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# Association between asthma and lung function in adolescents born very preterm: results of the EPIPAGE cohort study

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## ABSTRACT

Prematurity and bronchopulmonary dysplasia (BPD) affect long-term lung function. We studied the respiratory outcome of adolescents born very preterm and controls from the Etude EPIdémiologique sur les Petits Ages Gestationnels cohort and analysed their current lung function in relation to asthma symptoms (categorised in three age groups) from birth. In models including BPD, asthma at each age and confounding factors in the preterm group, BPD and preschool wheeze were the only independent variables associated with FEV<sub>1</sub>. Preschool wheeze is an independent factor associated with FEV<sub>1</sub> impairment in adolescents born very preterm. These results highlight the need for optimal management of early respiratory symptoms in preterm-born infants.

**Trial registration number** Results, NCT01424553.

## INTRODUCTION

Prematurity persistently affects respiratory outcome.<sup>1–3</sup> Postnatal asthma symptoms could have an additive effect on functional alterations related to prematurity. We studied lung function in relation to asthma symptoms from birth in adolescents born very preterm and in controls from the Etude EPIdémiologique sur les Petits Ages Gestationnels (EPIPAGE) cohort.

## METHODS

### Study design

The EPIPAGEADO study was registered at clinicaltrials.gov (NCT01424553). The study population was part of the EPIPAGE cohort (see online Supplementary file 1 for details) and was restricted to children born very preterm and at term in four French regions. The inclusion criteria were complete participation in EPIPAGE from birth, available assessment at 5 and/or 8 years, national health insurance and written parental informed consent. Inclusions took place between November 2011 and June 2013.

### Data collection

Numerous data were prospectively collected from birth to 8 years during EPIPAGE. Data analysed for EPIPAGEADO are detailed in the online supplementary data. Asthma and atopic symptoms were collected at age 2, 3, 4, 5 and 8 years (online Supplementary table S1).

At 15 years, the investigator completed a

questionnaire with parents and participants (data detailed in the online Supplementary file 1). Teenage asthma and rhinitis were defined according to the French version of the standardised International Study of Asthma and Allergies in Childhood auto-questionnaire.<sup>4</sup>

### Lung function tests (LFTs)

LFTs were performed according to the recommendations of the American Thoracic Society/European Respiratory Society task force (detailed in the online Supplementary file 1).<sup>5</sup>

### Statistical analyses

BPD was defined as the need for supplemental oxygen and/or ventilatory support at 36 weeks of postmenstrual age. Asthma was categorised into preschool wheeze (from birth to 5 years), school age asthma (at 8 years) and teenage asthma. LFT parameters were expressed as Z-score. Asthma groups and LFT parameters were analysed according to gestational age and BPD. Associations between asthma and perinatal and postnatal characteristics were studied in the group of preterm subjects. A similar analysis was performed for FEV<sub>1</sub>. In the group of preterm subjects, multiple linear regression models were used to quantify relationships between FEV<sub>1</sub>, BPD and each asthma group before and after adjustment for potential confounders that were smoking during pregnancy, environmental tobacco smoke exposure during infancy,<sup>6</sup> atopy (composite variable defined in the online Supplementary file 1), parents' occupational level<sup>7</sup> and gender. Active smoking was not considered as only 4.1% and 2.8% of preterm-born adolescents declared weekly and daily smoking, respectively. The beta coefficient for each variable was estimated for an increase of 0.1 in FEV<sub>1</sub> Z-score. Results were statistically significant when  $p < 0.05$ . Analyses were performed with SAS V.9.4.

## RESULTS

### Study population's characteristics

The study included 304 adolescents born very preterm and 47 controls (flow chart in online Supplementary figure S1); 273 and 44 performed complete prebronchodilator spirometry. There were more girls among included control subjects and parents' occupational level in the preterm group was higher among the included subjects (online Supplementary table S2).



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**Table 1** Lung function measurements according to gestational age and the occurrence of BPD

	Preterm children (24–32 wPMA)			Term children (39–40 wPMA)		Preterm children with BPD		Preterm children without BPD		P values	
	n	Mean (SD)		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Pre-BD spirometry											
Z-score FEV <sub>1</sub>	274	−0.6 (1.3)		44	−0.1 (1.0)	0.03	49	−1.4 (1.2)	225	−0.4 (1.2)	<0.001
Z-score FEF <sub>25–75</sub>	274	−0.6 (1.2)		44	0.0 (1.2)	0.003	49	−1.4 (1.2)	225	−0.4 (1.2)	<0.001
Z-score FVC	273	−0.3 (1.2)		44	−0.2 (0.8)	0.41	49	−1.1 (1.4)	224	−0.2 (1.1)	<0.001
Z-score FEV <sub>1</sub> /FVC	273	−0.3 (1.3)		44	0.2 (1.2)	0.05	49	−0.6 (1.4)	224	−0.2 (1.3)	0.05
DLCO % predicted	143	113.1 (23.3)		15	116.6 (27.4)	0.59	22	112.5 (21.3)	121	113.2 (23.7)	0.90
FeNO (ppb)	191	13.6 (14.9)		31	18.4 (38.9)	0.22	29	9.6 (6.8)	162	14.3 (15.8)	0.12
Post-BD spirometry											
Z-score FEV <sub>1</sub>	263	−0.2 (1.3)		41	0.2 (0.9)	0.06	46	−1.0 (1.3)	217	−0.1 (1.2)	<0.001
Z-score FEF <sub>25–75</sub>	264	−0.1 (1.2)		41	0.5 (1.0)	<0.001	46	−0.9 (1.2)	218	0.0 (1.1)	<0.001
Z-score FEV <sub>1</sub> /FVC	263	0.1 (1.2)		41	0.6 (0.9)	0.01	46	−0.4 (1.1)	217	0.2 (1.2)	0.005

Comparisons were performed by analysis of variance.

BD, bronchodilator; BPD, bronchopulmonary dysplasia; DLCO, diffusion capacity of carbon monoxide; FEF<sub>25–75</sub>, forced expiratory flow 25–75; wPMA, weeks of postmenstrual age.

### Asthma outcome and its determinants in adolescents born preterm

Preschool wheeze was significantly more frequent in preterm-born subjects than in controls (RR 1.71 (1.01–2.90),  $p=0.03$ ) and was more prevalent among preterm-born children with BPD than those without (RR 1.4 (0.98–1.90),  $p=0.04$ ) (online Supplementary table S3). Among preterm subjects, preschool wheeze was more prevalent in boys. Participants with atopy were at higher risk of being asthmatic at school age and as teenagers (online Supplementary table S4).

### Lung function and its determinants in adolescents born preterm

Main results are presented in table 1. Only 7% of preterm-born children showed improvement of FEV<sub>1</sub> by 12% or more. There was no correlation between FEV<sub>1</sub> and FeNO ( $p=0.34$ ) among preterm-born subjects. FeNO was significantly higher in adolescents having had school age asthma and in current asthmatic adolescents but

not in adolescents having had preschool wheeze (data not shown). Among preterm subjects, BPD was the only perinatal variable independently associated with FEV<sub>1</sub> at adolescence ( $p<0.001$ ) (online Supplementary table S5).

### Associations between FEV<sub>1</sub>, BPD and asthma in adolescents born preterm

Table 2 shows associations between FEV<sub>1</sub>, BPD and asthma symptoms at different ages before and after adjustment. BPD and preschool wheeze were the only variables independently associated with a lower mean prebronchodilator and postbronchodilator FEV<sub>1</sub> at adolescence (table 2).

### DISCUSSION

We confirm that prematurity and especially BPD not only lead to lower lung function at adolescence but also show that wheezing episodes during the preschool period are independently

**Table 2** Multivariate analysis between FEV<sub>1</sub>, BPD and asthma groups among preterm subjects

	Prebronchodilator FEV <sub>1</sub>				Postbronchodilator FEV <sub>1</sub>			
	n	Mean (SD)	$\beta$ a coeff* (95% CI)	P values	n	Mean (SD)	$\beta$ a coeff* (95% CI)	P values
BPD								
No	189	−0.3 (1.1)	0	<0.001	184	−0.1 (1.2)	0	<0.001
Yes	42	−1.4 (1.3)	−1.0 (−1.4 to −0.6)		40	−1.0 (1.3)	−0.9 (−1.3 to −0.5)	
Preschool wheeze								
No	133	−0.3 (1.2)	0	0.01	129	0.0 (1.2)	0	0.01
Yes	98	−0.9 (1.2)	−0.4 (−0.8 to −0.1)		95	−0.5 (1.3)	−0.5 (−0.8 to −0.1)	
School age asthma								
No	188	−0.4 (1.2)	0	0.22	182	−0.1 (1.3)	0	0.62
Yes	43	−1.0 (1.2)	−0.3 (−0.7 to 0.2)		42	−0.6 (1.2)	−0.1 (−0.6 to 0.4)	
Teenage asthma								
No	192	−0.5 (1.2)	0	0.50	187	−0.2 (1.3)	0	0.78
Yes	39	−0.6 (1.4)	0.1 (−0.3 to 0.6)		37	−0.3 (1.2)	0.1 (−0.4 to 0.5)	

Adjustment was performed for all the variables in the table and the selected confounders that are: smoking during pregnancy, environmental tobacco smoke exposure during infancy, atopy, parents' occupational level and gender. For example, analysis between FEV<sub>1</sub> and preschool wheeze was adjusted for the selected confounders and for BPD, school age asthma and teenage asthma.

\*Coefficient for an increase of 0.1 in FEV<sub>1</sub>.

BPD, bronchopulmonary dysplasia.

associated with late lung function.

Analysis of lung function in 11-years-old children born extremely preterm revealed that having ever been diagnosed with asthma, current asthmatic symptoms and treatment with  $\beta$ -agonists were each independently associated with lung function Z scores.<sup>8</sup> This study did not evaluate the impact of asthma symptoms at different ages on lung function, limiting the comparison of our results with theirs.

We showed that prematurity and BPD are associated with an increased risk of wheezing episodes and asthma symptoms in children. These results are consistent with previous reports.<sup>2,3</sup> No association of asthma at adolescence with preterm birth or BPD was found as previously described in one other study.<sup>9</sup>

A decrease in airway calibre was initially evoked as the mechanism of airflow limitation in ex-preterm individuals, with stabilised and non-progressive structural damage following disrupted development.<sup>10</sup> This is consistent with the low number of children with significant reversibility observed in our population and others.<sup>8</sup> Aside from anatomical origins, several studies argue for the additive role of dynamic processes in the airways of preterm-born subjects, with on-going disease, that may be induced by preterm birth per se and postnatal environmental factors.<sup>11</sup> Lifelong environmental factors may have a deleterious synergistic effect, like environmental tobacco smoke exposure in infancy and later active smoking.<sup>12</sup> Here, we provide arguments for an independent impact of a postnatal clinical factor, preschool wheeze, on alterations of lung function in preterm-born subjects at adolescence. Preschool wheeze would therefore be both a consequence of reduced airway calibre, due to prematurity, and an aggravating factor of lung function deficit. The potential inflammation associated with these early symptoms, in the setting of prematurity and BPD, seems likely different from that observed in atopic asthma, as suggested by FeNO values in our preschool wheeze group.

The main limitation of this study is the items used to define asthma and is shared by many others studies. One other limitation is the risk of selection bias. Like many other similar cohorts, the number of evaluable patients decreased over time. However, comparison between included and non-included subjects did not show significant differences regarding perinatal characteristics and asthma status. We could not correlate the long-term pulmonary outcomes to the severity of BPD that was not assessed in EPIPAGE. We were not able to assess the impact of palivizumab prophylaxis that was not yet routinely used in 1997 in France on the subsequent development of asthma as recently suggested.<sup>13</sup>

In conclusion, we showed that early childhood asthma symptoms are independent factors associated with alterations in lung function in adolescents born very preterm. Although our study does not allow us to conclude that better prevention of these early episodes of wheezing could limit the loss of respiratory function in these children, it strongly encourages the evaluation of such strategies.

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**Contributors** Study concept and design: AH, CD, CA, J-CR, SM and P-YA. Data acquisition: CD, MM, MV, LC, AB and the members of the EPIPAGEADO study group. Analysis and interpretation of data: AH, CD, P-YA and JR. Drafting the article: AH, CD, P-YA and JR. Critical revision of the manuscript for important intellectual content: AH, CD, P-YA. CA, J-CR, SM, MM, MV, LC, JR and the members of the EPIPAGEADO study group. Final approval of the version to be published: AH, CD, P-YA, JR, AB, CA, J-CR, SM, MM, MV, LC, and the members of the EPIPAGEADO study group. AH and P-YA had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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