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Early View

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Development of lung diffusion to adulthood following extremely preterm birth

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Take home message

Pulmonary diffusing capacity following extremely preterm (EP) birth was reduced when compared to term-born subjects. From mid-childhood to adulthood, development tracked in parallel in the EP and term-born groups, with preterms following lower trajectories.

ABSTRACT

Background: Gas exchange in extremely preterm (EP) infants must take place in foetal lungs. Childhood lung diffusing capacity for carbon monoxide (DL_{CO}) is reduced; however, longitudinal development has not been investigated. We describe growth of DL_{CO} and its sub-components to adulthood in EP-born compared to term-born subjects.

Methods: Two area-based cohorts born at gestational age ≤ 28 weeks or birth weight ≤ 1000 grams in 1982–1985 (*n*=48) and 1991–1992 (*n*=35) were examined twice, at ages 18 and 25, and 10 and 18 years, respectively, and compared to matched term-born controls. Single-breath DL_{CO} was measured at two oxygen pressures, with sub-components [membrane diffusion (D_M) and pulmonary capillary blood volume (V_C)] calculated using the Roughton–Forster equation.

Results: Age-, sex- and height-standardized transfer coefficients for carbon monoxide (K_{CO}), and DL_{CO} were reduced in EP-born compared to term-born and remained so during puberty and early adulthood (*P*-values for all time points and both cohorts ≤ 0.04), whereas alveolar volume was similar. Development occurred in parallel to term-born controls, with no signs of pubertal catch-up growth nor decline at 25 years (*P*-values for lack of parallelism within cohorts 0.99, 0.65, 0.71, 0.94, and 0.44 for *z*-DL_{CO}, *z*-V_A, z-K_{CO}, D_M, and V_C, respectively). Split by membrane and blood volume components, findings were less clear; however, membrane diffusion seemed most affected.

Conclusion: Pulmonary diffusing capacity was reduced in EP-born compared to term-born, and development from childhood to adulthood tracked in parallel to term-born, with no signs of catch-up growth nor decline at age 25.

INTRODUCTION

Extremely preterm (EP) born infants (born before 28 weeks of pregnancy) currently account for one in 200 live births in high income countries [1], with survival approaching 90% for infants born at 27 weeks gestation [2]. EP birth requires that foetal lungs develop in an extra-uterine environment while providing gas exchange for the new-born individual. The lungs at this stage have no proper gas exchanging units, as alveolarization has hardly commenced [3, 4]. Lifesaving intensive care is required and relies on measures that are harmful to developing lungs, such as positive pressure ventilation and hyperoxia. The pulmonary complication of this scenario is labelled bronchopulmonary dysplasia (BPD) [5]. The few autopsy studies that have been published from infants who have died with BPD reveal "acinar dysplasia", characterized by fewer and larger alveoli, and thickened alveolar-capillary membranes [6, 7]. We do not know how these *structural* injuries evolve later in life, but recent MRI studies suggest continued alveolar development until adolescence [8].

The standard *functional* measure of alveolar gas exchange is lung diffusing capacity for carbon monoxide (DL_{CO}) [9]. DL_{CO} is a compound measure reflecting lung volumes, surface area accessible for gas exchange, thickness of the alveolar-capillary barrier, and pulmonary capillary blood volume. By using two different oxygen pressures during measurements, DL_{CO} can be split into two components – transfer across the alveolar-capillary membrane (D_M), and the rate of reaction with haemoglobin, reflecting the pulmonary capillary blood volume (V_C) [10].

Studies report reduced DL_{CO} in EP-born children and adolescents, suggesting persistent deficits of acinar function, [11-15], although with surprisingly little influence from BPD [13, 15, 16]. Airway versus blood vessel interactions during lung development is poorly understood, and the relative impact from D_M and V_C for DL_{CO} is therefore of interest [14, 17-19]. We aimed to test the hypothesis that impaired DL_{CO} in EP-born subjects persists over time, without age-related catch-up or decline when compared to term-born controls. For this purpose, we measured DL_{CO}

with its sub-components twice in two EP-born cohorts with matched term-born controls and constructed longitudinal trajectories from 10 to 18 and 18 to 25 years of age.

METHODS.

Study subjects and study design

Two area-based cohorts of subjects born at GA ≤ 28 weeks or with BW ≤ 1000 grams in 1982–1985 (n = 48) and 1991–1992 (n = 35) were included. Subjects were examined in 2001–2002 and in 2008–2009 at Haukeland University Hospital, Norway. The temporally nearest term-born same-sex subject with birth weight 3–4 kg (approximately Norwegian 10–90 percentiles) was invited as a control. If that subject declined, the next term-born was approached, and so on. There were no exclusion criteria except inability to perform lung function tests. Clinical data were accessed from patients' hospital charts. The cohorts are described in detail elsewhere [20] and their neonatal and background data are summarized in Table 1 and 2. Mild and moderate/severe BPD were defined as a requirement for supplemental oxygen ≥ 28 postnatal days or at postmenstrual age ≥ 36 weeks, respectively [21]. No subjects were examined within two weeks of a respiratory tract infection or an asthma exacerbation. Participants were asked to discontinue inhaled long-acting β2 agonists and corticosteroids as well as oral leukotriene blockers 24 hours before testing, to avoid inhaled short-acting β2 agonists unless needed, and to refrain from smoking on the test day. Data on self-reported smoking have been verified in the 1982–1985 cohort by measuring urinary cotinine, with 3 positive tests in 57 self-declared non-smokers [22]. The Regional Ethics Committee approved the study (REK-Vest 240.07). Informed written consent was obtained from participating subjects and/or parents.

Pulmonary function tests

The same experienced respiratory physiologist (ODR) performed all tests on pulmonary function on both occasions, blinded to results obtained in previous test sessions. Single Breath (SB) DL_{CO} was measured with a Vmax 22 (*SensorMedics, Yorba Linda, Ca., USA*) in sitting position wearing a nose clip, in accordance with the guidelines of the European Respiratory Society (ERS) [23].

The single-breath method

The test gas contained a mixture of 0.3% carbon monoxide (CO), 0.3 % methane (CH_4), and 21% O_2 (80% O_2 in the hyperoxic test gas), balanced with nitrogen. A mid-expiratory sample of alveolar gas was collected and analysed. Alveolar volume (V_A) and the transfer coefficient of the lung for carbon monoxide (K_{CO}) were recorded and DL_{CO} calculated. D_M and V_C were measured with a hyperoxic test-gas (80% oxygen), and calculated according to the Roughton–Forster equation [10]. Test criteria were applied as recommended by the ERS Task Force [23]. Details regarding the SB-DL_{CO} measurements have previously been described [11]. *Z*-scores for V_A, K_{CO}, and DL_{CO} were calculated using the Stanojevic GLI-2017 regression equations (updated version, October 2020) for transfer factor for CO for Caucasians [24].

Statistical methods

Results are reported as counts with proportions, means with 95% confidence intervals (CI) or ranges, as appropriate. The number of patients each analysis is based on is reported separately due to some missing data, particularly at the second follow-up (Figure 1).

To estimate mean values and differences in mean values for the clinical variables *z*-DL_{CO}, DL_{CO} %-predicted, *z*-V_A, z-K_{CO}, K_{CO} %-predicted, D_M, and V_C for the two groups at each time points, we fitted linear mixed-effects longitudinal models. The explanatory variables were cohort, age (categorical) and EP vs. term-born (or grade of BPD severity in the supplemental

table). To make the models maximally flexible, we included all interactions. Subjects were included as a random effect (as expected, there was no "EP–term-born pair" effect, so this was not included as a random effect). These models take the correlations between measurements at various follow-up times from the same subject into account, which makes it possible to also include subjects with incomplete follow-up data. This was done to reduce any bias caused by missing data and to increase the precision of the estimates [25]. Residual plots were examined and any errors in the original data corrected. To examine if the development for EP subjects tracked the development for term-born subjects, we fitted simplified models with parallel lines for the two groups (but possibly different slopes for the two cohorts) and compared these with the fully flexible models using likelihood ratio tests. To examine effects of smoking and if smoking impacted EP and term-born differently, we added smoking and the interaction EP versus term-born to the *z*-DL_{CO} model.

Associations between perinatal exposures and outcome were tested in a linear regression model with *z*-DL_{CO} at 18 years of age (in both cohorts) as response variable and the following as explanatory variables: maternal smoking, GA, antenatal steroids, surfactant, days on mechanical ventilation (with values above 30 days set to 30 days), days on oxygen supplementation (with values above 100 days set to 100 days) and cohort.

For the background variables (Tables 1 and 2), differences between groups were assessed with Welch's *t*-test for continues variables, and Pearson χ^2 test for categorical variables.

The original project was in 2001 designed to address a series of outcomes, and the sample size was calculated to detect a clinically relevant decrease in the EP-born groups for the main outcome measure for the overall study, which was FEV_1 [22].

The data were analysed with SPSS 25 (SPSS, Inc., Chicago, IL, USA) and R version 4.0.2 [26]. The mixed-effects models were fitted with the R package "lme4" version 1.1-23 [27]. *P*-values ≤ 0.05 are characterized as statistically significant.

RESULTS

Subjects

A total of 130 preterms were admitted to the neonatal intensive care unit (NICU) in the two inclusion periods. Neonatal mortality was 39% and 27% in 1982–1985 and 1991–1992, respectively. Altogether in both EP-born cohorts, 86 subjects survived, 81 attended the first, 74 attended both, and 83 attended at least one follow-up.

Subject demographics are summarized in Table 1. Mean GA was similar in both cohorts. The younger cohort had fewer days on ventilator and higher use of antenatal and postnatal steroids. No subjects in the 1982–1985 cohort received surfactant, contrasting almost half of the preterm subjects in the 1991–1992 cohort (Table 1).

There were no differences between EP and term-born subjects regarding weight (Table 2). Regarding height, EP-born females in the 1982–1985 cohort were significantly shorter at both examinations (both *P*-values 0.006), as were EP-born males in the 1991–92 cohort at the first (*P*-value 0.01), but not the second examination (*P*-value 0.29).

Most participants were able to perform the DL_{CO} measurements (Figure 1). Success rates at first follow-up (10 and 18 years) were 97% and 89% for EP-born and 100% for term-born (both cohorts). Corresponding numbers at second follow-up (18 and 25 years) were 94% and 87% for EP-born subjects and 93% and 100 % for term-born. Some of those who struggled with performing satisfactory measurements at 21% oxygen tension did not perform

measurements at 80% oxygen pressure, and thus D_M and V_C measurements were obtained for fewer subjects (Figure 1).

DL_{CO}, V_A, and K_{CO}

Raw data (for DL_{CO} and K_{CO}) are presented in Supplemental Table A, whereas *z*-scores are used in Figure 2 and Table 3. Table 3 also includes percentages of predicted. *Z*-DL_{CO} and *z*-K_{CO} were lower in EP compared to term-born in both cohorts and at both examinations, whereas *z*-V_A was similar. Data for preterm participants split by neonatal BPD is presented in Supplemental Table B. Within the EP-born cohorts, BPD did not influence *z*-DL_{CO}, *z*-V_A, and *z*-K_{CO} (*P*-values 0.14, 0.45, and 0.15, respectively).

Smokers had on average 0.6 lower *z*-DL_{CO} values (95% CI 0.2–1.0, *P*-value 0.002). The effect did not differ between the EP and term-born subjects (*P*-value 0.31 for the interaction).

There were no associations between the addressed perinatal variables or cohort versus *z*-DL_{CO} at 18 years, with *P*-values 0.28, 0.12, 0.21, 0.93, 0.90, 0.66 and 0.74 for maternal smoking, GA, antenatal steroids, surfactant, days on mechanical ventilation, days on oxygen supplementation, and cohort, respectively.

D_M and V_C

D_M was numerically lower in the EP compared to the term-born cohorts, statistically significantly so only in the 1991–92 cohort at 10 years of age. V_C did not differ between the EP and term-born cohorts at any of the measurements.

Development over time

For both EP-born cohorts, *z*-DL_{CO}, *z*-K_{CO}, *z*-V_A, D_M, and V_C developed in parallel to their respective term-born control cohorts over the age span covered by the study, i.e., from 18 to 25 years of age in the 1982–1985 cohort, and from 10 to 18 years of age in the 1991–1992 cohort.

The *P*-values for overall tests for a lack of parallelism between the EP and term-born cohorts from each of the two decades were 0.99, 0.65, 0.71, 0.94, and 0.44 for *z*-DL_{CO}, *z*-V_A, *z*-K_{CO}, D_M, and V_C, respectively. This indicates that development between the two examinations did not differ between the preterm and term-born groups for any of the measured variables.

DISCUSSION

This is the first controlled population-based study describing longitudinal development of lung diffusing capacity after EP birth from mid-childhood to adulthood. We found that DL_{CO} and K_{CO} were persistently reduced in EP-born, and that development tracked below but in parallel to term-born over the study period, with no signs of pubertal catch-up growth nor any signs of decline at 25 years age. Split by membrane and blood volume components, findings were less clear; however, the membrane diffusion component seemed most affected.

Gas exchange takes place in the acini, where air and blood are in proximity, with an ultrathin alveolar-capillary membrane separating the compartments. The diffusing capacity of the lungs is structurally limited by the magnitude of the alveolar surface area, the thickness of the blood-gas barrier, and the pulmonary capillary blood volume. Formation of the alveoli is the final stage of lung development, and much of this process takes place after birth also in term-born individuals [28]. Nevertheless, postnatal development builds on premises established during the last trimester, which is a period EP-born spend in a NICU. New alveoli form by alveolar ducts dividing into alveolar sacs by septation, and the pulmonary capillary bed expands in parallel via angiogenesis, gradually increasing the area available for gas exchange [17]. This is a continuous process that commences in the last trimester and continues for years after birth. Extreme preterm birth, with accompanying dramatic events and lifesaving respiratory interventions, radically change the premises under which this developmental program must take place. Autopsy studies of children who died from BPD have shown impaired acinar development [6, 7, 29], but we have little knowledge of structural features in

survivors, and future prospects for growth or repair after the neonatal period are unknown. Judged by aerosol-derived airway morphometry studies, the size of a child's alveolus expands into adulthood, accounting for increased lung volume with age and height [30]. On the other hand, studies applying stereological approaches indicate that the alveolar number closely relates to total lung volume, with a constant alveolar size over a range of volumes, suggesting that the number of alveoli must increase during growth, as adult lung volume numerically multiply that of a child's [31]. This relatively simple line of reasoning was recently confirmed by MRI studies, showing continued alveolarization to adolescence and catch-up growth in ex-preterm children [8]. These studies provide optimism that repair mechanisms might come into play as preterm born children grow and mature. However, judged by the development of the pulmonary capacity for carbon monoxide transfer of the two preterm-born cohorts of our study, a corresponding functional catch-up is difficult to detect; the EP-born cohorts had consistently reduced gas exchanging capacity that tracked from 10 to 25 years of age.

At quiet breathing, both volume and effective surface area of the capillary bed changes with changes of the blood flow that reflects the stroke volume [32]. The blood stays very briefly in the pulmonary capillaries, but still, venous blood entering the lung capillaries equilibrates completely with alveolar air in a highly efficient process requiring approximately 0.3 seconds. Healthy individuals have large ventilatory reserves, and deficits in gas diffusing capacity are therefore well tolerated at rest. During exercise, the transit time through the lung capillaries is shortened, challenging gas exchange capacity in patients with low DL_{CO}, with 50 percent predicted suggested as a threshold before symptoms occur [33-35]. In EP-born, deficits in DL_{CO} raw-data are generally around 10 percent [13, 16], which was also found in the present study (see Supplemental Table A). We have previously shown that compared to controls, these same EP-born subjects have close to normal peak exercise capacity [36], findings replicated also by others [13, 37, 38]. Taken together, close-to-normal gas diffusing and

exercise capacities challenge the notion that EP birth leads to severe persistent acinar impairment, since one would expect more austere physiological findings if this was the case. Airway obstruction can lead to a higher DL_{CO} [39] and we know that EP-born (including these cohorts) have persistent airway obstruction, particularly those who had neonatal BPD [40, 41]. Thus, bronchial obstruction might mask or counteract deficits of DL_{CO} and therefore explain a surprising finding in our dataset, that EP-born with BPD tended to have a higher *z*-$DL_{CO,}$ although not significant (see Supplemental Table B).

Impaired alveolar development could theoretically hamper lung diffusing capacity through reduced area and/or a thickening or impairment of the alveolar-capillary membrane, or by impaired vascular components. We found that the membrane component of DL_{CO} was numerically reduced at both measuring time points in both the EP-born cohorts, although significantly so only at the first examination in the youngest cohort. Data for V_C did not exhibit corresponding deficits, and increased over time in both cohorts, also from 18 to 25 years of age, indicating similar growth and development in the EP and term-born groups, presumably in parallel to the increases of body size. Reduced DL_{CO} in the EP-born groups must reflect comparable reductions in its sub-components D_M and/or V_C. Given the data of our study, it is enticing to conclude that reduced DL_{CO} after preterm birth is more related to impairments of membrane diffusion than the vascular components of acinar development. Future studies preferably including more participants may disentangle the underlying mechanisms of impaired DL_{CO} following EP birth.

Disruption of alveolar growth associated with EP birth may be linked to early-onset chronic obstructive pulmonary disease (COPD) in adult life [42]. In clinical practice, DL_{CO} is used to assess severity and prognosis of COPD, as spirometry alone poorly reflects the disability in these patients. Reduced DL_{CO} is a prognostic marker independent of forced spirometry in

COPD patients [43], and associated with increased morbidity across multiple domains [43]. Moreover, lung diffusing capacity has been shown to be a significant predictor of the all-cause mortality rate within a general population, independent of standard spirometry measures, and even in the absence of apparent clinical respiratory disease [44]. There is ample data to argue that airway obstruction tracks at a reduced level from EP birth via early childhood to adulthood, and that few of these individuals reach their expected peak FEV_1 [41, 45]. Our study indicates a similar tracking also for DL_{CO}, a scenario suggesting that DL_{CO} should be included in follow-up programs after EP birth.

Strengths and limitations.

The major strengths of the study were the population-based, longitudinal and controlled design, the long follow-up period, and the high rate of attendance at the both follow-up assessments of both EP-born and term-born participants. A strict algorithm for recruitment of control subjects minimized the risk of selection bias in this group. Development during the age-span covered by the study was described by examining two birth-cohorts that overlapped in age but were born during two different NICU eras. This was not an ideal approach to address longitudinal development over the full recruitment period, but we consider it adequate to compare the trajectories for the EP and term-born groups. We cannot comment on a potential for early onset age related decline of DL_{CO}, as studies of the general population have shown that the decline starts to accelerate later than by the age of 25 years [46].

Preterm infants were exposed to highly different treatment algorithms and techniques in the 1980s and the 1990s, reflected in this study by, for example, a higher rate of subjects treated with antenatal steroids and surfactant, and also by a higher rate of survival in the younger cohort. Caution is therefore warranted for direct comparisons between the cohorts. However, this line of thinking can be turned the other way around; i.e., one may argue that similar findings in two birth-cohorts born nine years apart and treated so very differently strengthen

the notion that parameters of lung diffusion is in fact tracking from childhood to adulthood. The continuous development of NICU treatment during the last decades challenges the generalizability of these findings to today's NICU dwellers, as their outcomes may differ. Numerically our data from all the various measuring time points were in line with most previous reports on lung diffusing capacity [18, 47]. As observed also by others, we found no clear associations in our dataset between neonatal BPD and subsequent lung diffusing capacity [13, 15, 16]. Recent studies of other indices of lung function in groups and cohorts born EP in the modern era of neonatology also suggest weaker associations with BPD [48]. Thus, we should perhaps contemplate revising the use of this neonatal diagnosis to predict and label subsequent lung function in EP-born adults.

Asthma therapy was stopped approximately 24 hours prior to testing. This time frame did not allow full washout of inhaled corticosteroids. DL_{CO} is linked to the ventilation/perfusion ratio, which may be affected by bronchial obstruction. Increased airway conductance and accessible alveolar volume caused by sustained effects from asthma therapy could possibly influence the findings in the few participants with asthma. The available data in this area is scarce [49], and the 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung does not provide specific advice regarding discontinuation of asthma medications [9].

Inclusion to this study was based on both GA and BW criteria, preventing generalization of the results to all EP-born cohorts, as some dysmature infants were included based on the BW criteria alone. Potential relationships between perinatal characteristics and subsequent measures of pulmonary gas transfer should be addressed in future, larger studies.

CONCLUSION

EP-born subjects had impaired lung diffusing capacity with membrane diffusion seemingly more implicated than the capillary blood volume component. The deficits tracked from mid-childhood to adulthood, below but in parallel to matched term-born control cohorts. Preterm birth represents a significant perturbation to lung development in the short term but also long term. A life-long obligation for proper follow-up, treatment and guidance falls upon the health profession that once made survival of these young individuals possible.

Table 1. *Neonatal Characteristics of the extremely preterm (EP) subjects (n = 83).*

Variable	Group	1991–1992 Cohort		1982–1985 Cohort	
		Mean/*n*	**SD**	**Mean/*n***	**SD**
Birth weight, g, mean (range)	All EP	933 (570–1400)	204	1012 (580–1480)	189
	No/mild BPD	976 (620–1400)	195	1056 (580–1480)	191
	Moderate/severe BPD	851 (570–1200)	203	892 (670–1080)	122
Gestational age, weeks, mean (range)	All EP	27 (23–31)	2	27 (23–32)	1
	No/mild BPD	27 (24–31)	2	27 (23–32)	2
	Moderate/severe BPD	26 (23–28)	1	27 (26–30)	1
Postnatal days with oxygen, mean (range)	All EP	57 (2–180)	48	48 (1–257)	39
	No/mild BPD	31 (2–70)	23	33 (1–71)	18
	Moderate/severe BPD	108 (61–180)	43	85 (44–257)	54
Days on ventilator, mean (range)	All EP	8 (0–55)	12	11 (0–54)	12
	No/mild BPD	4 (0–40)	9	7 (0–35)	8
	Moderate/severe BPD	16 (2–55)	13	21 (1–54)	16
Antenatal steroids, *n* (%)	All EP	16 (46)	–	16 (33)	–
	No/mild BPD	11 (48)	–	10 (29)	–
	Moderate/severe BPD	5 (42)	–	6 (46)	–
Surfactant, *n* (%)	All EP	17 (49)	–	0 (0)	–
	No/mild BPD	7 (30)	–	0 (0)	–
	Moderate/severe BPD	10 (83)	–	0 (0)	–

	All EP	10 (29)	–	4 (8)	–
Postnatal steroids, *n* (%)	No/mild BPD	2 (9)	–	1 (3)	–
	Moderate/severe BPD	8 (67)	–	3 (23)	–
Maternal smoking in pregnancy, ***n*** (%)	All EP	13 (38%)		22 (48%)	–
	No/mild BPD	10 (43%)		17 (50%)	–
	Moderate/severe BPD	3 (27%)		5 (42%)	–

Abbreviations: EP: extremely preterm; SD: standard deviation; g: grams; *n*: number of subjects; BPD: bronchopulmonary dysplasia; No/mild BPD: no need for oxygen supplementation at 28 days postnatal age; Moderate/severe BPD: oxygen supplement at gestational age 36 weeks.

The number of subjects differed slightly between variables. In the 1991–1992 cohort: All EP = 34–35 subjects; No/mild BPD = 23 subjects; Moderate/severe BPD = 11–12 subjects. In the 1982–1985 cohort: All EP = 46–48 subjects; Mild/moderate BPD = 34–35 subjects; Moderate/severe BPD = 12–13 subjects.

***Table 2**. Background variables for subjects born extremely preterm and term-born controls.*

			1991–1992 cohort		1982–1985 cohort	
Examination			**First follow-up**	**Second follow-up**	**First follow-up**	**Second follow-up**
Age, years (SD)			**10.6 (0.4)**	**17.8 (0.4)**	**17.7 (1.2)**	**24.9 (1.2)**
Subjects, n (% females)	**Term-born**		35 (63)	28 (71)	46 (46)	40 (4)
	Extreme preterm		35 (63)	31 (58)	46 (46)	45 (42)
Height, cm	**Term-born**	Female	144 (141 to 147)	166 (163 to168)	168 (165.4 to 171.0)	168 (165 to 171)
		Male	145 (142 to 150)	178 (171 to 185)	177 (174 to 179)	177 (175 to 180)
	Extreme preterm	Female	141 (137 to 145)	162 (159 to 166)	163 (162 to 166)	163 (162 to 165)
		Male	139 (135 to 143)	174 (171 to 178)	175 (172 to 177)	176 (173 to 178)
Weight, kg	**Term-born**	Female	39 (36 to 41)	64 (59 to 69)	67 (60 to 73)	69 (61 to 77)
		Male	38 (34 to 42)	75 (65 to 85)	68 (65 to 71)	76 (71 to 81)
	Extreme preterm	Female	35 (30 to 41)	62 (51 to 72)	61 (53 to 68)	67 (57 to 76)
		Male	35 (27 to 42)	73 (62 to 83)	66 (59 to 72)	80 (74 to 87)
Self-reported smoking, n (%)	**Term-born**		0 (0)	5 (18)	14 (30)	8 (21)
	Extreme preterm		0 (0)	1 (3)	15 (33)	17 (38)
Maternal smoking in pregnancy, n (%)	**Term-born**		9 (26)	–	10 (22)	–
	Extreme preterm		13 (37)	–	22 (48)	–
Z-FEV$_1$	**Term-born**		−0.09 (−0.4 to 0.2)	−0.06 (−0.5 to 0.3)	0.3 (−0.4 to 0.6)	0.05 (−0.3 to 0.4)

	Extreme preterm	−0.9 (−1.2 to −0.6)	−0.8 (−1.1 to −0.5)	−1.05 (−1.6 to −0.5)	−1.0 (−1.5 to −0.5)
Z-FVC	**Term-born**	−0.1 (−0.4 to 0.2)	−0.08 (−0.4 to 0.2)	−0.05 (−0.4 to 0.3)	0.09 (−0.3 to 0.4)
	Extreme preterm	−0.6 (−0.9 to −03)	−0.3 (−0.6 to 0.03)	−0.9 (−1.5 to −0.4)	−0.5 (−1.0 to 0.04)
	Term-born	−0.2 (−0.6 to 0.2)	−0.2 (−0.6 to 0.3)	0.5 (0.1 to 0.8)	−0.004 (−0.3 to 0.3)
Z-FEF25-75	**Extreme preterm**	−1.1 (−1.5 to −0.7)	−0.9 (−1.3 to −0.5)	0.8 (−1.2 to −0.5)	−1.2 (−1.5 to −0.8)

Abbreviations: FEV_1- forced expiratory volume in 1 second; FVC- forced vital capacity; FEF_{25-75}- forced expiratory flow between 25 and 75% of vital capacity. Numbers are group means (95% confidence interval) unless stated otherwise.

Table 3. *Lung diffusing capacity data from 10 to 25 years of age for extreme preterm subjects compared to term-born control subjects (n = 160*).*

	1991–1992 cohort								1982-85 cohort							
Examination	**First follow-up**					**Second follow-up**				**First follow-up**				**Second follow-up**				
Age, mean (SD)	10.6 (0.4) years					17.8 (0.4) years				17.7 (1.2) years				24.9 (1.2) years				
	Mean	95% CI			*P*-value	Mean	95% CI		*P*-value	Mean	95% CI		*P*-value	Mean	95% CI		*P*-value	
Z-DL_{CO}																		
Term-born	−0.3	−0.6	to	0.0		0.2	−0.1	to	0.6		−0.3	−0.6	to	−0.0		0.0	−0.2	to	0.3	
Extreme preterm	−1.2	−1.5	to	−0.8		−0.6	−1.0	to	−0.3		−0.8	−1.1	to	−0.6		−0.5	−0.8	to	−0.2	
Difference	0.9	0.4	to	1.3	< 0.001	0.9	0.4	to	1.4	< 0.001	0.6	0.2	to	1.0	0.007	0.6	0.2	to	1.0	0.007
DL_{CO} %-predicted																		
Term-born	95.7	91.3	to	100.1		104.0	99.1	to	108.9		96.6	92.8	to	100.4		101.3	97.3	to	105.3	
Extreme preterm	83.1	78.6	to	87.5		92.1	87.5	to	96.8		89.1	85.1	to	93.2		93.7	89.6	to	97.8	
Difference	12.6	6.4	to	18.9	< 0.001	11.9	5.1	to	18.6	< 0.001	7.4	1.9	to	13	0.009	7.6	1.9	to	13.4	0.009
***Z*-V_A**																		
Term-born	−0.4	−0.7	to	−0.1		0.1	−0.2	to	0.4		0.1	−0.2	to	0.4		−0.1	−0.3	to	0.2	
Extreme preterm	−0.7	−1.0	to	−0.4		−0.3	−0.6	to	0.0		0.0	−0.2	to	0.3		0.0	−0.3	to	0.3	
Difference	0.3	−0.1	to	0.7	0.17	0.4	−0.0	to	0.9	0.07	0.0	−0.3	to	0.4	0.82	−0.1	−0.4	to	0.3	0.77
***Z*-K_{CO}**																		
Term-born	0.0	−0.3	to	0.3		0.1	−0.3	to	0.5		−0.4	−0.7	to	−0.1		0.1	−0.2	to	0.4	
Extreme preterm	−0.6	−0.9	to	−0.3		−0.4	−0.8	to	−0.1		−0.9	−1.2	to	−0.6		−0.6	−0.9	to	−0.2	
Difference	0.6	0.1	to	1.1	0.01	0.5	0.0	to	1.0	0.04	0.5	0.1	to	1.0	0.01	0.6	0.2	to	1.1	0.003
K_{CO} %-predicted																		
Term-born	100.5	95.9	to	105.1		101.5	96.5	to	106.4		95.5	91.5	to	99.5		101.9	97.8	to	106.1	
Extreme preterm	90.5	85.9	to	95.1		94.9	90.1	to	99.7		88.6	84.4	to	92.7		93.7	89.5	to	97.9	
Difference	10.0	3.5	to	16.4	0.003	6.6	−0.3	to	13.5	0.06	6.9	1.2	to	12.7	0.02	8.2	2.3	to	14.1	0.006

D_M																			
Term-born	9.7	8.3	to	11.2		15.1	13.5	to	16.7		17.0	15.7	to	18.2		17.0	15.6	to	18.3	
Extreme preterm	7.5	6.0	to	9.0		13.2	11.7	to	14.7		15.3	13.9	to	16.6		15.4	14.0	to	16.7	
Difference	2.3	0.2	to	4.3	0.03	1.9	−0.3	to	4.1	0.09	1.7	−0.1	to	3.5	0.07	1.6	−0.3	to	3.5	0.10
V_C																			
Term-born	52.5	45.6	to	59.4		86.8	78.8	to	94.8		79.4	73.4	to	85.4		93.0	86.4	to	99.6	
Extreme preterm	51.9	44.7	to	59.2		82.8	75.3	to	90.3		72.5	65.9	to	79.0		92.2	85.5	to	98.8	
Difference	0.5	−9.4	to	10.5	0.91	4.0	−7.0	to	14.9	0.47	7.0	−1.9	to	15.8	0.12	0.8	−8.6	to	10.2	0.87

Abbreviations: SD: standard deviation; CI: confidence interval; DL_{CO}: Diffusing capacity of the lung for carbon monoxide; V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide; D_M: Alveolar-capillary membrane conductance; V_C: Pulmonary-capillary blood volume.

The numbers are estimated group means with 95% confidence interval from longitudinal mixed-effects models. The values for DL_{CO}, V_A, and K_{CO} are reported as Z-scores and percentages of predicted (DL_{CO} and K_{CO}), while values for D_M and V_C are absolute numbers. D_M= mmol/min/kPa, V_C= ml.

* The number of subjects included in at least one regression model. The number of cases and controls for each variable and at each time point is shown in Figure 1 in the main paper.

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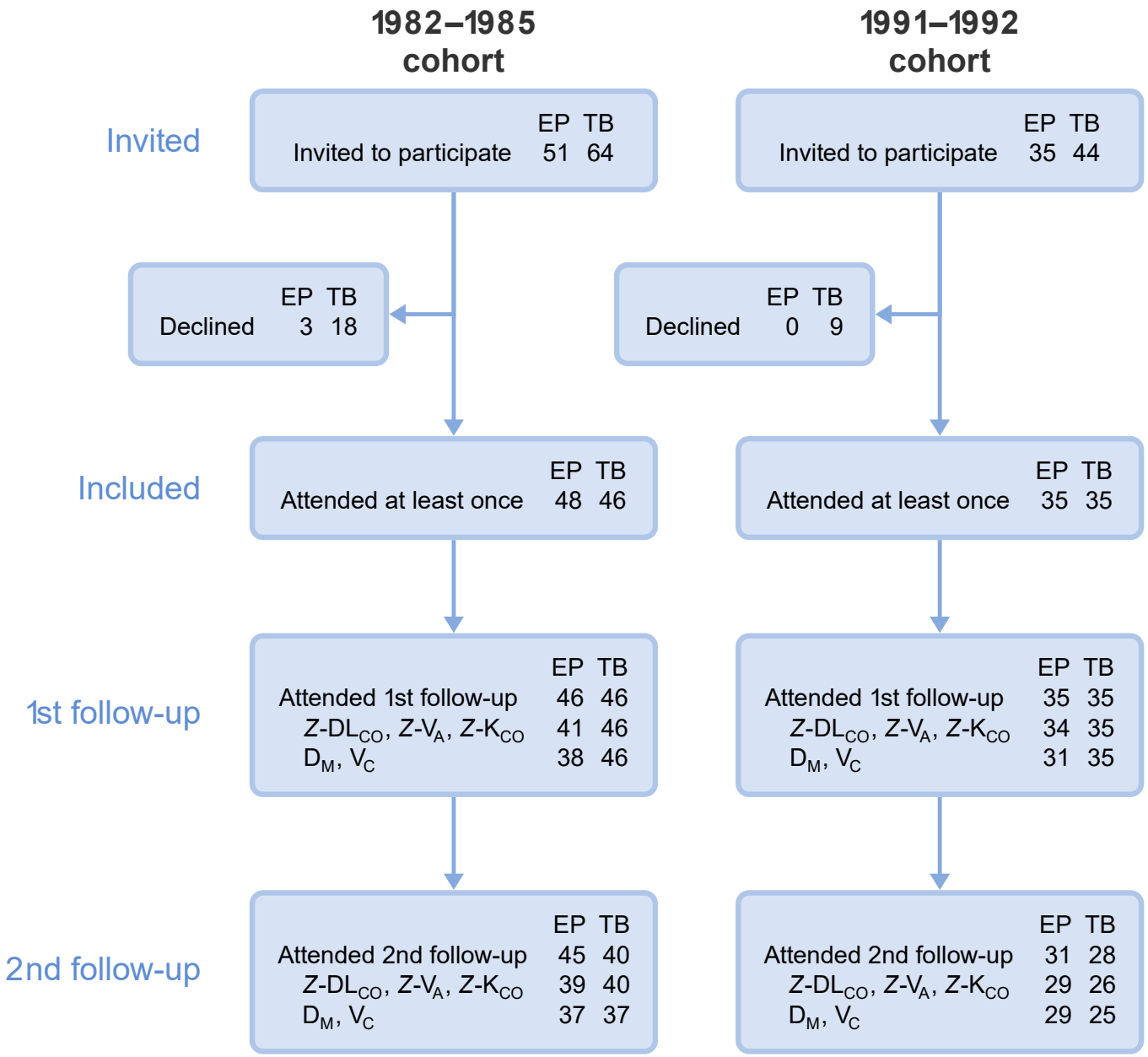
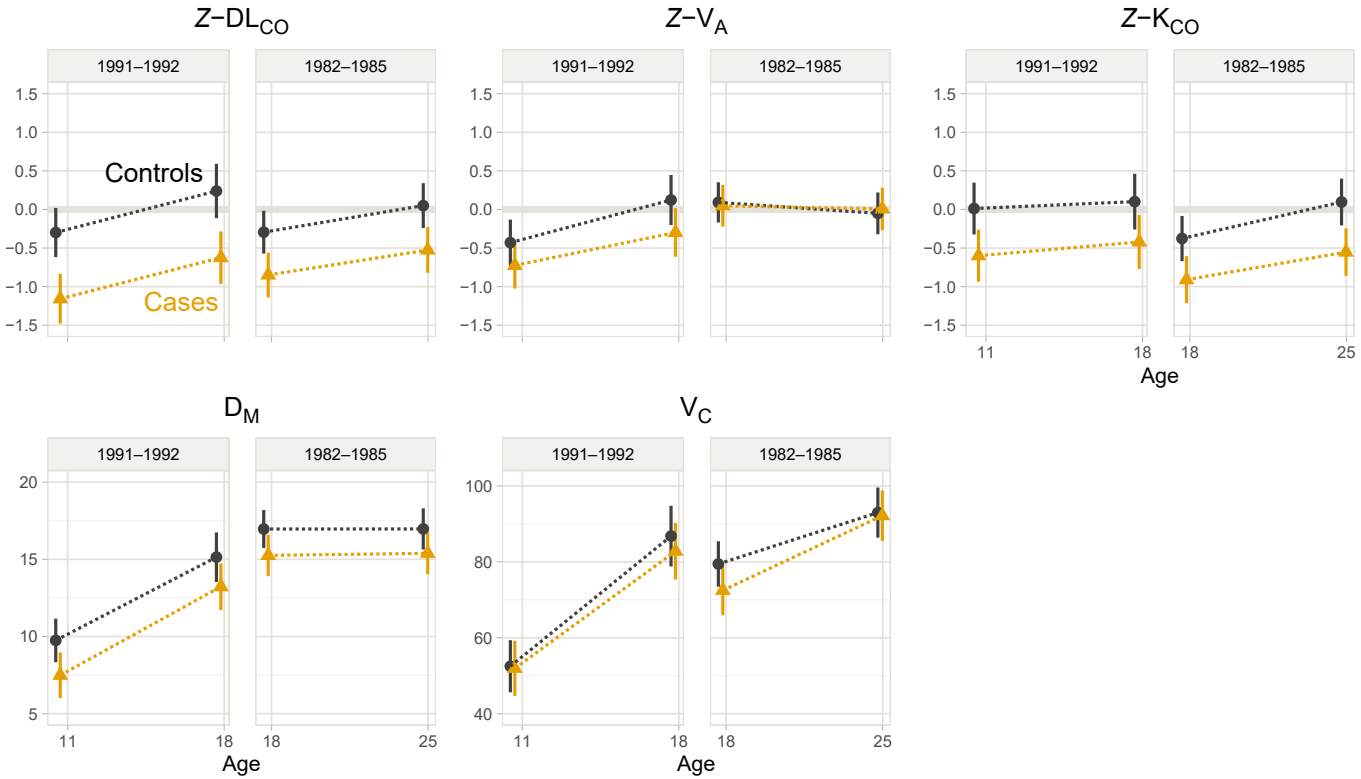
Figure 1. Recruitment process of the study (*n* = 164).



Recruitment of the extremely preterm (EP) born cohorts and their term-born (TB) age- and sex-matched control subjects. Two subjects in the 1982-1985 cohort participated in the second follow-up in 2008/2009 but not in the first in 2001/2002. $DL_{CO:}$ Diffusing capacity of the lung for carbon monoxide; V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide; D_M: Alveolar-capillary membrane conductance; V_C: Pulmonary-capillary blood volume.

Figure 2. Mean lung diffusing capacity (with 95% confidence intervals) from approximately 10 to 25 years of age for EP-born compared to term-born subjects (*n* = 160*).



The numbers are estimated group means with 95% confidence interval from longitudinal mixed-effects models. The points/lines for the two groups have been slightly adjusted horizontally to avoid overlapping. The values for DL_{CO}, V_A, and K_{CO} are reported as *z*-scores, while values for D_M and V_C are absolute numbers. D_M= mmol/min/kPa, V_C= ml.

Abbreviations: EP: extremely preterm; $DL_{CO:}$ Diffusing capacity of the lung for carbon monoxide; V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide; D_M: Alveolar-capillary membrane conductance; V_C: Pulmonary-capillary blood volume.

* The number of subjects included in at least one regression model. The number of cases and controls for each variable and at each time point is shown in Figure 1.

Supplemental Table A. *Raw data for lung diffusing capacity from 10 to 25 years of age for extreme preterm subjects compared to term-born control subjects (n = 160*).*

	1991–1992 cohort								1982–1985 cohort							
Examination	**First follow-up**				**Second follow-up**				**First follow-up**				**Second follow-up**			
Age, mean (SD)	10.6 (0.4) years				17.8 (0.4) years				17.7 (1.2) years				24.9 (1.2) years			
	Mean	95% CI			Mean	95% CI			Mean	95% CI			Mean	95% CI		
DL_{CO} ($mmol \cdot min^{-1} \cdot kPa^{-1}$)																
Term-born	5.4	5.2	to	5.6	8.7	7.8	to	9.6	8.9	8.3	to	9.5	9.6	8.9	to	10.4
EP-born	4.4	4.1	to	4.7	7.9	7.2	to	8.6	8.0	7.4	to	8.5	8.7	8.1	to	9.4
V_A (liter)																
Term-born	3.0	2.9	to	3.1	5.2	4.8	to	5.6	5.6	5.3	to	5.9	5.9	5.5	to	6.3
EP-born	2.7	2.5	to	2.8	5.0	4.6	to	5.3	5.3	5.0	to	5.6	5.7	5.3	to	6.0
K_{CO} ($mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$)																
Term-born	1.8	1.8	to	1.9	1.7	1.6	to	1.8	1.6	1.5	to	1.7	1.6	1.6	to	1.7
EP-born	1.7	1.6	to	1.7	1.6	1.5	to	1.7	1.5	1.4	to	1.6	1.5	1.5	to	1.6
D_M ($mmol \cdot min^{-1} \cdot kPa^{-1}$)																
Term-born	9.7	9.0	to	10.5	15.1	13.6	to	16.6	17.0	15.6	to	18.4	17.0	15.6	to	18.5
EP-born	7.4	6.5	to	8.3	13.2	11.5	to	14.8	15.0	13.4	to	16.6	15.3	13.4	to	17.2
V_C (mL)																
Term-born	52.5	48.2	to	56.8	86.9	73.5	to	100.2	79.4	73.8	to	85.1	92.9	85.2	to	100.6
EP-born	51.3	43.5	to	59.0	52.6	74.8	to	90.4	72.6	68.0	to	77.1	91.8	84.5	to	99.2

Abbreviations: SD: standard deviation; CI: confidence interval; DL_{CO}: Diffusing capacity of the lung for carbon monoxide; V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide; D_M: Alveolar-capillary membrane conductance; V_C: Pulmonary-capillary blood volume.

The numbers are estimated group means with 95% confidence interval. The values are reported as absolute numbers.

* The number of subjects included in at least one regression model. The number of cases and controls for each variable and at each time point is shown in Figure 1 in the main paper.

***Supplemental Table B**- Lung Diffusing capacity in two cohorts of extremely preterm and term-born subjects born 1991–1992 and 1982–1985, stratified by grade of BPD severity (n = 160*).*

	1991–1992 cohort							1982–1985 cohort						
Examination	**First follow-up**				**Second follow-up**			**First follow-up**				**Second follow-up**		
Age, mean (SD)	10.6 (0.4) years				17.8 (0.4) years			17.7 (1.2) years				24.9 (1.2) years		
	Mean	95% CI			Mean	95% CI		Mean	95% CI			Mean	95% CI	
Z-DL_{CO}														
Term-born	−0.3	−0.6	to	0.0	0.2	−0.1	to	0.6	−0.3	−0.6	to	−0.0	0.0	−0.2	to	0.3
EP non/mild BPD	−1.4	−1.8	to	−1.0	−0.7	−1.1	to	−0.3	−0.8	−1.2	to	−0.5	−0.6	−1.0	to	−0.3
EP mod/sev BPD	−0.7	−1.2	to	−0.2	−0.4	−1.0	to	0.1	−0.9	−1.4	to	−0.3	−0.2	−0.8	to	0.4
***Z*-V_A**																
Term-born	−0.4	−0.7	to	−0.1	0.1	−0.2	to	0.4	0.1	−0.2	to	0.4	−0.0	−0.3	to	0.2
EP non/mild BPD	−0.8	−1.2	to	−0.4	−0.5	−0.9	to	−0.1	0.1	−0.2	to	0.4	0.0	−0.3	to	0.3
EP mod/sev BPD	−0.6	−1.1	to	−0.1	0.1	−0.5	to	0.6	−0.1	−0.6	to	0.4	−0.0	−0.5	to	0.5
***Z*-K_{CO}**																
Term-born	0.0	−0.3	to	0.3	0.1	−0.3	to	0.5	−0.4	−0.7	to	−0.1	0.1	−0.2	to	0.4
EP non/mild BPD	−0.8	−1.2	to	−0.3	−0.4	−0.8	to	0.1	−1.0	−1.3	to	−0.6	−0.6	−1.0	to	−0.3
EP mod/sev BPD	−0.3	−0.9	to	0.3	−0.5	−1.1	to	0.1	−0.8	−1.4	to	−0.2	−0.3	−0.9	to	0.3
D_M																
Term-born	9.7	8.3	to	11.2	15.1	13.5	to	16.7	17.0	15.7	to	18.2	17.0	15.6	to	18.3
EP non/mild BPD	7.7	5.8	to	9.5	12.4	10.5	to	14.3	15.5	13.9	to	17.1	15.5	13.9	to	17.1
EP mod/sev BPD	7.2	4.7	to	9.7	14.8	12.2	to	17.4	14.7	12.2	to	17.2	15.2	12.6	to	17.8
V_C																
Term-born	52.5	45.6	to	59.3	86.8	78.8	to	94.8	79.4	73.5	to	85.4	93.0	86.4	to	99.6
EP non/mild BPD	48.5	39.5	to	57.5	78.8	69.6	to	88.0	71.2	63.4	to	79.0	90.1	82.4	to	97.9
EP mod/sev BPD	58.2	46.0	to	70.3	90.4	77.7	to	103.1	75.6	63.4	to	87.8	97.5	84.7	to	110.2

Abbreviations: SD: standard deviation; CI: confidence interval; DL_{CO}: Diffusing capacity of the lung for carbon monoxide; V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide; D_M: Alveolar-capillary membrane conductance; V_C: Pulmonary-capillary blood volume.

The numbers are estimated group means with 95% confidence interval from longitudinal mixed-effects models. The values for DL_{CO}, V_A, and K_{CO} are reported as Z-scores, while values for D_M and V_C are absolute numbers. D_M= mmol/min/kPa, V_C= ml.

* The number of subjects included in at least one regression model. The number of cases and controls for each variable and at each time point is shown in Figure 1 in the main paper.