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] FEV_1 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), FEV_1, 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 $FEV_1 > 12\%$ after inhalation of salbutamol. An obstructive ventilatory defect was defined by a FEV_1 Z-score < -1.64. FeNO and DLCO were also measured.

References

1 Larroque B, Breart G, Kaminski M, *et al.* Survival of very preterm infants: Epipage, a population based cohort study. *Arch Child Fetal Neonatal Ed* 2004;**89**:F139-44.

2 Larroque B. [EPIPAGE: epidemiologic study of very premature infants. Protocol of the survey]. *Arch Pediatr Organe Off Soc Francaise Pediatr* 2000;**7 Suppl 2**:339s–342s.

3 Larroque B, Ancel PY, Marret S, *et al.* Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* 2008;**371**:813–20.

4 Asher MI, Keil U, Anderson HR, *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–91.

5 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38. doi:10.1183/09031936.05.00034805

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?	Asthmatic bronchitis between the ages of 1 and 2?
	Did your child have eczema in the last 12 months?	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?	NA
	Since the age of 3, has your child had eczema?	NA
5	NA	Asthma attacks or asthmatic bronchitis in the last 12 months?
	NA	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)		22	(47)	69	(52)	
	Low income	53	(18)	162	(32)		5	(11)	24	(18)	
	NA	2		3						
Smoking during pregnancy	No	244	(81)	353	(76)	0.13	39	(83)	100	(77)	0.39
	Yes	59	(19)	112	(24)		8	(17)	30	(23)	
	NA	1		36					3		
Preschool wheeze	No	166	(57)	242	(56)	0.64	33	(75)	92	(78)	0.69
	Yes	124	(43)	194	(44)		11	(25)	26	(22)	
	NA	14		65			3		15		
School age asthma	No	242	(83)	360	(88)	0.10	43	(91)	100	(92)	1.00
	Yes	48	(17)	50	(12)		4	(9)	9	(8)	
	NA	14		91					24		

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)			Preterm children with BPD (N = 55)		Preterm children without BPD (N = 249)		
	%	(n/N)	%	(n/N)	p	%	(n/N)	%	(n/N)	p
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 EPIPAGE questionnaires. School age asthma: asthma at 8 years of age, assessed from the EPIPAGE questionnaires.

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

		Preschool wheeze			School age asthma			Teenage asthma		
	N	%	(n/N)	p	%	(n/N)	p	%	(n/N)	p
Gestational age at birth				0.38			0.25			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			0.79			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			0.21			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			0.63			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			0.10			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			0.72			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			0.003			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			0.51			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: FEV_1 and neonatal and postnatal environmental factors among preterm-born adolescents

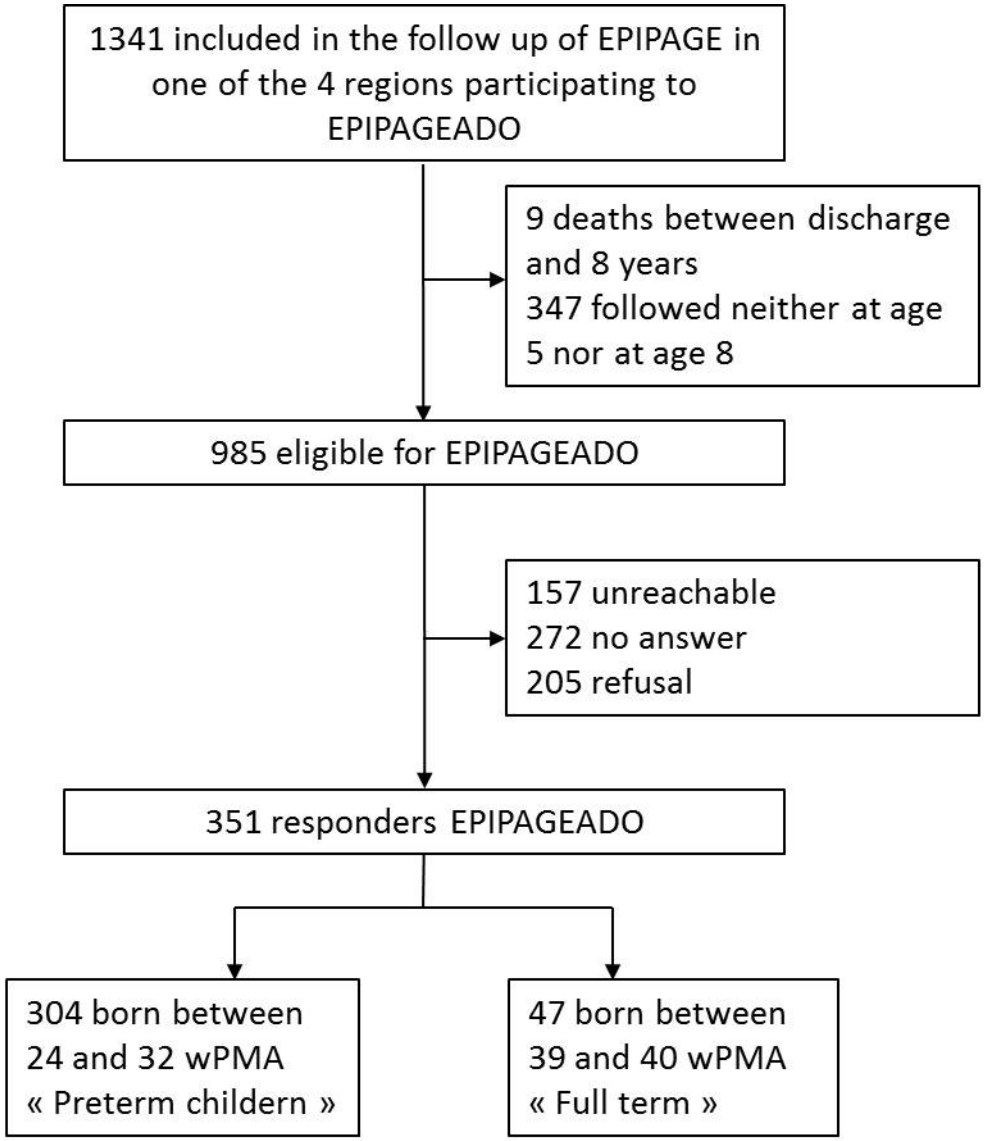
		Pre-BD FEV_1			
		n	mean (SD)	p_1	p_2
Gestational age at birth				0.003	1.00
	24-28 w PMA	87	-0.9 (1.2)		
	29-32 w PMA	187	-0.4 (1.3)		
BPD				<0.001	<0.001
	No	225	-0.4 (1.2)		
	Yes	49	-1.4 (1.2)		
Birth weight				0.002	0.37
	< 1000gr	78	-0.9 (1.1)		
	[1000gr-1500gr[	104	-0.6 (1.3)		
	≥ 1500gr	92	-0.2 (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