value is worse. Lung function measures followed a reasonably symmetric distribution and so were not transformed. Exercise test distance and self-reported exercise were categorized as their distributions were irregular and could not be transformed to normal. These and the other categorical outcomes were adjusted for postnatal corticosteroids[32] only as frequencies were too small for full adjustment. Results of modeling are presented as estimates with 95% confidence intervals. Analyses were done using Stata v17.

3 | RESULTS

One hundred and fifty UKOS participants attended for lung function assessment at a mean age of 18 years. The mean height and weight were greater in the males than females. There were no other significant differences in the demographics by sex although the administration of postnatal corticosteroids in the neonatal period was more common among males than females (Table 1). The participants who were assessed at age 16–19 years had higher mean birthweight and gestational age 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 a pulmonary hemorrhage (Supporting Information: E-Table 1).

Males had poorer mean FEF_{75}, FEF_{50}, FEF_{25-75} FEV_1:FVC ratio, DLCO, and D_LCO/VA compared with females and the differences remained significant after adjusting for neonatal factors and age at assessment (Table 2). These differences in mean *z* scores ranged from 0.19 to 0.71 and translated into substantial differences in the percentage of participants with lung function below the 5th centile (below the limit of normal). For example, for FEF_{75}, 39.6% males and 20.1% females had lung function that was below the limit of normal with an adjusted difference of 19.5 percentage points (Table 3).

Males were able to complete a significantly greater distance during the shuttle sprint test and reported doing more exercise each week (Table 4). Sixteen percent of participants reported wheeze in the past 12 months and around 9% reported asthma but neither varied significantly by sex (Table 4).

A post hoc analysis of lung function was conducted including an interaction term for sex × exercise in the model to attempt to explore the finding that boys had poorer mean lung function but had greater mean exercise capacity. This showed that for most lung function measures, the interaction term was not significant (Supporting Information: E- Table 2), but significant interactions were observed for FRC_{He} and resistance at 20 Hz.

TABLE 1 Demographics by sex.

	Male	Female	*p* value[a]
N (max)	70	80	
Gestation (wks)	26.8 (1.5)	27.0 (1.4)	0.474
Birthweight (g)	925 (211)	882 (225)	0.207
Birthweight *z* score	−0.57 (0.93)	−0.58 (1.08)	0.797
Antenatal steroids	63 (91%)	72 (90%)	0.375
Postnatal surfactant	68 (97%)	77 (96%)	0.763
High frequency oscillation ventilation (vs. CV) at birth	37 (53%)	40 (50%)	0.714
Oxygen dependency at 36 wks	42 (60%)	36 (45%)	0.089
Postnatal steroids	24 (34%)	17 (21%)	0.085
Age at assessment (yrs)	18.1 (0.8)	17.9 (0.8)	0.281
Height at assessment (cm)	173.3 (6.5)	161.7 (7.0)	<0.001
Weight at assessment (kg)	70.0 (18.3)	57.9 (10.9)	<0.001
Maternal smoking in pregnancy	15 (22%)	13 (18%)	0.568
Participant active smoker[b]	10 (14%)	8 (10%)	0.448
Past history of asthma	21 (31%)	20 (25%)	0.441

Note: Data are demonstrated as the mean (SD) or *n* (%).

[a]*p* value allows for nonindependence due to multiple births.

[b]Either self-reported or salivary cotinine >15 ng/mL.

4 | DISCUSSION

We have demonstrated that at 16–19 years of age, males compared with females had a significantly lower mean FEF_{75}, indicating they had poorer small airway function. This difference is equivalent to a difference of 20 percentage points in the proportion with lung function below the limit of normal. This difference remained after adjusting for neonatal factors including postnatal corticosteroid exposure and age at assessment. Similar differences were seen for many of the lung function measurements including obstruction (FEV_1/FVC) and diffusion capacity of the lungs for carbon dioxide. There were no significant differences seen with regard to restrictive lung disease. The poorer lung function in the males, however, was not associated with poorer exercise capacity, indeed the males had better exercise performance.

Physical fitness within the general population is due to a combination of factors such as muscle strength [33] and cardiovascular fitness.[34] The complex relationships between individual factors and exercise performance have rarely been studied in the context of investigating differences between males and females.[35] In studies that have been undertaken, it has been shown that muscle mass relative to lean mass was higher in males compared with females and this correlated with improved exercise performance.[33] Higher birthweight has been associated with greater hand grip strength in adolescents especially in females, these associations may be explained by fat-free mass.[36] In addition, improved cardiovascular markers such as resting heart rate and blood pressure were also positively associated with improved exercise capacity as measured by VO_2max.[34] In one study, VO_2max was 10% higher in elite male athletes compared with elite female athletes.[37] These factors may have benefited male participants and overcome any deficiencies in lung function in males compared with females. It is important to note, however, that it has been shown that those with the poorest lung function have impaired exercise capacity suggesting that, while it is not a linear relationship, lung function is an important contributor to exercise capacity.[24]

Airway hyper-responsiveness has been shown to be higher in those born prematurely.[38] There were no significant differences seen between males and females in this cohort with regard to reported respiratory symptoms. This was despite more males having obstructive lung disease defined as an FEV_1/FVC ratio below the 5%

TABLE 2 Lung function by sex lung function is demonstrated as *z* scores, with the exception of LCI (*N* = 150 maximum).

	Total[a]	Males mean (SD)	Females mean (SD)	Difference (95% CI) (Males-females)[b]	Adjusted Difference (95% CI)[c] (Males-females)	*p* value
FEF_{75}	150	−1.42 (1.25)	−0.63 (1.16)	−0.71 (−1.09, −0.33)	−0.60 (−0.97, −0.24)	0.001
FEF_{50}	150	−1.23 (0.98)	−0.74 (1.09)	−0.45 (−0.78, −0.12)	−0.39 (−0.72, −0.07)	0.017
FEF_{25}	150	−0.81 (1.13)	−0.46 (1.16)	−0.36 (−0.71, −0.01)	−0.28 (−0.62, 0.06)	0.104
FEF_{25-75}	150	−1.86 (1.25)	−1.08 (1.20)	−0.71 (−1.09, −0.32)	−0.62 (−0.98, −0.26)	0.001
FEV_1	150	−1.17 (1.32)	−0.85 (1.31)	−0.33 (−0.74, 0.09)	−0.19 (−0.59, 0.22)	0.364
FVC	150	−0.07 (1.27)	−0.38 (1.39)	0.26 (−0.17, 0.69)	0.38 (−0.07, 0.82)	0.098
FEV_1/FVC	150	−1.55 (1.15)	−0.75 (1.15)	−0.73 (−1.10, −0.36)	−0.71 (−1.09, −0.34)	<0.001
PEF	150	−0.54 (1.04)	−0.36 (1.14)	−0.17 (−0.49, 0.16)	−0.15 (−0.48, 0.18)	0.375
DLCO	146	−1.20 (1.05)	−0.83 (1.11)	−0.37 (−0.72, −0.02)	−0.41 (−0.78, −0.03)	0.033
DLCO/VA	146	−2.36 (0.86)	−1.82 (0.87)	−0.54 (−0.82, −0.27)	−0.57 (−0.86, −0.28)	
FRC_{pleth}	149	0.74 (1.53)	0.47 (1.15)	0.27 (−0.16, 0.70)	0.37 (−0.07, 0.80)	0.097
FRC_{He}	144	0.80 (2.16)	0.45 (1.92)	0.35 (−0.30, 1.00)	0.51 (−0.16, 1.18)	0.133
RV	149	1.04 (1.30)	1.04 (1.37)	0.00 (−0.43, 0.43)	0.11 (−0.31, 0.53)	0.610
TLC	149	0.88 (1.25)	0.79 (1.10)	0.07 (−0.31, 0.44)	0.18 (−0.21, 0.57)	0.370
Resistance at 5 H_z	148	−0.08 (1.13)	−0.21 (1.12)	0.13 (−0.23, 0.49)	0.10 (−0.26, 0.47)	0.578
Resistance at 20 H_z	148	0.29 (1.02)	0.33 (1.00)	−0.04 (−0.36, 0.28)	−0.09 (−0.42, 0.24)	0.612
LCI	120	9.12 (1.71)	9.39 (1.47)	−0.26 (−0.82, 0.31)	−0.34 (−0.92, 0.23)	

Abbreviations: FEF_{75}, forced expiratory flow at 75%; FEF_{50}, forced expiratory flow at 50%; FEF_{25}, forced expiratory flow at 25%; FEF_{25-75}, forced expiratory flow at 25-75%; FEV_1, forced expiratory volume in the first one second; FRC_{pleth}, funtional residual capacity measured by plethsmogprahy; FVC, forced vital capacity of the lungs; LCI, lung clearance index; PEF, peak expiratory flow; RV, residual volume.

[a]Totals vary due to missing data.

[b]Difference allows for nonindependence of multiple births.

[c]Lung function adjusted for antenatal steroids, birthweight, gestation, oxygen dependency at 36 weeks corrected gestation, postnatal steroids, maternal smoking in pregnancy, participant age at assessment, and allows for nonindependence of multiple births.

centile.[20] Indeed, only 16% of both males and females stated they had wheeze in the last 12 months, yet 22% of females and 46% of males had obstructive lung disease. Indeed, while it is noted that this study did not have a control group, both males and females were noted to have *z* scores for airway function and DLCO that are below zero in keeping with another study that showed deficits in FEV_1 in both boys and girls born prematurely.[39] This suggests there may be under-reporting of symptoms in both groups. These data are in contrast to a previous study using population-based questionnaires that reported that, in those born at less than 32 weeks gestation, females born prematurely (29%) were more likely to have asthma at 19 years of age compared with their male peers (17%).[7] Furthermore, in that study, a regression analysis of factors influencing wheeze, female gender was found to be a significant variable (odds ratio [OR]: 2.0, 95% confidence interval [CI]: 1.2 to 3.2). These differences may be due to differences in populations as in that study where infants were born at a later gestational age and were not routinely exposed to antenatal corticosteroids or postnatal surfactant. In our study, only 15% of the study population had wheeze and 9% had asthma whereas in the previous study 30% had wheeze and 13% reported having asthma. Similar to our results, that study found no significant relationship of sex and a diagnosis of asthma.

Our results do not explain the findings of one study where females born prematurely were more likely to develop COPD in adulthood.[8] It has been shown that lung function may improve in both boys and girls born prematurely[40] yet, while it is recognized that lung function declines throughout adulthood,[21] few data exist to describe the decline in those born prematurely and routinely exposed to antenatal corticosteroids and postnatal surfactant. It would therefore be important to examine in longitudinal studies, if there are differences in the decline in lung function between males and females born prematurely.

This study has strengths and limitations. More than 90% of the study population were exposed to antenatal corticosteroids and postnatal surfactant and the participants underwent a comprehensive suite of lung function tests. Although there were some significant

TABLE 3 Percentage with abnormal lung function (<5th centile) by sex ($N = 150$ max).

Lung function measure	Males % with abnormal lung function	Females % with abnormal lung function	Adjusted difference: percentage points (95% CI) (Males-females)	*p* value[a]
FEF_{75}	39.6	20.1	19.5% (10.0, 29.0)	0.001
FEF_{50}	32.1	18.7	13.5% (4.6, 22.3)	0.017
FEF_{25}	21.1	14.1	7.0% (−0.3, 14.2)	0.104
FEF_{25-75}	57.2	34.3	22.9% (12.2, 33.5)	0.001
FEV_1	32.6	27.0	5.6% (−4.1, 15.3)	0.364
FVC	10.4	16.8	−6.4% (−12.4, −0.3)	0.098
FEV_1/FVC	46.0	22.4	23.7% (13.8, 33.5)	<0.001
PEF	14.4	11.3	3.1% (−2.7, 9.0)	0.375
DLCO	34.3	21.7	12.6% (3.2, 22.1)	0.033
DLCO/VA	NA			
FRC_{pleth}	24.6	16.3	8.3% (0.3, 16.2)	0.097
FRC_{He}	36.2	26.9	9.3% (−0.8, 19.4)	0.133
RV	33.0	29.8	3.2% (−6.7, 13.1)	0.610
TLC	1.2	1.8	−0.6% (−1.7, 0.5)	0.370
Resistance at 5 H_z	4.6	3.7	0.9% (−1.6, 3.4)	0.578
Resistance at 20 H_z	6.9	8.1	−1.3% (−5.3, 2.7)	0.612
LCI	NA			

Abbreviations: FEF_{75}, forced expiratory flow at 75%; FEF_{50}, forced expiratory flow at 50%; FEF_{25}, forced expiratory flow at 25%; FEF_{25-75}, forced expiratory flow at 25-75%; FEV_1, forced expiratory volume in the first one second; FRC_{pleth}, funtional residual capacity measured by plethsmogprahy; FVC, forced vital capacity of the lungs; LCI, lung clearance index; NA, not available as cannot be calculated; PEF, peak expiratory flow; RV, residual volume.

[a]Adjusted difference in percentages lung function adjusted for antenatal steroids, birthweight, gestation, oxygen dependency at 36 weeks corrected gestation, postnatal steroids, maternal smoking in pregnancy, participant age at assessment, and allows for nonindependence of multiple births.

TABLE 4 Exercise and respiratory outcomes by sex.

	Total	Males *n* (%) in category	Females *n* (%) in category	Unadjusted *p* value[a]	Adjusted *p* value[b]
Exercise distance test	126			<0.001	<0.001
<1000 m		12 (19%)	38(60%)		
1000–1249 m		22 (35%)	22 (35%)		
1250–1500 m		29 (46%)	3 (4.8%)		
Self-reported exercise	143			0.053	0.016
None		18 (26%)	24 (32%)		
Up to 1 h/day		31 (45%)	41 (55%)		
More than 1 h/day		20 (29%)	9 (12%)		
Any wheeze in last 12 months	148	11 (16%)	13 (16%)	0.935	0.906
Current asthma	149	7 (10%)	7 (8.8%)	0.770	0.779

[a]Logistic regression model that allows for non-independence of multiple births.

[b]Logistic regression model that allows for non-independence of multiple births and adjusts for postnatal steroids.

differences between those who were and were not recruited, these were the minority of factors and thus we do feel our results are generalizable. Participants completed a standardized exercise capacity test, while not the gold standard of assessing VO_2max, the results of the shuttle test have been shown to correlate well with those of VO_2max.[25] Furthermore, using this test in a rehabilitation program, a difference of 48 m correlated with symptomatic benefit and a further benefit was seen with a difference of 79 m.[41] The mean difference between males and females in this study was 227 m and therefore clinically significant and higher than the 10% difference in VO_2max observed within a previous population.[37] We do acknowledge that this is a single measure of physical fitness and more comprehensive testing may be of benefit in the future.[42] Puberty was not assessed at this follow-up, however, as the average length of puberty is between 2 and 5 years[27,28] and almost all participants had entered puberty at an earlier assessment, we are confident that we are presenting postpubertal lung function. In general, the interaction results were inconclusive, probably due to the relatively low power and hence we will be further investigated in a proposed larger study.

In conclusion, among young people born prematurely, males had poorer lung function compared with females, but this was not accompanied by reduced exercise capacity or increased respiratory symptoms at that time. Whether this difference persists into young adulthood needs assessing.

AUTHOR CONTRIBUTIONS

Christopher Harris: Conceptualization; data curation; formal analysis; writing — original draft; writing — review & editing. **Alan Lunt**: Data curation. **Janet Peacock**: Conceptualization; formal analysis; writing — original draft; writing — review & editing. **Anne Greenough**: Conceptualization; formal analysis; writing — original draft; writing — review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable 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.

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