Lung function in young adulthood in relation to moderate-to-late preterm birth

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Shareable abstract (@ERSpublications)
Peak lung function is impaired in males born moderate-to-late preterm, while preterm females catch up between ages 16 and 24 years in this regard (FEV_1). Several phenotypes of lung function impairment exist in individuals born moderate-to-late preterm. https://bit.ly/3R8xBc3

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Abstract

Background Moderate-to-late preterm birth (32 to <37 weeks of gestation) has been associated with impaired lung function in adolescence, but data in adulthood and physiological phenotyping beyond spirometry are scarce. We aimed to investigate lung function development from adolescence into young adulthood and to provide physiological phenotyping in individuals born moderate-to-late preterm.

Methods Lung function data from individuals born moderate-to-late preterm (n=110) and term (37 to <42 weeks of gestation, n=1895) in the Swedish birth cohort BAMSE were used for analysis and included dynamic spirometry, fractional exhaled nitric oxide and multiple breath nitrogen wash-out. Data from 16- and 24-year follow-ups were analysed using regression models stratified on sex and adjusted for smoking. Data-driven latent class analysis was used to phenotype moderate-to-late preterm individuals at 24 years, and groups were related to background factors.

Results Males born moderate-to-late preterm had lower forced expiratory volume in 1 s (FEV_1) at 24 years of age (−0.28 z-score, p=0.045), compared to males born term. In females, no difference was seen at 24 years, partly explained by a significant catch up in FEV_1 between 16 and 24 years (0.18 z-score, p=0.01). Lung function phenotypes described as "asthma-like", "dysanapsis-like" and "preterm reference" were identified within the preterm group. Maternal overweight in early pregnancy was associated with "asthma-like" group membership (OR 3.59, p=0.02).

Conclusion Our results show impaired FEV_1 at peak lung function in males born moderate-to-late preterm, while females born moderate-to-late preterm had significant catch up between the ages of 16 and 24 years. Several phenotypes of lung function impairment exist in individuals born moderate-to-late preterm.

Introduction

Preterm birth is common and associated with severe and chronic complications. Every year, an estimated 15 million (~10%) infants are born preterm, and the incidence is increasing [1]. The vast majority of children born preterm are born moderate-to-late preterm, *i.e.*, between 32 and 37 weeks of gestation. Traditionally, there has been less focus on this group of individuals, as they have fewer complications and less need for specialised care compared to those born even more preterm. However, several studies have reported significant respiratory morbidity and lung function deficits also in individuals born moderate-to-late preterm [2].

There is a growing consensus that impaired lung function early in life predicts respiratory morbidity later in life [3–5]. COPD was earlier considered to originate from exposure to environmental factors such as

smoking, but a substantial proportion of the incidence of COPD can be explained by other factors, such as impaired lung function development from birth until early adulthood [6]. To date, studies investigating lung function longitudinally in individuals born moderate-to-late preterm are sparse, the results are conflicting regarding the possibility of lung function catch up in adolescence [7, 8] and potential physiological phenotypes within the group remain unexplored.

The concept of physiological phenotyping has gained increased attention within the field of respiratory diseases in the last decade as part of the shift towards precision medicine and identification of treatable traits, and unbiased data-driven approaches based on different measured physiological aspects have been a suggested methodology [9, 10]. Earlier research on lung function in individuals born moderate-to-late preterm has had an emphasis on dynamic spirometry, and hence not investigated other potentially important physiological lung function aspects beyond expiratory flows and volumes such as airway inflammation and ventilation inhomogeneity [2].

In the current cohort study, we aimed to investigate the association between moderate-to-late preterm birth and detailed lung function outcomes including physiological phenotyping in young adulthood. We also aimed to investigate lung function longitudinally, from adolescence to early adulthood, hypothesising that lung function deficits associated with moderate-to-late preterm birth track into adulthood.

Material and methods

Study population

The birth cohort BAMSE (Swedish acronym for Children, Allergy, Milieu, Stockholm, Epidemiology) included 4089 infants born in predefined areas of Stockholm, Sweden, between 1994 and 1996 [11]. Exclusion criteria were poor Swedish language comprehension, plan to move within the coming year, sibling already included or infant with severe disease. Baseline background data were collected using a parental questionnaire at 2 months of age, and information on demographics and exposures were collected in subsequent questionnaires at ages 1, 2, 4, 8 and 16 years of age. At ages 16 and 24 years, the included individuals were invited to follow-up visits including lung function measurements. The present study included subjects with valid lung function data from either of the three modalities presented below, at the 24-year follow-up (figure 1). Ethical permission was granted by the ethical review board of Stockholm (no 2016/1380–31/2), and written informed consent was obtained.

Lung function measurements

Spirometry data from the 16-year follow-up were included for longitudinal analyses [8]. Lung function testing at the 24-year follow-up included fractional exhaled nitric oxide (F_{ENO}) and multiple breath nitrogen wash-out (MBW) [12, 13]. In addition, pre- and post-bronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured using a Vyaire Vyntus system (Vyaire Medical, Chicago, IL, USA). F_{ENO} was measured using a NIOX vero (Aerocrine AB, Solna, Sweden). To facilitate the interpretation and relate to clinical guidelines [14], we used 25 parts per billion (ppb) as a cut-off for elevated F_{ENO}. Lung clearance index (LCI) was measured using an Exhalyzer D (Ecomedics Technologies™, San Diego, CA, USA) and analysed using Spiroware software 3.3.1 [15]. Spirometry variables were converted to z-scores using Global Lung Initiative (GLI) reference equations [16]; all other lung function variables were used as measured.

Description of variables used for analyses

Gestational age at birth and additional perinatal background factors were obtained from the Swedish medical birth register [17]. Subjects born moderate-to-late preterm (32 to <37 weeks) or term (37 to <42 weeks) were included for further analyses. Time-weighted average particle matter with a diameter <10 µm (PM_{10}) and nitrogen oxides (NO_x) exposures in the first year of life were calculated using a validated geo-coded dispersion model based on emission inventories [18]. Definitions of other perinatal, childhood and current characteristics used are given in detail in the footnote of table 1.

Statistical analyses

t-test, chi-squared test and Wilcoxon's rank sum test were used when comparing demographic factors between groups. Linear regression was used for investigating associations with normally distributed continuous lung function outcomes, and quantile regression when variables were non-normally distributed. Binary outcomes were assessed using logistic regression. Lung function regression models were stratified on sex. Age and height were included as fixed covariates when analysing raw lung function data.

Potential confounding factors were identified from previous literature. For the main lung function analyses, maternal smoking during pregnancy and the study subjects' current smoking at the 24-year follow-up were

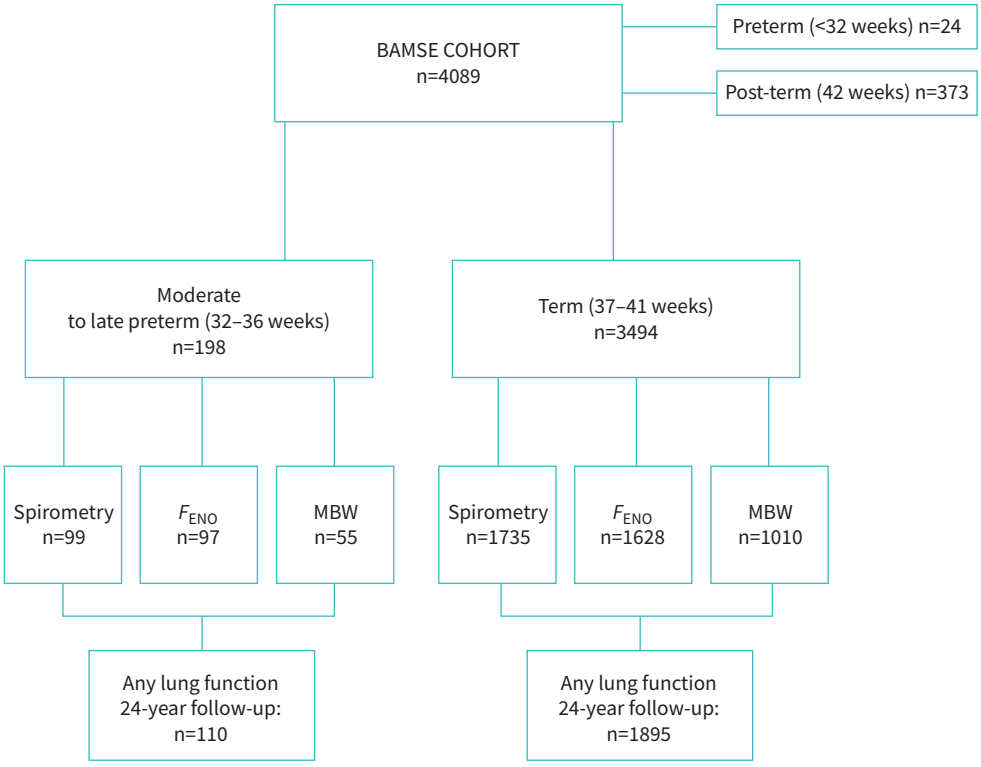

FIGURE 1 Overview of study participants in the BAMSE cohort and accepted lung function tests at 24-year follow-up. F_{ENO}: fractional exhaled nitric oxide; MBW: multiple breath nitrogen wash-out.

included as covariates. Socioeconomic index at birth, small for gestational age at birth, paternal smoking at baseline questionnaire, maternal over- and underweight, exclusive breastfeeding first 4 months of life, PM_{10} exposure in the first year of life and subjects' body mass index (BMI) at 24 years of age were all evaluated as confounders but were not included in the final model since they did not consistently change the estimates. Additionally, during revision, we investigated the potential influence of respiratory syncytial virus (RSV) infection in the first year of life on the main lung function analyses and found no consistent changes of the estimates.

A general estimating equation model based on spirometry data from the 16- and 24-year follow-ups was used to longitudinally investigate the influence of preterm birth on lung function over time. Height and age at examination were included as time-dependent covariates. Preterm/term birth, sex and maternal smoking during pregnancy were included as fixed covariates.

Latent class analysis (LCA) was used to identify latent lung function phenotype classes within the group of individuals born preterm based on variables derived from spirometry, MBW and F_{ENO} examinations at the 24-year follow-up. Pre-bronchodilator FEV_1, FVC and FEV_1/FVC ratio z-scores, per cent post-bronchodilator FEV_1 change compared to the initial value, low or high F_{ENO} value ($\leqslant$25 or >25 ppb) and LCI were used to obtain maximal physiological input from the data available in an LCA model that accepted missing data. The latent class model with the lowest Bayesian information criterion was selected [19]. To clarify the discussion, latent classes were assigned a "summary label". Sex-stratified analysis was performed as sensitivity analysis. A p-value <0.05 was considered significant. Statistical analyses were performed using Stata version 17.1 (Stata Corp LP, College Station, TX, USA).

Results

A total of 198 infants included in the original BAMSE cohort were born moderate-to-late preterm. Of these, 110 (56%) contributed with any lung function data at the 24-year follow-up and were included in the study population. The corresponding numbers for individuals born term were 3494 in the original cohort, of which 1895 (54%) contributed with lung function data at the 24-year follow-up (figure 1).

TABLE 1 Perinatal, childhood and current characteristics of individuals born moderate-to-late preterm and term who contributed any lung function data at the 24-year follow-up, stratified by sex

	Females			Males		
	Preterm	Term	p-value	Preterm	Term	p-value
Individuals n	65	1080		45	815	
Perinatal characteristics						
Gestational age weeks, mean (range)	35.1 (32–36)	39.6 (37–41)	NA	35.0 (32–36)	39.6 (37–41)	NA
Allergic heredity[#]	24 (37.5)	320 (29.9)	0.20	13 (28.9)	276 (34.0)	0.48
Maternal overweight in early pregnancy[¶]	7 (13.0)	167 (17.9)	0.35	15 (36.6)	128 (18.3)	<0.01
Maternal smoking during pregnancy[+]	9 (13.9)	136 (12.6)	0.77	8 (17.8)	91 (11.2)	0.18
High socioeconomic index at birth[§]	57 (89.1)	881 (83.6)	0.25	36 (80.0)	688 (85.7)	0.29
Birthweight g	2592±472	3505±473	NA	2671±469	3617±467	NA
Small for gestational age[f]	3 (5)	24 (2.3)	0.18	3 (6.8)	11 (1.4)	<0.01
Neonatal ventilator respiratory support[##]	2 (3.3)	10 (1.0)	0.09	3 (7.5)	6 (0.8)	<0.01
Neonatal CPAP respiratory support[##]	2 (3.3)	7 (0.7)	0.03	6 (14.0)	7 (0.9)	<0.01
Respiratory syncytial virus (RSV) infection, 1st year of life[¶¶]	6 (9.2)	51 (4.7)	0.10	5 (11.1)	34 (4.2)	0.04
PM_{10} exposure 1st year of life[++], median (IQR)	14.9 (2.75)	14.4 (2.95)	0.27	14.9 (4.06)	14.6 (3.12)	0.58
NO_x exposure 1st year of life[++], median (IQR)	32.9 (22.6)	28.3 (23.5)	0.22	34.4 (28.2)	30.5 (24.7)	0.63
24-year examination						
Age years	22.7±0.52	22.6±0.63	0.69	22.6±0.57	22.6±0.62	0.82
Height m	1.68±0.05	1.68±0.06	0.94	1.83±0.07	1.82±0.07	0.73
Body mass index kg·m^{-2}, median (IQR)	22.7 (4.12)	22.1 (3.88)	0.18	24.4 (3.56)	23.0 (4.15)	0.01
University education[§§]	24 (36.9)	449 (41.7)	0.45	16 (35.6)	268 (33.1)	0.73
Asthma in the last 12 months[ff]	13 (20.0)	173 (16.1)	0.40	8 (17.8)	99 (12.2)	0.27
Asthma during childhood[###]	17 (32.1)	177 (20.4)	0.04	13 (34.2)	164 (24.6)	0.18
Prescription of ICS in the last 12 months	4 (6.4)	78 (7.3)	0.79	5 (11.4)	49 (6.1)	0.16
Respiratory symptoms in the last 12 months[¶¶¶]	20 (30.8)	300 (27.8)	0.61	13 (28.9)	177 (21.8)	0.27
Current smoking[+++]	12 (18.5)	242 (22.4)	0.46	6 (13.3)	144 (17.7)	0.45

Because of missing data for some variables, the numbers in each column do not always sum up to the total sum of preterm and term subjects. Data are presented as n (%) or mean±SD unless otherwise indicated. CPAP: continuous positive airway pressure; PM: particle matter: NO_x: nitrogen oxides; ICS: inhaled corticosteroids; NA: not applicable. [#]: mother and/or father with a doctor's diagnosis of asthma and asthma medication and/or hay fever combined with a furred pet allergy and/or pollen allergy at the time of the baseline questionnaire; [¶]: body mass index ⩾25 kg·m^{-2} in early pregnancy obtained from the Swedish medical birth register; [+]: mother smoked at least one cigarette per day during pregnancy and/or at baseline questionnaire; [§]: socioeconomic status for household in dominance order divided into two classes (low *versus* high); [f]: defined as birthweight below −2 SDS of the Swedish standard population [32]; [##]: neonatal respiratory support defined as a need for ventilator or CPAP support shortly after birth; [¶¶]: parent-reported RSV infection during first year of life; [++]: time-weighted average particle matter with a diameter <10 µm (PM_{10}) and nitrogen oxides (NO_x) exposures in the first year of life; [§§]: any university education defined as at least one semester at college or university after high school degree; [ff]: fulfilling the MeDALL definition of asthma [33] – at least two of the following criteria: 1) breathing difficulties in the last 12 months, 2) ever doctor's diagnosis of asthma and 3) asthma medication occasionally or regularly in last 12 months; [###]: asthma diagnosis at any time point during follow-up from 1 to 16 years of age; [¶¶¶]: at least one episode of breathing difficulties (trouble breathing, chest tightness, wheezing) in the last 12 months; [+++]: any current smoking at 24 years follow-up.

Sensitivity analysis investigating differences in baseline background characteristics between the study population and individuals in the original cohort lost to follow-up (*i.e.* no lung function data at 24-year follow-up) are shown in supplementary table S1a and b. The study population had less maternal overweight and maternal smoking during pregnancy, but more allergic heredity and higher socioeconomic index, compared to the group lost to follow-up. First year of life median levels of PM_{10} and NO_x exposure at the home address were higher in those included.

Perinatal, childhood and current characteristics of the study population are given in table 1. There were no significant differences in characteristics between female individuals born moderate-to-late preterm or term, except for neonatal continuous positive airway pressure (CPAP) respiratory support and asthma during childhood both being more frequent in the preterm group (3.3 *versus* 0.7%, p=0.03 and 32.1 *versus* 20.4%, p=0.04, respectively). Males born moderate-to-late preterm had a significantly higher proportion of mothers that were overweight in early pregnancy (36.6 *versus* 18.3%, p<0.01), were more likely to be small for gestational age (6.8 *versus* 1.4%, p<0.01), were more likely to have had a need for respiratory support after birth (ventilator 7.5 *versus* 0.8%, p<0.01; CPAP 14.0 *versus* 0.9%, p<0.01), were more likely to have an RSV infection in their first year of life (11.1 *versus* 4.2%, p=0.04) and had a higher median BMI (25.5 *versus* 23.5 kg·m^{-2}, p⩽0.01) when compared to males born term.

TABLE 2 Differences in pre-bronchodilator lung function between individuals born moderate-to-late preterm and term at the 24-year follow-up stratified on sex, with and without adjustment for smoking

	Crude model[#]				Adjusted model[¶]			
	Female	p-value	Male	p-value	Female	p-value	Male	p-value
Spirometry (n=1834)								
FEV_1, z-score	0.03 (−0.19–0.26)	0.78	−0.29 (−0.57– −0.02)	0.04	0.04 (−0.18–0.26)	0.72	−0.28 (−0.56– −0.01)	0.05
FVC, z-score	0.09 (−0.12–0.31)	0.40	−0.06 (−0.34–0.22)	0.68	0.10 (−0.12–0.32)	0.36	−0.05 (−0.33–0.23)	0.72
FEV_1/FVC, z-score	−0.11 (−0.34–0.12)	0.36	−0.38 (−0.67– −0.10)	<0.01	−0.11 (−0.34–0.13)	0.37	−0.38 (−0.67– −0.09)	0.01
Exhaled nitric oxide (n=1725)								
F_{ENO} >25 ppb, OR	1.19 (0.50–2.87)	0.69	0.54 (0.21–1.41)	0.21	1.25 (0.52–3.01)	0.62	0.52 (0.20–1.35)	0.18
Multiple breath wash-out (n=1065)								
LCI	−0.18 (−0.34– −0.02)	0.03	−0.03 (−0.22–0.16)	0.76	−0.11 (−0.27–0.05)	0.20	−0.01 (−0.20–0.18)	0.94

Spirometry data were analysed using linear regression and expressed as coefficient change in mean (95% CI). MBW data were analysed using linear quantile regression and expressed as coefficient change in median (95% CI). F_{ENO} data were analysed using logistic regression and expressed as odds ratio (OR) (95% CI). Z-scores were computed according to 2012 Global Lung Initiative reference values. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: fractional exhaled nitric oxide; LCI: lung clearance index. [#]: included adjustment for age and height for LCI; [¶]: further adjusted using maternal smoking during pregnancy and current smoking.

Associations between moderate-to-late preterm birth and lung function at 24 years of age

Differences in lung function between individuals born moderate-to-late preterm and term are given in table 2. Moderate-to-late preterm birth was negatively associated with FEV_1 in males (z-score −0.28, p=0.045), but not in females (z-score 0.04, p=0.72). The FEV_1/FVC ratio was lower in males born preterm (z-score −0.38, p=0.01). There were no significant associations between FVC and preterm birth. A bronchodilator response of >12% increase from baseline FEV_1 was found in none of the individuals born moderate-to-late preterm (n=0) and in 18 individuals (males n=10, females n=8) born term. Sensitivity analysis excluding individuals whose mother smoked during pregnancy showed no major differences to the main adjusted model (preterm compared to term males FEV_1 z-score −0.36, p=0.02; females 0.08, p=0.52). Absolute lung function values and spirometric differences in millilitres are given in supplementary tables S2a and b, respectively.

There was no significant association between preterm birth and F_{ENO}. LCI was negatively associated with preterm birth in females (−0.18, p=0.03), though this association did not remain significant after adjustment for smoking.

Lung function longitudinally between 16 and 24 years of age

The change in lung function z-score over time was generally positive in the moderate-to-late preterm group when compared to those born term; however, a statistically significant difference was only seen for FEV_1 in females (z-score 0.18, p=0.01, see table 3 and supplementary table S3). Sensitivity analysis excluding individuals whose mothers smoked during pregnancy showed no major differences to the main adjusted model (females FEV_1 z-score 0.21, p⩽0.01).

TABLE 3 Difference in mean adjusted pre-bronchodilator lung function change from 16 to 24 years of age between individuals born moderate-to-late preterm and term, stratified on sex and adjusted for maternal smoking during pregnancy and current smoking

	Female	p-value	Male	p-value
FEV_1, z-score	0.18 (0.04–0.32)	0.01	0.10 (−0.10–0.30)	0.31
FVC, z-score	0.11 (−0.02–0.25)	0.11	0.09 (−0.10–0.27)	0.36
FEV_1/FVC, z-score	0.14 (−0.03–0.30)	0.10	0.06 (−0.16–0.28)	0.58

Spirometry data were analysed using a longitudinal effects model with an interaction term between term/preterm groups and time (GEE) and expressed as change in mean (95% CI). Term/preterm group was included as a fixed covariate. In this model, the number of subjects contributing with data comprised 1102 females and 806 males (number of observations: 1862 in the female group, 1277 in the male group). p-values for interaction were obtained from the longitudinal effects model. Z-scores were computed according to 2012 Global Lung Initiative reference values. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Lung function phenotyping in individuals born moderate-to-late preterm

Using LCA based on data from spirometry, F_{ENO} and MBW measured at the 24-year follow-up in individuals born moderate-to-late preterm, a three-class model showed the best goodness of fit (see supplementary table S4 for details). The individuals in class 1 (n=50, 45.5%) were labelled "preterm reference" based on mean spirometric output z-scores close to zero, low LCI and low probability of having high F_{ENO} (table 4). Individuals in class 2 (n=40, 36.4%) had the lowest FEV_1 and FEV_1/FVC z-scores, the highest increase in FEV_1 after bronchodilation, the highest LCI and F_{ENO}, and were labelled "asthma-like". Individuals in class 3 (n=20, 18.2%) had the highest FEV_1 and FVC z-scores, but a low FEV_1/FVC z-score. F_{ENO}, LCI and increase in FEV_1 after bronchodilation were more comparable to the "preterm reference" than the "asthma-like" group. Class 3 was labelled "dysanapsis-like" based on the relatively higher FEV_1 and FVC, but lower FEV_1/FVC ratio, suggesting a mismatch in airway calibre and lung volume. Sex-stratified sensitivity analyses identified a similar pattern in females (the male model collapsed due to few individuals) (see supplementary table 5).

Investigating associations between latent lung function classes and perinatal and current characteristics showed that individuals whose mothers were overweight in early pregnancy were significantly more likely to belong to the "asthma-like" group (OR 3.59, p=0.02) compared to the "preterm reference". There were no significant associations between other perinatal background factors or current symptoms, asthma diagnosis or treatment, and membership in either of the groups (see supplementary table S6 for more details). The association between "asthma-like" group membership and maternal overweight prevailed in additional sensitivity analysis adjusting for parental asthma and the individual's own overweight (OR 4.92, p=0.01).

Discussion

In the current population-based cohort study, males born moderate-to-late preterm had reduced FEV_1 in young adulthood, near presumed peak lung function, while females caught up towards the term-born population between adolescence and young adulthood. We identified three latent lung function phenotypes within the moderate-to-late preterm group, labelled "asthma-like", "dysanapsis-like" and "preterm reference", and an association where maternal overweight in early pregnancy increased the probability for "asthma-like" group membership.

Associations between moderate-to-late preterm birth and lung function at 24 years of age

Our finding of a lasting negative impact on FEV_1 in males after moderate-to-late preterm birth is in accordance with a recently published review and meta-analysis [2]. However, there are relatively few studies following this group of individuals up to adulthood. Näsänen *et al.* [20] and Landry *et al.* [21] found reductions in FEV_1 z-scores of a magnitude similar to ours in their studies of young adults born moderate-to-late preterm in the post-surfactant era. Näsänen *et al.* reported a more pronounced deficit in males compared to females in sensitivity analyses, which is in line with our results. In addition, Landry *et al.* found a negative association with FVC, whereas the results by Näsänen *et al.* were in line with ours, with no effect found on FVC. The results of primarily affected spirometry indices associated with airway obstruction are in accordance with a recent multicentre cohort study, including data from our cohort, that identified preterm birth as a risk factor for an obstructive lung function phenotype throughout childhood and into adulthood [22]. Given the compiled evidence, it seems possible that moderate-to-late preterm birth

TABLE 4 Characteristics of identified latent lung function classes in individuals born moderate-to-late preterm

	Class 1: "Preterm reference"	Class 2: "Asthma-like"	Class 3: "Dysanapsis-like"
n (%)	50 (45.5)	40 (36.4)	20 (18.2)
Probability for F_{ENO} >25 ppb (95% CI)	0.06 (0.02–0.22)	0.18 (0.09–0.35)	0.07 (0.01–0.36)
FEV_1, z-score	−0.24±0.49	−1.23±0.54	1.05±0.54
FEV_1/FVC, z-score	0.04±0.63	−1.28±0.60	−0.52±0.51
FVC, z-score	−0.30±0.45	−0.41±0.75	1.29±0.49
LCI	5.88±0.33	6.08±0.39	5.84±0.25
Post-bronchodilator FEV_1 increase, %	1.38±2.54	6.72±2.40	2.92±2.35

Analysis based on input from spirometry, F_{ENO} and MBW data at 24-year follow-up. Data presented as mean±SD unless otherwise indicated. Z-scores were computed according to 2012 Global Lung Initiative reference values. F_{ENO}: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LCI: lung clearance index.

interrupts lung development *in utero* with long-term consequences, or that individuals with this background are more susceptible to negative effects of environmental factors after birth. Although relatively modest, the reductions in expiratory airflow found in our study and others [2] might still predispose for later airway morbidity, including COPD development, as shown in a longitudinal study following individuals born very- and moderate-to-late preterm in the pre-surfactant era until the age of 53 years [4].

We found no association between moderate-to-late preterm birth and F_{ENO}. While similar studies following individuals until adulthood are scarce, two studies investigating F_{ENO} in childhood [23] and adolescence [24] found results similar to ours, suggesting that type 2 airway inflammation does not define the general moderate-to-late preterm group.

We found no significant differences in ventilation inhomogeneity measured as LCI between individuals born moderate-to-late preterm and term, after adjustment for smoking habits. In the absence of studies on adults, studies investigating LCI in childhood [25, 26] and adolescence [27] show similar results to ours, with no significant associations between moderate-to-late preterm birth and LCI.

Lung function between 16 and 24 years

Our main longitudinal finding was a catch up in FEV_1 between adolescence and young adulthood in moderate-to-late preterm females. To our knowledge, our study is the first to assess lung function into adulthood in a cohort of substantial study size and including both males and females. Kaczmarczyk *et al*. [28] reported findings of a reduced FEV_1 in adolescence that normalised in adulthood from a small cohort study in Poland, including only females born moderate-to-late preterm in the late 1980s and early 1990s with unclear surfactant administration practice status. There is evidence that sex affects the incidence, susceptibility and severity of several airway diseases [29]. Regarding sex-specific lung function effects, females reach their peak lung function plateau earlier than males, where peak lung function is usually set at 20–25 years of age [3, 30]. However, in analysis stratified on sex, an earlier peak FEV_1 level in females should not affect the results, unless females born moderate-to-late preterm reach their peak earlier than those born term. Theoretically, a true sex-specific difference in the association between moderate-to-late preterm birth and catch up between adolescence and peak lung function can be caused by either or an interplay of differences in anatomy/respiratory mechanics, sex hormones or genetics/epigenetics [6]. If our novel findings of a catch up to peak lung function in predominantly females were to be replicated, further studies investigating etiological/mediating hormonal and genetic mechanisms should be warranted.

Lung function phenotyping in individuals born moderate-to-late preterm

Using a data-driven approach, we identified three latent lung function phenotypes in young adulthood within the group of individuals born moderate-to-late preterm: “asthma-like”, “dysanapsis-like” and “preterm reference”. To our knowledge, this is the first study to apply this concept to a preterm-born population.

We found a strong association between maternal overweight and the “asthma-like” phenotype in a logistic regression model using the latent class “preterm reference” as a reference. Maternal overweight is a known risk factor for preterm birth, and preterm birth and overweight are known risk factors for asthma or asthma-like disease [10, 31]. Disentangling these associations is challenging, but the fact that the observed association prevails after additional adjustment for parental asthma and the subjects’ own overweight at 24 years of age suggests that this finding deserves further attention. Interestingly, we found no associations between asthma diagnosis, symptoms or treatment and the “asthma-like” phenotype, although this subgroup had clinical features resembling asthma (higher F_{ENO} levels, lower FEV_1/FVC ratio, higher bronchodilator response). The lack of symptoms might be due to the modest reduction in lung function, or individual adaptation, *i.e.*, if a symptom occurs daily over time, it is no longer perceived as a symptom but as something normal for that individual and hence not reported.

Strengths and weaknesses

A major strength of our study includes the longitudinal data collection from a large population-based cohort followed from childhood into early adulthood. Further, using multiple lung function techniques enables physiological data-driven phenotyping at presumed peak lung function in early adulthood. As a part of a prospective birth cohort, our study population has contributed information on exposures and background factors continuously during the study period, hence reducing the risk of information bias. The exposure considered, moderate-to-late preterm birth, was obtained from the Swedish medical birth register, where gestational age was based on ultrasound in the absolute majority of pregnancies [17], minimising the risk of misclassification of the exposure.

A possible weakness is the number of individuals born moderate-to-late preterm that contributed to the lung function assessment at 24 years of age. A larger population of individuals born moderate-to-late preterm would have increased the power of our regression models and potentially identified a larger subset of physiological lung function phenotypes. The differences between included and lost individuals regarding maternal overweight and smoking, allergic heredity and high socioeconomic index could, to some extent, constitute a risk of selection bias and hence a reduced external validity of our findings. However, we argue that this risk was minimised by additional sensitivity analysis of our main findings.

Conclusion

In conclusion, our results suggest that in individuals born moderate-to-late preterm, spirometry indices associated with obstructive airway disease are impaired at peak lung function in males, while females show an ability to catch up to this time point. The demonstrated deficits in males suggest that lung function deficits associated with moderate-to-late preterm birth track from adolescence into adulthood and might predispose to later respiratory morbidity in this group. The observed differences in lung function catch up suggest possible differences between the sexes in this regard. Further, we identified latent "asthma-like" and "dysanapsis-like" lung function phenotypes in this group where especially the "asthma-like" phenotype might represent a treatable trait.

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Conflict of interest: G. Wang reports receiving lecture fees from Sanofi outside the submitted work. E. Melén reports payment for lectures and/or advisory board fees from ALK, AstraZeneca, Chiesi, Novartis and Sanofi, outside the submitted work. The remaining authors have nothing to disclose.

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