

Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight: a meta-analysis of individual participant data



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Summary

Background Maximal expiratory airflow peaks early in the third decade of life, then gradually declines with age. The pattern of airflow through adulthood for individuals born very preterm (at <32 weeks' gestation) or with very low birthweight (<1501 g) is unknown. We aimed to compare maximal expiratory airflow in these individuals during late adolescence and early adulthood with that of control individuals born with normal birthweight (>2499 g) or at term.

Methods We did a meta-analysis of individual participant data from cohort studies, mostly from the pre-surfactant era. Studies were identified through the Adults born Preterm International Collaboration and by searching PubMed and Embase (search date May 25, 2016). Studies were eligible if they reported on expiratory flow rates beyond 16 years of age in individuals born very preterm or with very low birthweight, as well as controls born at term or with normal birthweight. Studies with highly selected cohorts (eg, only participants with bronchopulmonary dysplasia) or in which few participants were born very preterm or with very low birthweight were excluded. De-identified individual participant data from each cohort were provided by the holders of the original data to a central site, where all the data were pooled into one data file. Any data inconsistencies were resolved by discussion with the individual sites concerned. Individual participant data on expiratory flow variables (FEV₁, forced vital capacity [FVC], FEV₁/FVC ratio, and forced expiratory flow at 25–75% of FVC [FEF_{25–75%}]) were converted to Z scores and analysed with use of generalised linear mixed models in a one-step approach.

Findings Of the 381 studies identified, 11 studies, comprising a total of 935 participants born very preterm or with very low birthweight and 722 controls, were eligible and included in the analysis. Mean age at testing was 21 years (SD 3·4; range 16–33). Mean Z scores were close to zero (as expected) in the control group, but were reduced in the very preterm or very low birthweight group for FEV₁ (–0·06 [SD 1·03] vs –0·81 [1·33], mean difference –0·78 [95% CI –0·96 to –0·61], p<0·0001), FVC (–0·15 [0·98] vs –0·38 [1·18], –0·25 [–0·40 to –0·10], p=0·0012), FEV₁/FVC ratio (0·14 [1·10] vs –0·64 [1·35], –0·74 [–0·85 to –0·64], p<0·0001), and FEF_{25–75%} (–0·04 [1·10] vs –0·95 [1·47], –0·88 [–1·12 to –0·65], p<0·0001). Similar patterns were observed when we compared the proportions of individuals with values below the fifth percentile.

Interpretation Individuals born very preterm or with very low birthweight are at risk of not reaching their full airway growth potential in adolescence and early adulthood, suggesting an increased risk of chronic obstructive pulmonary disease in later adulthood.

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Introduction

Maximal expiratory airflow, which reflects airway growth, increases throughout childhood and peaks early during the third decade of life, then slowly declines with age, with only small differences in the pattern of change with age between male and female individuals.¹ In older people with normal lung function, the gradual decline in

airflow with age is not a concern because these individuals are likely to die from other causes before airflow declines enough to cause symptoms. However, an excessive rate of decline in airflow, as can occur with tobacco smoking, is of concern and leads to a higher incidence of chronic obstructive pulmonary disease (COPD) in adulthood.² Similarly, individuals who do not

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Research in context

Evidence before this study

Airflow capacity peaks early in the third decade of life, then slowly declines with age in healthy people, but this trajectory is less clear in individuals born very preterm (<32 weeks' gestational age) or with very low birthweight (<1501 g). We identified relevant studies through the Adults born Preterm International Collaboration (APIC) and through searching PubMed and Embase for studies of lung function in late adolescence or early adulthood in humans using the terms "respiratory function OR lung function OR spirometry" combined with "preterm OR low birth weight" (searched May 25, 2016). Individual cohort studies of airflow capacity in late adolescence or early adulthood in individuals born very preterm or with very low birthweight have mainly reported reductions in airflow compared with controls (born at term or with normal birthweight), particularly in individuals who had bronchopulmonary dysplasia in the neonatal period. However, the size of the reductions reported is variable, and airflow trajectory in later adulthood is unclear.

Added value of this study

This meta-analysis of individual participant data showed that individuals born very preterm or with very low birthweight are not reaching the normal peak of airway capacity in adolescence and early adulthood, in terms of four different measures of

expiratory flow (FEV₁, forced vital capacity [FVC], FEV₁/FVC ratio, and forced expiratory flow at 25–75% of FVC).

The reductions in airflow capacity at this age in these individuals were substantial, and a significantly higher proportion had expiratory flow rates in concerning clinical ranges (below the fifth percentile) compared with people born at term or with normal birthweight. There was no evidence to suggest that the rate of change in airway capacity improves between the ages of 18 years and 25 years in those born very preterm or with very low birthweight compared with controls, and it could even be worse. Bronchopulmonary dysplasia in the neonatal period exacerbates this disadvantage.

Implications of all available evidence

General practitioners or specialists seeing adult patients need to be aware that increasing numbers of infants born very preterm or with very low birthweight are now surviving into adulthood, and that many of them will present with symptoms of airflow obstruction. These physicians should know the gestational age and birthweight of their patients with respiratory disease and be aware that patients who were born very preterm or with very low birthweight, particularly those who had bronchopulmonary dysplasia, are at high risk of chronic obstructive pulmonary disease in later life.

reach their expected peak airflow might also develop symptoms of COPD earlier in adulthood than expected.

The development of prenatal and neonatal care in the past 40 years has improved the prognosis for infants born very preterm (<32 weeks' gestation) or with very low birthweight (<1501 g), who constitute 1–2% of all births worldwide.³ Many people who survived very preterm birth or very low birthweight in this period have reached adulthood, with the number of such survivors born in the 1970s and 1980s estimated to be more than half a million in the USA.^{4,5} Therefore, questions related to their health are increasingly relevant. These individuals have reduced airflow in childhood compared with those born with normal birthweight (>2499 g), a difference that persists into early adulthood.^{6–14} Furthermore, bronchopulmonary dysplasia in the neonatal period is associated with even lower airflow among survivors of very preterm birth or very low birthweight.^{6–8,10,11,13,14} Apart from bronchopulmonary dysplasia, it is unclear how airflow in early adulthood in these survivors is related to other perinatal events (such as antenatal corticosteroid treatment, gestational age at birth, fetal growth rate), sex, or tobacco smoking, partly because existing studies are based on single cohorts with limited statistical power. Moreover, the rate of decline in airflow with age beyond the peak of maximal airflow capacity in adults born very preterm or with very low birthweight is unknown.

In this individual patient data meta-analysis, we aimed to compare airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight, mostly in the pre-surfactant era, with that in normal birthweight or term-born controls, including the trajectory of airflow after the expected peak early in the third decade of life, and to identify perinatal and demographic risk factors and protective associations with airflow among individuals born preterm. We hypothesised that individuals born very preterm or with very low birthweight would have worse airflow than that of controls, and that those who additionally had bronchopulmonary dysplasia or were smokers would have even worse airflow.

Methods

Search strategy and selection criteria

Through the Adults born Preterm International Collaboration (APIC), we identified studies potentially suitable for inclusion in an individual patient data meta-analysis. APIC was formed in 2011 and comprises research groups from around the world with health data on cohorts of participants born very preterm or with very low birthweight who had been followed up into late adolescence or early adulthood.¹⁵ We also searched PubMed and Embase for published studies of lung function in late adolescence or early adulthood in humans using the terms "respiratory function OR lung function OR spirometry" combined

with “preterm OR low birth weight” (searched May 25, 2016), with no language or other restrictions.

We included cohort studies of survivors born very preterm or with very low birthweight, in which normal birthweight or term-born controls were also studied, and in which the age of participants when measuring expiratory flows was 16 years or older. We excluded highly selected cohorts, such as just those with bronchopulmonary dysplasia from a single site or for which controls were not included, cohort studies in which all birthweights or gestational ages were studied but very few were born very preterm or with very low birthweight relative to the number of participants more mature and heavier at birth, and studies in which it was impossible to ascertain whether the individuals studied represented the sample of all possible survivors from the hospitals or geographical regions concerned. Methods and criteria for the selection of controls varied from study to study (appendix).

Participants in each cohort had been recruited after providing informed consent and each study had been approved by the appropriate institutional review boards. When required, investigators obtained separate permission from their institutional review board to submit data for the individual patient data meta-analysis. Written agreements were obtained for transfer of data between the Murdoch Children’s Research Institute, where the data were pooled and analysed, and the other centres that provided data. Non-identifiable data were then transferred for analysis.

Data requested

Perinatal data including year of birth, antenatal corticosteroid therapy, gestational age at birth, birthweight, sex, and presence of bronchopulmonary dysplasia, were requested from the holders of the data for each study and pooled at a central site. Birthweight Z scores were computed for age and sex, relative to the British Growth Reference.¹⁶ The definition of bronchopulmonary dysplasia varied between studies, from either oxygen dependency at age 28 days with or without chest X-ray changes consistent with Northway’s classification,¹⁷ to oxygen dependency at 36 weeks’ postmenstrual age.¹⁸ At the time of lung function assessment, a history of current tobacco smoking was obtained.

Measures of expiratory flow

In all cohorts, forced expiratory flow was measured by spirometry according to the American Thoracic Society and European Respiratory Society guidelines,¹⁹ or equivalent guidelines at the time when the cohorts were studied. The following values were obtained: FEV₁, forced vital capacity (FVC), FEV₁/FVC ratio, and forced expiratory flow at 25–75% of FVC (FEF_{25–75%}). We did not collect data on bronchodilator responses because these responses were not measured in all studies or were measured only in subsets of participants with low expiratory flows.

Expiratory flows were converted to Z scores for age, height, sex, and ethnicity, relative to the Global Lung

Initiative 2012 reference values.²⁰ The proportions of participants with clinically important values for airflow (below the fifth percentile) were computed.

Statistical analysis

We were primarily interested in the difference in mean scores between the group born very preterm or very low birthweight and the control groups, and the difference in the proportions of participants with values less than the fifth percentile between those two groups. Within the group born very preterm or very low birthweight, we were also interested in the independent contributions of perinatal events, active smoking, age at testing, and year of birth. Data were analysed with use of Stata 15.1 software, using generalised linear mixed models with robust standard errors in a one-step approach. For each dependent variable, we considered both a random intercept model (including a random effect for study site) and a random intercept and slope model (by adding a random effect to allow for different relationships between very preterm birth or very low birthweight and control groups among the different study sites), and compared these models by the change in likelihood ratio χ^2 between the two. We also attempted to add a third random effect to account for more than one measurement being taken at two different ages at two study sites; however, in some analyses, the models did not converge with the third random effect, so it was not included in any analyses. Expiratory flow data from participants born very preterm or with very low birthweight were compared with those of controls by the inclusion of a fixed effect for group.

The proportions of participants with low values for each expiratory value were also contrasted between groups using mixed models, with a random effect for study site and random effect to allow for different relationships between very preterm birth or very low birthweight and control groups among the different study sites, as well as a fixed effect for group.

To establish the trajectory of decline after the expected peak of maximal airway capacity in individuals born very preterm or with very low birthweight, the relationships of expiratory flows with age at testing were repeated in subgroup analyses limited to those participants older than 21 years of age. In the two studies where the same participants were tested at two ages (around 18 years and 25 years), the differences in airway capacity between the ages were analysed with use of mixed models with a random effect for the two different sites, with and without adjustment for the baseline expiratory flow values for each variable. Within the very preterm birth or very low birthweight group, univariable relationships of expiratory flows with antenatal corticosteroids, gestational age, birthweight Z score, sex, bronchopulmonary dysplasia, current smoking, year of birth, and age at testing were explored, and then all variables were entered in multivariable analyses to ascertain the independent associations of these variables with expiratory flows.

See Online for appendix

	Country	Data source	Birth years	Eligibility criteria*	Mean age (range) at testing, years*	Very preterm or very low birthweight group (n)	Control group (n)
Doyle et al (2006); ²¹ Gibson et al (2015) ⁶	Australia	Single hospital	1977–82	Birthweight <1501 g	First measured at age 19 (18–22), then at age 26 (24–29)	146 at first measurement; 87 at second measurement	37 at first measurement; 19 at second measurement
Saarenpää et al (2015) ⁷	Finland	Single hospital†	1978–85	Birthweight <1501 g	22 (18–27)	160	162
Gough et al (2014) ⁸	Northern Ireland, UK	Single hospital	1978–93	Bronchopulmonary dysplasia and birthweight <1501 g	26 (18–33)	100	78
Narang et al (2008) ⁹	England, UK	Single hospital	1979–80	Birthweight <2000 g and <37 weeks' gestational age at birth	22 (19–25)	38	48
Vrijlandt et al (2006) ¹⁰	Netherlands	Two hospitals	1983	Birthweight <1500 g or <32 weeks' gestational age at birth	20 (19–21)	41	53
Vollsaeter et al (2013, 2015); ^{11,13} Halvorsen et al (2004) ²²	Norway	Regional	1982–85	Birthweight <1001 g or <29 weeks' gestational age at birth	First measured at age 18 (16–20), then at age 25 (24–26)	41 at first measurement; 45 at second measurement	42 at first measurement; 39 at second measurement
Evensen et al (2009) ¹²	Norway	Regional	1986–88	Birthweight <1501 g	18 (17–19)	38	63
Vollsaeter et al (2015) ¹³	Norway	Regional	1991–92	Birthweight <1001 g or <29 weeks' gestational age at birth	19 (17–20)	31	28
Doyle et al (2017) ¹⁴	Australia	Regional	1991–92	Birthweight <1000 g or <28 weeks' gestational age at birth	18 (16–20)	208	153

*Criteria for inclusion in original study; the numbers in this table relate only to very preterm or very low birthweight groups or control groups (ie, individuals born preterm at ≥ 32 weeks' gestational age and with birthweight ≥ 1501 g are not included). †The only tertiary hospital within a geographical region.

Table 1: Demographic characteristics of published studies with expiratory flow data reported in late adolescence or early adulthood in individuals born very preterm or with very low birthweight and controls

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

After searching the literature, and from prior knowledge of existing studies, a total of 381 studies were screened, of which 11 met the eligibility criteria (table 1).^{6–14,21,22} In two cohorts, measurements were obtained twice from some participants, at around 18 years of age^{11,21,22} and again at around 25 years of age.^{6,11,22} One site recruited cohorts from two different eras.¹¹ Two studies did not measure $FEF_{25-75\%}$.^{10,12} A repeat literature search in January, 2018, did not identify any additional potentially eligible cohorts. Across the 11 studies, there were 935 individuals born very preterm or with very low birthweight and 722 controls with airflow data available for analysis. The studies were from six different high-income countries. Around half were regional studies, with years of birth ranging from 1977 to 1993, and the mean age of participants at the time of testing was 21 years (SD 3; range 16–33). Among the 1657 participants in both birth groups, 1592 (96.1%) were white, 30 (1.8%) were southeast Asian, 25 (1.5%) were other or mixed race, nine (0.5%) were black, and one (0.1%) was northeast Asian.

Among the participants born very preterm or with very low birthweight, the proportions who received antenatal corticosteroid therapy ranged from 6% to 71%

across the cohorts, mean gestational ages and birthweights decreased over time, around 47% were male and 53% were female, and surfactant treatment was uncommon until births in the 1990s (table 2). The proportion of participants who were current smokers ranged from 3% to 39%.

There was some evidence of improved model fit with the random intercepts and slope models compared with the random intercept only models for FEV_1 and $FEF_{25-75\%}$ Z scores, but not for FVC or for FEV_1/FVC ratio Z scores (appendix). Importantly, the conclusions regarding differences between the very preterm or very low birthweight group and control group were unchanged, with little changes in the estimates of the differences between groups for the two models (appendix). We subsequently report data only from models with both the random intercepts and random slopes for all outcomes for consistency.

Mean Z scores for expiratory flow rates in the control group were close to the expected values of zero, whereas the very preterm or very low birthweight group had significantly lower mean Z scores for all measures of expiratory flow, with mean difference ranging from -0.25 (95% CI -0.40 to -0.10) for FVC to -0.88 (-1.12 to -0.65) for $FEF_{25-75\%}$ (table 3). Maternal smoking in pregnancy (for which data were missing for 540 [33%] participants) was associated with reductions in Z scores for all airflows except FVC; adding maternal smoking to the models changed the differences between the very preterm birth or very low birthweight group and control group by less than 0.03 SD and altered no conclusions.

In the very preterm or very low birthweight group,

	N	Antenatal corticosteroid use	Gestational age at birth, weeks	Birthweight		Sex		Surfactant use	Bronchopulmonary dysplasia	Current smoking of participants
				Mean, g	Z score	Female	Male			
Doyle et al (2006) ²¹	146	77 (53%)	28.8 (2.0)	1095 (234)	-0.73 (1.00)	76 (52%)	70 (48%)	0	33 (23%)*	49 (34%)
Gibson et al (2015) ⁶	87	46 (53%)	28.4 (1.9)	1035 (212)	-0.78 (1.02)	49 (56%)	38 (44%)	0	24 (28%)*	28 (32%)
Saarenpää et al (2015) ⁷	160	10 (6%)	29.2 (2.2)	1126 (218)	-0.80 (1.11)	92 (58%)	68 (43%)	7 (4%)	29 (18%)*	60 (38%)
Gough et al (2014) ⁸	100	31 (31%)	28.9 (2.9)	1078 (280)	-0.92 (1.20)	53 (53%)	47 (47%)	18/58 (31%)†	58 (58%)‡	16 (16%)
Narang et al (2008) ⁹	38	11 (29%)	30.1 (2.4)	1250 (239)	-0.86 (1.31)	14 (37%)	24 (63%)	0	7 (18%)*	15 (39%)
Vrijlandt et al (2006) ¹⁰	41	4 (10%)	29.9 (2.5)	1247 (232)	-0.66 (1.58)	20 (49%)	21 (51%)	0	9 (22%)*	13 (32%)
Halvorsen et al (2004) ²²	41	12 (29%)	27.3 (1.5)	1035 (185)	-0.05 (1.05)	19 (46%)	22 (54%)	0	31 (76%)‡	15 (37%)
Vollsaeter et al (2013), ¹¹ Vollsaeter et al (2015) ¹³	45	16 (36%)	27.4 (1.5)	1006 (193)	-0.27 (1.16)	19 (42%)	26 (58%)	0	34 (76%)‡	14 (31%)
Evensen et al (2009) ¹²	38	21 (55%)	29.2 (2.5)	1242 (203)	-0.26 (1.27)	18 (47%)	20 (53%)	0	7 (18%)‡	11/36 (31%)
Vollsaeter et al (2015) ¹³	31	12 (39%)	26.8 (1.8)	942 (209)	-0.21 (1.06)	18 (58%)	13 (42%)	16 (52%)	24 (77%)‡	1 (3%)
Doyle et al (2017) ¹⁴	208	148 (71%)	26.7 (2.0)	889 (162)	-0.35 (1.33)	115 (55%)	93 (45%)	83 (40%)	77 (37%)§	43 (21%)
Overall	935	388 (41%)	28.3 (2.4)	1054 (241)	-0.59 (1.21)	493 (53%)	442 (47%)	124/855 (15%)	333 (36%)	265 (28%)

Data are n (%), n/N (%), or mean (SD). *Bronchopulmonary dysplasia defined as oxygen requirement after 28 days and chest X-ray consistent with Northway Stage 3 or 4 changes.²⁷ †Reported for bronchopulmonary dysplasia subgroup only. ‡Bronchopulmonary dysplasia defined as oxygen requirement after 28 days. §Bronchopulmonary dysplasia defined as oxygen dependency at 36 weeks' postmenstrual age.

Table 2: Clinical characteristics of very preterm and very low birthweight participants by cohort

	Mean Z score (SD)		Mean difference in Z score (95% CI)*	p value*	Participants with values <5th percentile, n/N (%)		Odds ratio (95% CI)*	p value*
	Very preterm or very low birthweight group	Control group			Very preterm or very low birthweight group	Control group		
FEV ₁	-0.81 (1.33), N=935	-0.06 (1.03), N=722	-0.78 (-0.96 to -0.61)	<0.0001	221/935 (24%)	50/722 (7%)	4.16 (2.99 to 5.78)	<0.0001
FVC	-0.38 (1.18), N=935	-0.15 (0.98), N=722	-0.25 (-0.40 to -0.10)	0.0012	100/935 (11%)	42/722 (6%)	2.12 (1.44 to 3.14)	<0.0001
FEV ₁ /FVC ratio	-0.64 (1.35), N=935	0.14 (1.10), N=722	-0.74 (-0.85 to -0.64)	<0.0001	213/935 (23%)	40/722 (6%)	5.09 (3.54 to 7.30)	<0.0001
FEF _{25-75%}	-0.95 (1.47), N=851	-0.04 (1.10), N=606	-0.88 (-1.12 to -0.65)	<0.0001	247/851 (29%)	46/606 (8%)	4.50 (2.82 to 7.19)	<0.0001

FVC=forced vital capacity. FEF_{25-75%}=forced expiratory flow at 25–75% of FVC. *From individual participant data meta-analysis.

Table 3: Comparison of expiratory flow variables in very preterm and very low birthweight group and control group

23–29% of individuals had Z scores below the fifth percentile for FEV₁, FEV₁/FVC ratio, and FEF_{25-75%}, and 11% had FVC Z scores below the fifth percentile. All these proportions were significantly higher than those in the control group, which were close to the expected value of 5% (table 3).

There was little heterogeneity between the studies, with I² values of 2.0% for FEV₁, 0.4% for FVC, 0.2% for FEV₁/FVC ratio, and 5.7% for FEF_{25-75%} Z scores. Forest plots for each variable are shown in the appendix.

Because most cohorts were selected by birthweight only, most participants (927 [99%] of 935) in the very preterm birth or very low birthweight group had very low birthweight. However, 841 (90%) were also born very preterm. Summary values for expiratory flow variables were similar, regardless of the eligibility criteria used to define the very preterm birth or very low birthweight cohort (appendix).

669 participants were assessed at older than 21 years of age, of whom 360 were born very preterm or with very low birthweight, and 309 were controls. Among this

group of older participants, the rate of change in Z scores with age was less in the very preterm or very low birthweight group than in the control group for FVC (coefficient for difference in slopes between groups -0.06 [95% CI -0.10 to -0.02], p_{interaction}=0.0015), but not for FEV₁ (-0.05 [-0.09 to 0.001], p_{interaction}=0.058), FEV₁/FVC ratio (0.03 [-0.02 to 0.09], p_{interaction}=0.25), or FEF_{25-75%} (-0.04 [-0.11 to 0.03], p_{interaction}=0.28). For FVC Z score, the evidence for a positive association with age at testing was strong among the control group (0.05 [0.03 to 0.08], p=0.0001), but there was little evidence for any association with age among the very preterm or very low birthweight group (0.00 [-0.04 to 0.05], p=0.84).

117 participants in the very preterm or very low birthweight group and 53 in the control group had airflow measured on two occasions, aged 18 years and 25 years. FEV₁ Z scores increased between 18 years and 25 years of age in both groups by a similar amount (table 4). FVC Z scores increased between 18 years and 25 years of age in both groups, but less so in the very preterm or very low birthweight group, a

	Mean change (SD)		Mean difference in change* (95% CI)	p value	Adjusted mean difference in change*† (95% CI)	p value
	Very preterm or very low birthweight group (N=117)	Control group (N=53)				
FEV ₁ Z score	0.14 (0.67)	0.20 (0.51)	-0.07 (-0.25 to 0.12)	0.48	-0.16 (-0.37 to 0.06)	0.16
FVC Z score	0.20 (0.75)	0.46 (0.51)	-0.26 (-0.46 to -0.07)	0.0071	-0.32 (-0.52 to -0.11)	0.0024
FEV ₁ /FVC ratio Z score	-0.11 (0.77)	-0.43 (0.77)	0.32 (0.07 to 0.57)	0.011	0.02 (-0.23 to 0.27)	0.90
FEF _{25-75%} Z score	0.01 (0.72), N=114	-0.09 (0.70)	0.10 (-0.13 to 0.33)	0.39	-0.15 (-0.40 to 0.10)	0.24

FVC=forced vital capacity. FEF_{25-75%}= forced expiratory flow at 25–75% of FVC. *From individual participant data meta-analysis. †Adjusted for baseline value for expiratory flow.

Table 4: Changes in expiratory flow Z scores between 18 years and 25 years of age in a subset of participants tested at both ages

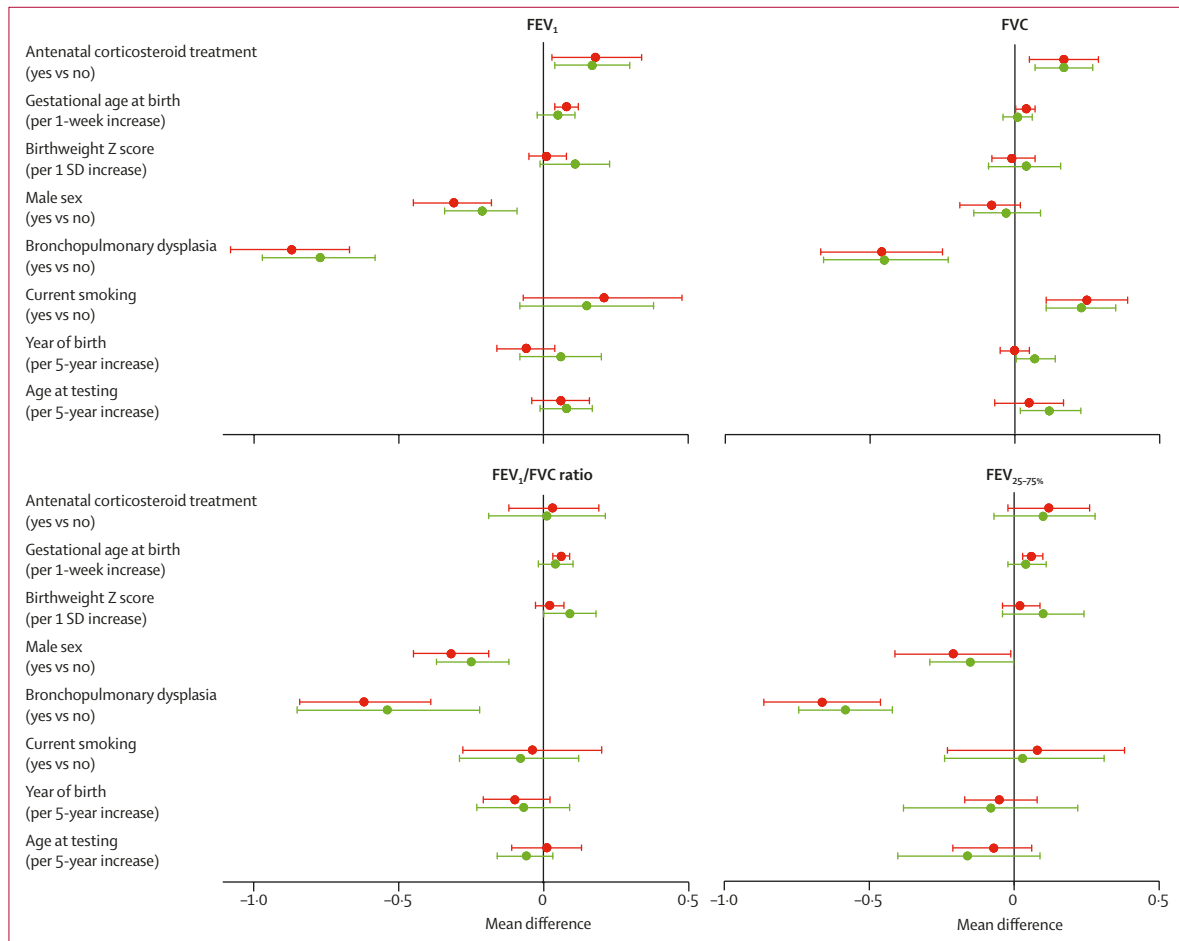


Figure: Associations of expiratory flow rates (Z scores) with perinatal and demographic variables among participants born very preterm or with very low birthweight
 Data are mean difference and 95% CI per change (indicated in brackets) in independent variable. Red lines represent univariable analyses; green lines represent multivariable analyses. See appendix for a table of values. FVC=forced vital capacity. FEF_{25-75%}=forced expiratory flow at 25–75% of FVC.

difference that was sustained after adjusting for the baseline FVC Z score. FEV₁/FVC ratio Z scores decreased in both groups between the two ages, but more so in the control group; however, the difference between the groups disappeared after adjustment for baseline FEV₁/FVC Z score (table 4).

In univariable analyses, gestational age at birth was positively associated with all flow rates, but the evidence for these associations disappeared in the multivariable analyses. FVC Z score increased with year of birth and age at testing, but only on multivariable analyses (figure, appendix). Univariable and multivariable analyses

showed that FEV₁ Z score was increased with antenatal corticosteroid treatment and decreased in individuals who were male or had bronchopulmonary dysplasia; that FVC Z score was increased in those who had antenatal corticosteroids or who were current smokers, and decreased in those who had bronchopulmonary dysplasia; and that both FEV₁/FVC ratio and FEF_{25–75%} Z scores were decreased in males and in those who had bronchopulmonary dysplasia.

Discussion

In this individual participant data meta-analysis, late adolescents and young adults born very preterm or with very low birthweight had substantially reduced airflow and were significantly more likely to have reduced values that were clinically important (ie, below the fifth percentile) than were controls. Among people born very preterm or with very low birthweight, various measures of airflow showed strong independent negative relationships with male sex and bronchopulmonary dysplasia, and positive relationships with antenatal corticosteroid treatment. An unexpected finding was that FVC Z score was increased in individuals exposed to smoking during gestation. As the range of ages of assessment included the age when peak lung growth normally occurs, early in the third decade, it is apparent that infants born very preterm or with very low birthweight are not achieving their full airway growth potential, showing substantially lower Z scores for all expiratory flow measures. In analyses restricted to those older than 21 years of age, there was little evidence for meaningful differences in the rate of change of airflow with age between the groups. Even if the maximal expiratory airflow declines at a normal rate with age in those born very preterm or with very low birthweight, proportionally more will develop COPD later in life than controls. In the general population, 26% of people will develop COPD if they fail to reach a normal airflow plateau in early adulthood.²³ If their maximal expiratory airflow declines at a faster rate, even more adults born very preterm or with very low birthweight will develop COPD; however, it is too soon to know for certain what the rate of decline might be throughout adulthood for these individuals.

The overall results of this meta-analysis are consistent with the data from the individual studies of young adults born very preterm or with very low birthweight compared with controls and, within very preterm or very low birthweight cohorts, data comparing those who did and did not have bronchopulmonary dysplasia.^{6–14} However, this meta-analysis of individual patient data has allowed more precise estimates of effect sizes, assessment of the rate of decline in airflow capacity beyond the early third decade of life, and an investigation of other independent associations of flow rates with variables that is not possible within a typical aggregate-data meta-analysis of cohort studies. We have confirmed that the differences between individuals born very preterm or with very low

birthweight and controls are large, and that a substantially higher proportion of these individuals have airflow values in concerning clinical ranges (below the fifth percentile) compared with controls. Furthermore, among people born very preterm or with very low birthweight, those who had bronchopulmonary dysplasia have even worse expiratory flow rates. The associations of airflow with sex and antenatal corticosteroid treatment have not been previously reported in cohorts of adults born very preterm or with very low birthweight, although one study combining individuals aged 10 years and 17 years did report improved airflow with antenatal corticosteroid treatment.²⁴

To the best of our knowledge, we have included all cohort studies of individuals born very preterm or with very low birthweight who met our eligibility criteria. Four cohort studies that did not meet our criteria were not included. In one of these studies, Northway and colleagues²⁵ investigated 26 highly selected individuals with bronchopulmonary dysplasia, 26 individuals born preterm without bronchopulmonary dysplasia, and 53 term-born controls, all born in the early era of assisted ventilation (1964–73). Because the mean birthweight was more than 1800 g and mean gestational age at birth was more than 33 weeks in the preterm groups, few individuals would have been very preterm or had very low birthweight. That study was also excluded because the results were unlikely to be typical of an era when assisted ventilation was more routine (ie, from the mid-1970s onwards). A study by Wong and colleagues²⁶ was also excluded from our analysis because it included only 21 of 133 individuals from a single hospital who survived bronchopulmonary dysplasia and were born between 1980 and 1987, and included no children born preterm without bronchopulmonary dysplasia and no controls. In a study by Landry and colleagues,²⁷ participants were recruited from those born in Quebec between 1987 and 1993 into one of four groups, with sample sizes of around 30 per group, based on gestational age and respiratory morbidity criteria. However, because it was not possible to ascertain how many infants from the same province might have been eligible within each group during the birth period of these participants, this study was excluded from our analysis. Moschino and colleagues²⁸ assessed lung function from childhood to 24 years of age in 17 participants who had bronchopulmonary dysplasia and who were born in 1991–93; however, that study was excluded because it included no participants without bronchopulmonary dysplasia and no term-born controls. We also excluded studies^{29,30} in which adults of all birthweights and gestational ages at birth were studied, because so few participants would have been very preterm or had very low birthweight relative to the number of potential controls.

The increased FVC Z score in participants who were current smokers versus those who were not (which was not observed for other expiratory flow measures), in both

the very preterm or very low birthweight group and control group, was unexpected. Others have, however, reported that adolescents and young adults who smoke have greater FVCs than those of non-smokers.³¹ Why FVC Z scores might be increased in those exposed to smoking is unclear, but, whatever the explanation, the finding needs to be replicated in individuals born very preterm or with very low birthweight. More importantly, participants in the studies included in our analysis should have airflow measured in later life to ascertain the long-term effects of smoking on expiratory flows in such individuals.

In a follow-up study of 5718 men born in Hertfordshire, UK, during 1911–30, lower birthweight, and presumably increasing prematurity, was associated with higher mortality from COPD and worse respiratory function at 59–70 years of age.³² In another study of 2984 adults born in Sweden between 1925 and 1949 with a birthweight of less than 2100 g or gestational age less than 35 weeks, COPD was more common with either diminishing birthweight or younger gestational age at birth.³³ To date, studies of expiratory airflow in individuals who survived preterm birth and who received modern perinatal or neonatal intensive care have only been done in participants up to around 30–35 years of age, which is too early to detect high incidences of COPD or of death caused by COPD.

Two studies published in 2018 showed that trajectories of expiratory flows track from childhood into adulthood, in one report into the sixth decade³⁴ and in the other report into the third decade of life.³⁵ However, because these studies would have had few participants born very preterm or with very low birthweight, tracking of expiratory flows from childhood into adulthood in this population remains to be shown.

The current study had several limitations. First, because the data were derived mostly from cohorts born before exogenous surfactant was available (from the early 1990s), they are mostly relevant to the thousands of people born very preterm or with very low birthweight before the early 1990s, who are now adults. Therefore, the rate of change in airflow capacity in adults born very preterm or with very low birthweight in the surfactant era remains to be established. Second, the studies included varied in their inclusion criteria, ages at assessment, definitions of bronchopulmonary dysplasia, and respiratory function tests done, resulting in heterogeneous cohorts being studied. The US National Institute of Child Health and Human Development (NICHD) definition of bronchopulmonary dysplasia was published in 2001,¹⁸ after the birth of all the participants in the current study, and the data required to define bronchopulmonary dysplasia per the NICHD definition were not available for all cohorts and thus could not be ascertained retrospectively. Variation between studies can be avoided by agreeing on common protocols and by doing meta-analyses of prospective individual participant data, which should be

the way forward in future studies. However, variation between the studies is also a strength because the reductions in airflow between very preterm birth or very low birthweight groups and control groups were consistent across the studies, and the conclusions are therefore widely applicable to very preterm or very low birthweight cohorts from the same era who have not been studied. Third, we could not analyse data that were not collected consistently across all studies, such as bronchodilator responses to determine the reversibility of airway obstruction, passive smoke exposure in childhood, pack-years of active smoking, or respiratory illnesses through childhood. We also had a substantial amount of missing data on maternal smoking, although adding this factor as a covariate had little effect on any conclusions concerning differences between very preterm or very low birthweight groups and control groups. We did not add asthma as a covariate to any group differences between very preterm or very low birthweight groups and control groups, as asthma might lie along the casual pathway between very preterm birth or very low birthweight and poor expiratory airflow. Fourth, we focused our analyses on participants born very preterm or with very low birthweight combined; however, summary results reported for either individuals born very preterm alone or those born with very low birthweight alone were almost identical. Finally, we did not have data on expiratory flow across a broad range of adult ages to assess the true longitudinal trajectory of expiratory flows into late adulthood in people born very preterm or with very low birthweight, in part because so few individuals survived into adulthood after very preterm birth or very low birthweight before the birth eras of the cohorts included in this study. However, given the clear reductions in airflow in individuals born very preterm or with very low birthweight compared with controls up to the early fourth decade of life in the current study, particularly in those who had bronchopulmonary dysplasia, follow-up into later adulthood of our cohorts is necessary.

Given that bronchopulmonary dysplasia was associated with worse expiratory flow rates among individuals born very preterm or with very low birthweight, we must try to reduce rates of bronchopulmonary dysplasia in the neonatal period. However, the incidence of bronchopulmonary dysplasia might be increasing rather than decreasing in individuals born at less than 28 weeks' gestational age in the 2000s compared with those born in the 1990s, and their expiratory flow rates in childhood might be deteriorating,³⁶ which, if true, will exacerbate the problem of airway obstruction during adulthood in individuals born very preterm or with very low birthweight in this era. General practitioners or specialist physicians of adult patients should be aware that increasing numbers of individuals born very preterm or with very low birthweight are surviving into adulthood, and that these people, particularly those who had bronchopulmonary dysplasia, are more likely to present with respiratory

problems than those born at term. Physicians should obtain a perinatal history, including birthweight, gestational age at birth, and bronchopulmonary dysplasia, when assessing adults with airway disease, and should be aware that those who were born very preterm or with very low birthweight or who had bronchopulmonary dysplasia are likely to be at higher risk of later COPD. In the absence of any bronchodilator data to the contrary, it is possible that such individuals could have fixed airway obstruction that might not respond to any COPD treatments, such as bronchodilators, and therefore therapeutic approaches in these people might need to be different to those used to treat other patients (eg, those with smoking-related disorders). Notwithstanding the higher FVC Z scores in smokers in the short-term in the current study, avoidance of smoking in the long term is paramount to avoiding COPD in later life.

In conclusion, individuals who survived very preterm birth or very low birthweight during the era of modern intensive care are not reaching their full airway growth potential in early adulthood, already being more likely to have clinically important reductions in airflow (values below the fifth percentile) at this age than individuals born with normal birthweight or at term. This disadvantage is exacerbated by bronchopulmonary dysplasia in the neonatal period. In individuals born very preterm or with very low birthweight, unless their rate of decline in airflow is lower than that which normally occurs with age in adulthood, many will develop COPD later in adult life.

Contributors

LWD, AB, JLYC, KAIE, TH, PH, EK, LM, MV, and EJLEV conceived and designed the study. LWD, SA, AB, HC, KAIE, AG, TH, PH, EK, LM, IN, SS, MV, and EJLEV were involved in data collection and interpretation. LWD, JLYC, and KJL were involved in data analysis. JLYC, KJL, and PN-G were involved in data interpretation. LWD and JLYC drafted the manuscript. All authors were involved in revising the manuscript and approved the final submitted version.

Declaration of interests

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