

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 FEV₁. Preschool wheeze is an independent factor associated with FEV₁ 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.^{1–3} 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.⁴

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).⁵

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 FEV₁. In the group of preterm subjects, multiple linear regression models were used to quantify relationships between FEV₁, BPD and each asthma group before and after adjustment for potential confounders that were smoking during pregnancy, environmental tobacco smoke exposure during infancy,⁶ atopy (composite variable defined in the online Supplementary file 1), parents' occupational level⁷ 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 FEV₁ 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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Brief communication

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)	P values	n	Mean (SD)	n	Mean (SD)	
Pre-BD spirometry										
Z-score FEV ₁	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 _{25–75}	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 ₁ /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 ₁	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 _{25–75}	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 ₁ /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_{25–75}, 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 FEV₁ by 12% or more. There was no correlation between FEV₁ 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 FEV₁ at adolescence ($p<0.001$) (online Supplementary table S5).

Associations between FEV₁, BPD and asthma in adolescents born preterm

[Table 2](#) shows associations between FEV₁, 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 FEV₁ 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 FEV₁, BPD and asthma groups among preterm subjects

	Prebronchodilator FEV ₁				Postbronchodilator FEV ₁			
	n	Mean (SD)	β a coeff* (95% CI)	P values	n	Mean (SD)	β 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 FEV₁ 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 FEV₁.

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 β -agonists were each independently associated with lung function Z scores.⁸ 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.^{2,3} No association of asthma at adolescence with preterm birth or BPD was found as previously described in one other study.⁹

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.¹⁰ This is consistent with the low number of children with significant reversibility observed in our population and others.⁸ 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.¹¹ Lifelong environmental factors may have a deleterious synergistic effect, like environmental tobacco smoke exposure in infancy and later active smoking.¹² 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.¹³

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 EPIPAGE0 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 EPIPAGE0 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 EPIPAGE0 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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Association between asthma and lung function in adolescents born very preterm: results of the
EPIPAGE cohort study

Online supplementary data

Supplementary methods

The EPIPAGE study

EPIPAGE (Etude EPIdémiologique sur les Petits Ages Gestationnels) was a prospective observational population-based cohort that included all births (live births and stillbirths) and late pregnancy terminations that occurred between 22 and 32 completed weeks of gestation in all maternity wards of nine French regions in 1997.[1] Two control groups were also included: one of individuals born at term (one in every four births at 39 or 40 weeks of gestation during 1 week in 1997), and one of moderate preterm infants, born between 33 and 34 weeks of gestation (inclusion during 2 months in 1997). At recruitment in the maternity or neonatal unit, parents were informed of the study and given written information. Oral consent was given to the medical team in charge of the study in accordance with French rules in force in 1997. The study was approved by the French Commission Nationale de l'Informatique et des Libertés (the French data protection agency). The objectives of the study were the following:[2]

- Description of obstetrical and neonatal practices for the care of very preterm new-borns
- Analysis of the causes of very preterm birth
- Measures of neonatal mortality and short- and long-term survival
- Evaluation of the children and their families during childhood
- Identification of the pre-, per-, and postnatal factors involved in the health of the child and his/her development
- Study of the adverse effects of intensive care techniques and treatments used for very preterm new-borns

Data for mothers, pregnancies, births, and neonatal outcomes were recorded on standardized questionnaires at each maternity and neonatal intensive care unit. Maternal data included ethnic origin, tobacco consumption during pregnancy, and causes of preterm birth. Neonatal data included gender, gestational age (determined from the last menstrual period and findings from early prenatal ultrasound scans, calculated in complete weeks), birth weight, postnatal sepsis (defined as a postnatally acquired infection treated with antibiotics for at least 7 days), necrotizing enterocolitis, and bronchopulmonary dysplasia (BDP). BPD was defined as the need for supplemental oxygen and/or ventilatory support at 36 weeks of post-menstrual age. Information about the health and the development of the children was subsequently collected by questionnaires sent to the families two months after discharge, and when the child was nine months, and one, two, three, and four years old. At two years of age, a questionnaire was also sent to the child's physician. At five years of age, the children were invited for a check-up with a physician and a psychologist at local centres in every region. At eight years of age, a questionnaire was sent to the families.

Of the 2901 preterm live born children that were included from January 1, 1997, to December 31, 1997 [1], 2459 (85%) were alive at discharge. At age five years, of the 2251 survivors (95%) whose parents agreed to follow-up at birth, 1812 (80%) had a clinical evaluation.[3] At age 8 years, 1444 questionnaires (64%) were completed by families. The full-term birth reference group consisted of 666 children. Follow-up rates were 59% (n = 396) at 5 years and 49% (n = 327) at 8 years.

EPIPAGEADO was restricted to the very preterm- and full-term born children in four French regions: Paris, Normandie, Pays-de-la-Loire, and Midi-Pyrénées.

Data collection from birth to 8 years of age

The following data collected in EPIPAGE were analysed for EPIPAGEADO:

- Parental data: parents' occupational level and mother's tobacco consumption during pregnancy
- Perinatal and neonatal: gestational age at birth, birth weight, gender, and BPD, defined as the need for supplemental oxygen and/or ventilatory support at 36 weeks of post-menstrual age.
- Data concerning asthma and atopic symptoms collected at 2, 3, 4, 5, and 8 years of age by a parental and/or a physician questionnaire (asked questions detailed in Online Supplementary Table S1).

Assessment at 15 years of age

Data collection

The investigator completed a questionnaire with the parents and the participant, with data on the family and school situation, parents' occupational level, tobacco habits of the parents and participants, current treatments and medical follow-up, and asthma, rhinitis, and eczema in the parents and siblings. Participant tobacco habits were assessed by the investigator during a confidential interview with each participant without his/her parents.

ISAAC questionnaire

Participants answered the French version of the standardized International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[4] Participants were considered to have symptoms compatible with current asthma (labelled as teenage asthma) when they answered yes to the question "Have you had wheezing or whistling in the chest in the past 12 months?". They were considered to have allergic rhinitis when they answered yes to the question "Have you ever had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?" and/or to the question "Have you ever had hay fever?".

Definition of the variable atopy

Atopy was defined by the presence of eczema and/or rhinitis in the participant and/or by the presence of these symptoms and/or asthma in first degree relatives

Lung function tests

LFT were performed according to the recommendations of the American Thoracic Society/European Respiratory Society task force.[5] FEV₁ measures were expressed as Z-score values according to GLI 2012 lung function regression equations (www.lungfunction.org). Forced vital capacity (FVC), slow vital capacity (SVC), FEV₁, functional residual capacity by plethysmography (FRC), total lung capacity (TLC), residual volume (RV), forced expiratory flow 50 (FEF50), and forced expiratory flow 25–75 (FEF25-75) were measured, before and 15 minutes after inhalation of 400µg salbutamol. A positive response to bronchodilators was defined by an increase in FEV₁ > 12% after inhalation of salbutamol. An obstructive ventilatory defect was defined by a FEV₁ Z-score < -1.64. FeNO and DLCO were also measured.

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Online Supplementary Table S1: Collected asthma and atopic items

Age at assessment (y)	Parental questionnaire	Physician questionnaire
2	Since birth, did your child have asthma attacks? Did your child have eczema in the last 12 months?	Asthmatic bronchitis between the ages of 1 and 2? NA
3	Since the age of 2, has your child had asthma attacks (wheezing in the chest)? Asthmatic bronchitis?	NA
4	Since the age of 3, has your child had asthma attacks (wheezing in the chest)? Asthmatic bronchitis? Since the age of 3, has your child had eczema?	NA NA
5	NA NA	Asthma attacks or asthmatic bronchitis in the last 12 months? Eczema in the last 12 months?
8	Does your child have asthma?	NA

NA: not assessed

Online supplementary Table S2: Characteristics of the study population and comparison with non-participant subjects

		Preterm children (24-32 wPMA)			Full term (39-40 wPMA)		
		Included (N = 304)	Not included (N = 501)		Included (N = 47)	Not included (N = 133)	
		n (%)	n (%)	p	n (%)	n (%)	p
Gestational age at birth	24-28 w PMA	97 (32)	140 (28)	0.23			
	29-32 w PMA	207 (68)	361 (72)				
Sex	Male	154 (51)	246 (49)	0.67	18 (38)	79 (59)	0.01
	Female	150 (49)	255 (51)		29 (62)	54 (41)	
BPD	No	249 (82)	422 (86)	0.13			
	Yes	55 (18)	69 (14)				
	NA		10				
Antenatal steroids	No	59 (20)	93 (19)	0.82	41 (87)	108 (81)	0.35
	Yes	235 (80)	386 (81)		6 (13)	25 (19)	
	NA	10	22				
Received surfactant	No	180 (60)	306 (62)	0.49			
	Yes	122 (40)	187 (38)				
	NA	2	8				
Postnatal steroids	No	213 (71)	373 (76)	0.12			
	Yes	89 (29)	121 (24)				
	NA	2	7				
Birth weight	< 1000gr	89 (29)	117 (23)	0.17			
	[1000gr-1500gr]	115 (38)	206 (41)				
	≥ 1500gr	100 (33)	178 (36)				
SGA	No	212 (73)	362 (76)	0.36	41 (95)	126 (95)	0.98
	Yes	78 (27)	114 (24)		2 (5)	6 (5)	
	NA	14	25		4	1	
ARDS	No	172 (57)	290 (59)	0.62			
	Yes	129 (43)	202 (41)				
	NA	3	9				
PDA requiring surgery	No	291 (96)	471 (95)	0.49			
	Yes	11 (4)	23 (5)				
	NA	2	7				
Vascular collapse	No	217 (73)	361 (74)	0.71			
	Yes	80 (27)	125 (26)				
	NA	7	15				

Postnatal sepsis	No	203 (67)	340 (69)	0.58			
	Yes	99 (33)	152 (31)				
	NA	2	9				
Parents' occupational level	High income	70 (23)	94 (19)	<0.001	20 (42)	40 (30)	0.23
	Medium income	179 (59)	242 (49)				
	Low income	53 (18)	162 (32)				
	NA	2	3				
Smoking during pregnancy	No	244 (81)	353 (76)	0.13	39 (83)	100 (77)	0.39
	Yes	59 (19)	112 (24)				
	NA	1	36				
Preschool wheeze	No	166 (57)	242 (56)	0.64	33 (75)	92 (78)	0.69
	Yes	124 (43)	194 (44)				
	NA	14	65				
School age asthma	No	242 (83)	360 (88)	0.10	43 (91)	100 (92)	1.00
	Yes	48 (17)	50 (12)				
	NA	14	91				

Comparisons were performed using the Chi-square test (Fisher's exact test when required).

BPD: bronchopulmonary dysplasia; ARDS: Acute respiratory distress syndrome; PDA: Persistent ductus arteriosus; SGA: small for gestational age, defined as birth weight below -2SD.

Online Supplementary Table S3: Asthma and wheezing outcomes

	Preterm children (N = 304)		Term children (N = 47)		p	Preterm children with BPD (N = 55)		Preterm children without BPD (N = 249)		p
	%	(n/N)	%	(n/N)		%	(n/N)	%	(n/N)	
Preschool wheeze	42.8	(124/290)	25.0	(11/44)	0.03	56.0	(28/50)	40.0	(96/240)	0.04
School age asthma	16.5	(48/290)	8.5	(4/47)	0.16	22.2	(12/54)	15.2	(36/236)	0.21
Wheezing or whistling in the chest at any time in the past	54.0	(163/302)	32.6	(15/46)	0.01	54.5	(30/55)	53.8	(133/247)	0.92
Teenage asthma (wheezing in the chest in the past 12 mo.)	13.9	(42/302)	17.4	(8/46)	0.53	18.2	(10/55)	13.0	(32/247)	0.31
Sleep disturbed by wheezing in the past 12 mo.	4.6	(14/302)	4.3	(2/46)	1.00	3.6	(2/55)	4.9	(12/247)	1.00
Speech limited by wheezing in the past 12 mo.	2.0	(6/302)	2.2	(1/46)	1.00	1.8	(1/55)	2.0	(5/247)	1.00
Ever having had asthma	30.1	(91/302)	15.2	(7/46)	0.04	36.4	(20/55)	28.7	(71/247)	0.27
Exercise-induced wheezing in the past 12 mo.	14.2	(43/302)	10.9	(5/46)	0.54	21.8	(12/55)	12.5	(31/247)	0.08
Nocturnal cough in the past 12 mo.	10.9	(33/302)	6.5	(3/46)	0.45	9.1	(5/55)	11.3	(28/247)	0.63

Comparisons were performed using the Chi-square test (Fisher's exact test when required).

mo: months. Preschool wheeze: wheezing symptoms between birth and 5 years old, assessed from the EIPAGE questionnaires. School age asthma: asthma at 8 years of age, assessed from the EIPAGE questionnaires.

Online supplementary Table S4: Asthma groups and neonatal and postnatal environmental factors among preterm-born adolescents

	N	Preschool wheeze		School age asthma		Teenage asthma	
		%	(n/N)	p	%	(n/N)	p
Gestational age at birth				0.38			0.82
24-28 w PMA	97	47	(41/88)		13	(12/93)	15 (14/96)
29-32 w PMA	207	41	(83/202)		18	(36/197)	14 (28/206)
Sex				0.02			0.93
Male	154	49	(74/150)		17	(25/146)	14 (21/153)
Female	150	36	(50/140)		16	(23/144)	14 (21/149)
BPD				0.04			0.31
No	249	40	(96/240)		15	(36/236)	13 (32/247)
Yes	55	56	(28/50)		22	(12/54)	18 (10/55)
Birth weight				0.88			0.69
< 1000gr	89	44	(36/81)		19	(16/86)	11 (10/89)
[1000gr-1500gr[	115	43	(48/111)		14	(15/108)	15 (17/113)
≥ 1500gr	100	41	(40/98)		18	(17/96)	15 (15/100)
Smoking during pregnancy				0.62			0.92
No	244	43	(100/231)		18	(43/234)	14 (34/242)
Yes	59	40	(23/58)		9	(5/55)	14 (8/59)
Environmental tobacco smoke exposure during infancy				0.88			0.43
No	202	43	(83/193)		16	(32/197)	13 (26/201)
Yes	98	42	(40/95)		18	(16/89)	16 (16/98)
Atopy				0.15			0.03
No	69	36	(25/69)		6	(4/69)	7 (5/69)
Yes	205	46	(92/199)		22	(42/193)	18 (37/205)
Parent's occupational level				0.21			0.12
High income	70	34	(24/70)		12	(8/64)	13 (9/69)
Medium income	179	47	(80/172)		18	(32/175)	17 (30/178)
Low income	53	40	(19/47)		14	(7/49)	6 (3/53)

Comparisons were performed using the Chi-square test.

BPD: bronchopulmonary dysplasia

Online supplementary Table S5: FEV₁ and neonatal and postnatal environmental factors among preterm-born adolescents

		Pre-BD FEV ₁		
		n	mean (SD)	p ₁ p ₂
Gestational age at birth				0.003 1.00
	24-28 w PMA	87	-0.9 (1.2)	
	29-32 w PMA	187	-0.4 (1.3)	
BPD				<0.001 <0.001
	No	225	-0.4 (1.2)	
	Yes	49	-1.4 (1.2)	
Birth weight				0.002 0.37
	< 1000gr	78	-0.9 (1.1)	
	[1000gr-1500gr[	104	-0.6 (1.3)	
	≥ 1500gr	92	-0.2 (1.3)	
Sex				0.41
	Male	141	-0.5 (1.3)	
	Female	133	-0.6 (1.2)	
Smoking during pregnancy				0.02 0.12
	No	223	-0.6 (1.2)	
	Yes	51	-0.2 (1.4)	
Environmental tobacco smoke exposure during infancy				0.10
	No	183	-0.6 (1.2)	
	Yes	87	-0.4 (1.2)	
Atopy				0.25
	No	60	-0.4 (1.3)	
	Yes	187	-0.6 (1.2)	
Parent's occupational level				0.91
	High income	65	-0.6 (1.2)	
	Medium income	157	-0.5 (1.3)	
	Low income	50	-0.5 (1.1)	
At least one cigarette in the last week				0.32
	No	260	-0.6 (1.2)	
	Yes	11	-0.2 (1.6)	

Comparisons were performed by ANOVA.

p1: p value of univariate analysis

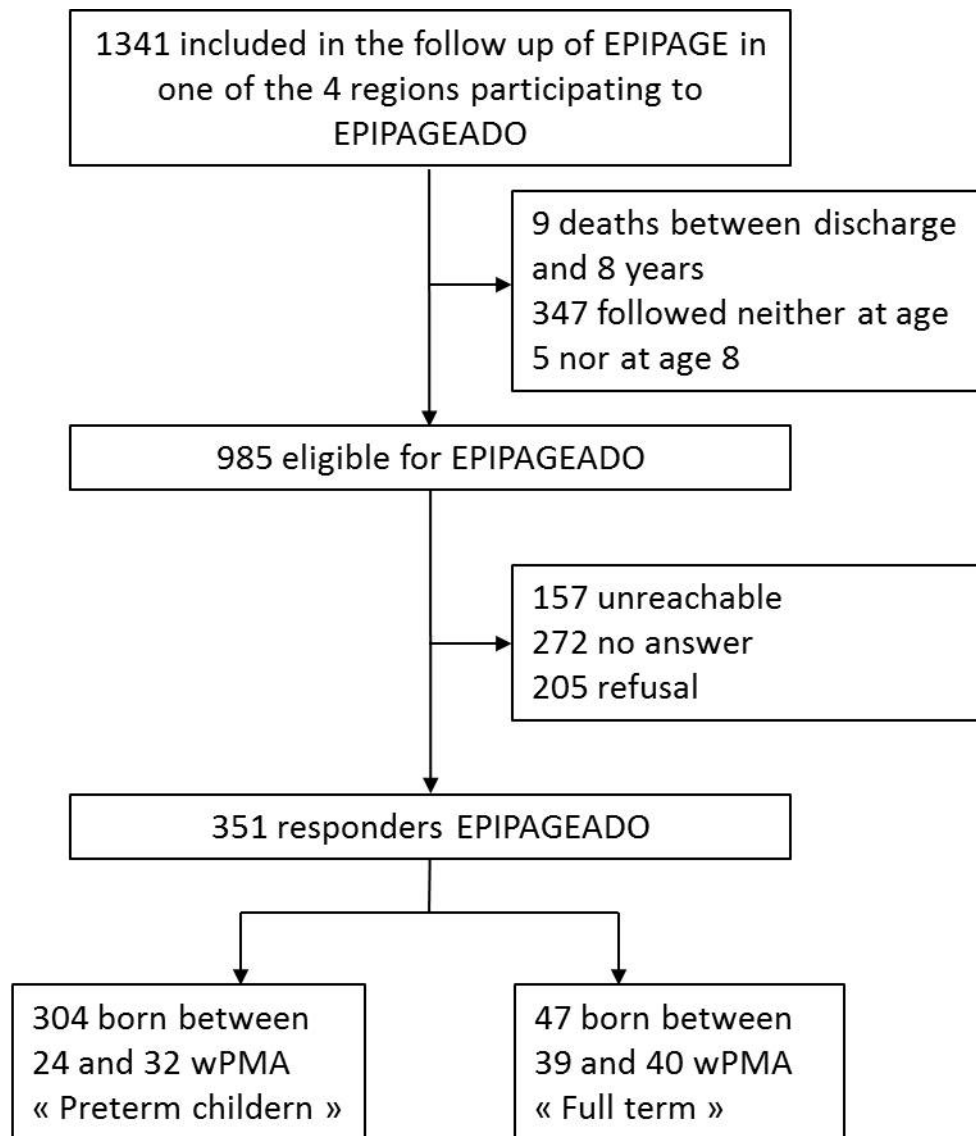
p2: p value of multivariate analysis including significantly associated variables in the univariate model

BPD: bronchopulmonary dysplasia

FIGURE LEGENDS

Online supplementary Figure S1: Flowchart of the study population.

This figure represents the flowchart of the study population.



Online supplementary Figure S1: Flowchart of the study population