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Associations of wheezing phenotypes with late asthma outcomes in ALSPAC: a population-based birth cohort

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*Online Data Supplement*

## 1 *Participants*

2 ALSPAC recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery  
3 1st April 1991 to 31st December 1992. 14,541 is the initial number of pregnancies for which the  
4 mother enrolled in the ALSPAC study and had either returned at least one questionnaire or  
5 attended a "Children in Focus" clinic by 19/07/99. Of these initial pregnancies, there was a total of  
6 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age.  
7 When the oldest children were approximately 7 years of age, an attempt was made to bolster the  
8 initial sample with eligible cases who had failed to join the study originally. As a result, when  
9 considering variables collected from the age of seven onwards (and potentially abstracted from  
10 obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above.  
11 The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are  
12 currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452  
13 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children  
14 being enrolled. The phases of enrolment are described in more detail in the cohort profile paper<sup>1</sup>.  
15 The total sample size for analyses using any data collected after the age of seven is therefore  
16 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775  
17 were live births and 14,701 were alive at 1 year of age.

18 A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended  
19 clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The  
20 CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families  
21 attended at least one clinic). Excluded were those mothers who had moved out of the area or were  
22 lost to follow-up, and those partaking in another study of infant development in Avon.

23 Please note that the study website contains details of all the data that is available through a fully  
24 searchable data dictionary" and reference the following webpage:

25 <<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>>

26 *Skin Prick Test*

27 Atopy was measured at a research clinic at age 7½ years, as previously described (1). A positive  
28 response was defined as a mean weal diameter of >2 mm with an absent response to negative  
29 control solution, and atopy was defined as a positive response to one or more of house dust mite,  
30 cat or grass pollen.

31 *FeNO at 14-15 years*

32 Fractional exhaled nitric oxide (FeNO) was measured online at a constant flow of 50mL/s  
33 according to European Respiratory Society (ERS) and American Thoracic Society (ATS)  
34 guidelines using a Sievers NOA-280i nitric oxide analyser (GE Analytical Instruments, Boulder,  
35 CO.).

36 Additionally, 758 children with less stringent criteria (individual blows >5% deviation but at least  
37 1 within acceptable rang of 10-200 ppb) were included. FeNO measurements were done before  
38 spirometry measurements. Children were requested to omit their inhaled corticosteroids if  
39 applicable 48 hours before their visit to the clinic. At the time of measurements, 14 children  
40 (0.3%) received oral steroids, 221 (5.2%) had a chest infection and/or fever with a cold in the  
41 preceding three weeks, and 39 (0.9%) and 89 (2.1%) had used short acting or long acting  
42 bronchodilators 6 or 24 hours, respectively, prior to the respiratory assessments. These children,  
43 and those with less stringent criteria of FeNO values, were included in our analyses since we  
44 observed no differences in results when they were included or excluded.

45 *Asthma status 0 to 14 years*

46 Using ever-reported doctor-diagnosed asthma at 91 and 166 months and maternal report of asthma  
47 at 166 months , we derived the following asthma status variable: “no asthma” if negative at both  
48 91 and 166 months, “remittent asthma” if positive at 91 months but negative at 166 months or  
49 positive at both 91 and 166 months but negative maternal report of asthma in the last 12 months at  
50 166 months , “incident asthma” if negative at 91 months but positive at 166 months and

51 “persistent asthma” if positive at both 91 and 166 months and positive maternal report of asthma  
52 in the last 12 months at 166 months.

### 53 *Potential Confounders*

54 We obtained details of maternal educational attainment (lower level defined as educated to school  
55 leaving certificate at 16 years or lower), smoking history and personal history of asthma or allergy  
56 from questionnaires sent to the mother during pregnancy . Sex of the child was obtained from  
57 delivery health care records. Postnatal maternal questionnaires from 3-15 months after birth were  
58 used to ascertain environmental tobacco smoke exposure.

59

### 60 *Statistical analysis*

61 In order to minimise the risk of bias due to misclassification, associations of wheezing phenotypes  
62 with late asthma outcomes (physician-diagnosed asthma and objective measurements of lung  
63 function and FeNO) were examined using logistic or linear regression models weighted for the  
64 probability of each individual of belonging to each phenotype. These probabilities were estimated  
65 previously and referred to as the *posterior probabilities* (2). Crude and adjusted odds ratios (for  
66 binary outcomes) and mean differences (for continuous outcomes) were derived in relation to the  
67 never/infrequent wheezing phenotype (reference group). Adjustment was done for potential  
68 confounders (gender, maternal lower education level, having at least one sibling (parity), maternal  
69 history of asthma or allergy, maternal smoking during pregnancy, maternal anxiety during  
70 pregnancy (as being in the 4<sup>th</sup> quantile of the Crown-Crisp Experiential Index (3)), low birth  
71 weight (<2.5kg), preterm delivery (<37 weeks) and daycare attendance during the first year.

### 72 **Table E1**

73 A total of 6330 (51.5%) participants were males, 5139 (46.2%) had an asthmatic or allergic  
74 mother, 2934 (26.1%) were exposed to maternal smoking during pregnancy and 6148 (54.9%) had  
75 at least one sibling. 575 (5.0%) had low birth weight and 682 (5.8%) were born preterm. 2529

76 (23.4%) were exposed to maternal smoking during the first year and 641 (6.0%) attended day care  
77 during the first year. 2874 (26.1%) participants had wheezing reported at 6 months: the proportion  
78 of participants with reported wheezing decreased to 1756 (17.6%) by 3½ years, 1050 (12.9%) by  
79 8½ years and 592 (10.5%) by 16½ years. Of 6691 participants with data available on skin prick  
80 tests at 7½ years, 1403 (21.0%) were atopic.

81 Comparing the samples of children with complete (n=3,170) and incomplete data (at least 2  
82 observations of wheeze, n=9,133) on wheezing, we observed that incomplete data are associated  
83 with markers of social deprivation: increased exposure to tobacco smoke (p=), maternal anxiety  
84 (p=), maternal lower education (p=), parity (p=), low birthweight (p=) and pre-term delivery (p=),  
85 in those subsequently lost to follow up. Also, the proportion of wheezing differs between 6 and 69  
86 months (p<) but its similar thereafter which is consistent with less wheezing reported among  
87 children with complete data, compared to those *subsequently lost to follow up*. Our analyses  
88 included children with incomplete data on wheeze, avoiding bias that could be introduced in  
89 complete case analyses.

## 90 **Table E2**

91 Male gender (adjusted multinomial odds ratios [mOR] range from 1.32 to 1.80) was associated  
92 with a similar higher risk of each phenotype (heterogeneity p-value=0.13). Maternal lower  
93 education level was associated with a higher risk of mid-childhood onset remitting wheeze (mOR  
94 1.22, 1.02 to 1.45 with little evidence of heterogeneity p-value=0.11). Having at least one sibling  
95 was associated with pre-school and mid-childhood onset remitting and continuous wheezing  
96 phenotypes and there was little evidence for association with the other phenotypes (heterogeneity  
97 p-value=0.0012). Maternal history of asthma or allergy was associated with a higher risk of each  
98 wheezing phenotype (mOR 1.27 to 2.30, heterogeneity p-value<0.0001), strongest associations  
99 were with mid-childhood onset remitting (mOR 1.65 95%CI 1.40 to 1.93) and continuous  
100 wheezing (mOR 2.30 95%CI 1.88 to 2.81). Maternal smoking during pregnancy was associated  
101 with a higher risk of pre-school and mid-childhood onset remitting and continuous wheeze

102 phenotypes (mOR 1.33 to 1.46, heterogeneity p-value=0.71). Prenatal maternal anxiety was  
103 associated with a higher risk of each wheezing phenotype (mOR 1.12 to 1.29, heterogeneity p-  
104 value=0.08). Low birth weight was associated with continuous wheeze (mOR 1.63 95%CI 1.00 to  
105 2.64, heterogeneity p-value=0.26). Preterm delivery was associated with higher risk of pre-school  
106 and mid-childhood onset remitting and continuous wheezing (mOR 1.35 to 1.63, heterogeneity p-  
107 value=0.30). Day care attendance during the first year was associated with a higher risk of pre-  
108 school onset remitting wheeze phenotype, although we found small evidence of heterogeneity p-  
109 value=0.16. We found small evidence for an association between maternal smoking during the  
110 first year and any of the wheezing phenotypes.

111

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120 useful and valid measure of psychoneurotic pathology. *Br J Med Psychol* 1988;61:255-66

121 **Table E1** Characteristics of children with at least 2 observations of wheeze (study population,  
 122 N=12,303) who did and did not have complete data on wheezing.

	Children with complete data on wheezing (n <sub>1</sub> =3,170)		Children with 2–13 observations of wheezing (n <sub>2</sub> =9,133)		Two-sample test of proportions P-value
	n/total	%	n/total	%	
<b>Potential confounders</b>					
Gender (Male)	1560/3170	49.2	4770/9133	52.2	0.003
Lower maternal education*	1547/3151	49.1	5614/8184	68.6	<0.0001
Having at least 1 sibling (parity)	1597/3118	51.2	4551/8072	56.4	<0.0001
Maternal history of asthma or allergy	1510/3107	48.6	3629/8025	45.2	0.001
Maternal smoking during pregnancy	439/3127	14.0	2495/8096	30.8	<0.0001
Maternal anxiety during pregnancy†	479/3020	15.9	1831/7520	24.3	<0.0001
Low birth weight (<2.5Kg)	134/3134	4.3	441/8397	5.3	0.032
Preterm delivery (<37 weeks)	153/3170	4.8	529/8504	6.2	0.004
Maternal smoking during first year	411/3122	13.2	2118/7690	27.5	<0.0001
Day care attendance during 1 <sup>st</sup> year	242/3124	7.7	399/7505	5.3	<0.0001
<b>Variables used in the Latent Class model</b>					
Reported wheezing at					
6 months	709/3170	22.4	2165/7834	27.6	<0.0001
18 months	780/3170	24.6	2205/7691	28.7	<0.0001
30 months	612/3170	19.3	1632/6775	24.1	<0.0001
42 months (3½ years)	487/3170	15.4	1269/6803	18.7	<0.0001
54 months	505/3170	15.9	1269/6221	20.4	<0.0001
69 months	435/3170	13.7	893/5426	16.5	.0007
81 months	393/3170	12.4	734/5225	14.0	0.70
91 months	334/3170	10.5	544/5032	10.8	0.14
103 months (8½ years)	386/3170	12.2	664/4990	13.3	0.41
128 months	376/3170	11.9	559/4475	12.5	0.37
140 months	360/3170	11.4	509/4229	12.0	0.83
157 months	338/3170	10.7	402/3828	10.5	0.44
166 months	339/3170	10.7	424/3760	11.3	0.86
198 months (16½ years)	335/3170	10.6	257/2465	10.4	0.39
Atopy at 7½ years (skin prick testing)	524/2433	21.5	879/4258	20.6	0.70

123 \*Educated to GCE level (school leaving certificate) or lower

124 † Defined as being in the 4<sup>th</sup> quantile of the Crown-Crisp Experiential Index



**Table E2** Associations of possible confounders with wheezing phenotypes 0 to 16½ years and asthma at 14 years (Based on 12,303 children with at least 2 observations of wheezing)

	Adjusted Multinomial OR (95% CI) for						Adjusted OR (95% CI) for Doctor ever diagnosed-asthma at 14 years N=5,838
	Pre-school onset remitting* N=1,605	Mid-childhood onset remitting* N=620	School-age onset persisting* N=346	Late-childhood onset persisting* N=324	Continuous wheeze* N=420	Heterogeneity p-value+	
<b>Demographic, maternal, pregnancy &amp; child characteristics (adjusted by each other)</b>							
Gender (Male)	1.39 (1.25, 1.55)	1.41 (1.21, 1.66)	1.54 (1.26, 1.89)	1.32 (1.09, 1.60)	1.80 (1.48, 2.19)	0.13	1.26 (1.11,1.42)
Maternal lower education level ±	0.96 (0.86, 1.08)	1.22 (1.02, 1.45)	0.92 (0.74, 1.13)	0.94 (0.77, 1.14)	0.95 (0.77, 1.16)	0.11	1.13 (1.00,1.28)
Parity	1.24 (1.11, 1.38)	1.38 (1.17, 1.62)	0.88 (0.72, 1.07)	1.02 (0.85, 1.24)	1.37 (1.12, 1.67)	1.2E-03	0.95 (0.84,1.07)
Maternal history of asthma or allergy	1.27 (1.14, 1.42)	1.65 (1.40, 1.93)	1.47 (1.20, 1.80)	1.42 (1.17, 1.72)	2.30 (1.88, 2.81)	1.9E-06	1.53 (1.35,1.73)
Maternal smoking during pregnancy	1.33 (1.17, 1.51)	1.46 (1.22, 1.75)	1.23 (0.97, 1.56)	1.24 (0.99, 1.56)	1.38 (1.10, 1.72)	0.71	1.19 (1.01,1.39)
Maternal anxiety during pregnancy	1.20 (1.14, 1.26)	1.25 (1.16, 1.35)	1.12 (1.02, 1.23)	1.14 (1.04, 1.24)	1.29 (1.18, 1.41)	0.08	1.13 (1.07,1.20)
<b>Perinatal characteristics adjusted by demographic, maternal, pregnancy and child characteristics</b>							
Low birthweight (<2.5Kg) ‡	1.00 (0.73, 1.37)	1.14 (0.73, 1.78)	1.47 (0.86, 2.52)	1.56 (0.93, 2.60)	1.63 (1.00, 2.64)	0.26	1.11 (0.77,1.61)
Preterm delivery (<37 weeks) ‡	1.35 (1.07, 1.70)	1.43 (1.03, 2.00)	1.04 (0.65, 1.67)	0.94 (0.59, 1.50)	1.63 (1.11, 2.39)	0.30	1.16 (0.87,1.56)
<b>Postnatal characteristics adjusted by demographic, maternal, pregnancy, child, perinatal &amp; other postnatal characteristics</b>							
Maternal smoking during first year	1.22 (0.98, 1.51)	1.15 (0.84, 1.58)	0.96 (0.64, 1.44)	1.01 (0.69, 1.49)	1.09 (0.74, 1.61)	0.80	1.06 (0.82,1.37)
Day care attendance during 1 <sup>st</sup> year	1.28 (1.02, 1.60)	0.97 (0.66, 1.41)	0.72 (0.44, 1.18)	0.92 (0.59, 1.42)	1.07 (0.70, 1.63)	0.16	0.90 (0.70,1.17)

\* compared with never/infrequent wheezing (N=6,305) and using each child's phenotype probability as weights.

± Educated to school leaving certificate at 16 years (GCE level) or lower

+ Chi-squared test across phenotypes

‡ Low birthweight was also adjusted by preterm delivery but preterm delivery was not adjusted for low birth weight (since birth weight does not influence gestational age)

**Table E3** Crude associations of wheezing phenotypes 0 to 16½ years with doctor-diagnosed asthma ever, FeNO and BDR>12% at 14-15 years (based on in 12,303 children with at least 2 observations of wheeze)

Wheezing phenotype 0 to 16½ years	Doctor-diagnosed asthma ever at 14 years		FeNO ≥35 ppb at 14-15 years		BDR >12% at 15 years	
	Number of asthmatic/total*	OR (95% CI)	n1/total*	OR (95% CI)	n2/total*	OR (95% CI)
Never/Infrequent	272/3661	1 (ref)	290/1157	1 (ref)	139/2003	1 (ref)
Pre-school onset remitting	173/ 870	2.74 (2.23, 3.36)	61/ 243	1.06 (0.79, 1.44)	33/ 472	1.10 (0.76, 1.59)
Mid-childhood onset remitting	231/ 337	25.0 (19.4, 32.2)	42/ 102	1.93 (1.28, 2.90)	21/ 204	1.66 (1.04, 2.63)
School-age onset persisting	187/ 223	49.9 (35.3, 70.7)	57/ 82	6.39 (3.95, 10.34)	27/ 127	3.28 (2.06, 5.22)
Late-childhood onset persisting	161/ 250	19.8 (15.0, 26.1)	38/ 66	3.67 (2.30, 5.85)	19/ 131	2.10 (1.26, 3.48)
Continuous wheeze	246/ 254	363 (179, 735)	49/ 71	6.95 (4.13, 11.72)	19/ 126	2.36 (1.40, 3.98)

\* Number of children with data available (approximated from modal assignment)

n1: Number of children with FeNO ≥20 ppb

n2: Number of children with BDR>12%

**Table E4** Crude association of wheezing phenotypes 0 to 16½ years with lung function measures at 15 years (z-scores) based on 12,303 children with at least to observations of wheezing

	FEV <sub>1</sub> (SDU) at 15 years		FVC (SDU) at 15 years		FEV <sub>1</sub> /FVC (SDU) at 15 years		FEF <sub>25-75</sub> (SDU) at 15 years	
<b>Wheezing phenotype 0 to 16½ years</b>	N	Mean diff. (95% CI)	N	Mean diff. (95% CI)	N	Mean diff. (95% CI)	N	Mean diff (95% CI)
Never/Infrequent	1997	0 (ref)	2094	0 (ref)	1997	0 (ref)	2094	0 (ref)
Pre-school onset remitting	463	-0.02 (-0.12, 0.07)	477	0.05 (-0.04, 0.14)	463	-0.15 (-0.24, -0.05)	477	-0.13 (-0.22, -0.03)
Mid-childhood onset remitting	203	0.09 (-0.05, 0.23)	209	0.21 (0.07, 0.35)	203	-0.23 (-0.37, -0.08)	209	-0.14 (-0.28, -0.00)
School-age onset persisting	127	0.08 (-0.10, 0.26)	131	0.18 (0.00, 0.35)	127	-0.21 (-0.39, -0.04)	131	-0.14 (-0.32, 0.03)
Late-childhood onset persisting	130	-0.02 (-0.19, 0.15)	135	0.02 (-0.14, 0.19)	130	-0.08 (-0.25, 0.08)	135	-0.21 (-0.37, -0.04)
Continuous wheeze	126	-0.08 (-0.26, 0.10)	131	0.04 (-0.14, 0.22)	126	-0.26 (-0.44, -0.08)	131	-0.30 (-0.48, -0.12)

N: Number of children with data available (approximated from modal assignment)

**Table E5** Adjusted associations of wheezing phenotypes 0 to 16½ years with lung function measures at 8 years (z-scores), in participants with at least 2 observations of wheeze.

Wheezing phenotype 0 to 16½ years	FEV <sub>1</sub> (SDU) at 8 years		FVC (SDU) at 8 years		FEV <sub>1</sub> /FVC (SDU) at 8 years		FEF <sub>25-75</sub> (SDU) at 8 years	
	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *
Never/Infrequent	3394	0 (ref)	3452	0 (ref)	3295	0 (ref)	3452	0 (ref)
Pre-school onset remitting	872	-0.20 (-0.28, -0.13)	884	-0.06 (-0.13, 0.02)	851	-0.24 (-0.31, -0.17)	884	-0.28 (-0.35, -0.21)
Mid-childhood onset remitting	336	-0.23 (-0.34, -0.12)	341	-0.01 (-0.11, 0.10)	329	-0.37 (-0.48, -0.26)	341	-0.41 (-0.51, -0.30)
School-age onset persisting	219	-0.30 (-0.43, -0.16)	222	-0.01 (-0.14, 0.12)	215	-0.44 (-0.58, -0.31)	222	-0.48 (-0.62, -0.35)
Late-childhood onset persisting	212	-0.23 (-0.36, -0.11)	215	-0.08 (-0.21, 0.05)	207	-0.21 (-0.34, -0.08)	215	-0.30 (-0.43, -0.18)
Continuous wheeze	245	-0.40 (-0.53, -0.27)	249	0.10 (-0.03, 0.23)	236	-0.78 (-0.91, -0.65)	249	-0.75 (-0.88, -0.62)

\* Adjusted for gender, parity, maternal history of asthma or allergy, maternal smoking and anxiety during pregnancy, preterm delivery, low birth weight and daycare attendance during first year.

N: Number of participants with data available (approximated from modal assignment)

**Table E6** Adjusted associations of wheezing phenotypes 0 to 16½ years with **pre-salbutamol lung function measures at 15 years** (z-scores), in participants with at least 2 observations of wheeze.

Wheezing phenotype 0 to 16½ years	FEV <sub>1</sub> (SDU) at 15 years		FVC (SDU) at 15 years		FEV <sub>1</sub> /FVC (SDU) at 15 years		FEF <sub>25-75</sub> (SDU) at 15 years	
	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *
Never/Infrequent	2064	0 (ref)	2092	0 (ref)	2064	0 (ref)	2091	0 (ref)
Pre-school onset remitting	473	-0.06 (-0.16, 0.03)	477	0.05 (-0.05, 0.14)	473	-0.21 (-0.31, -0.12)	476	-0.16 (-0.25, -0.06)
Mid-childhood onset remitting	207	-0.03 (-0.17, 0.11)	209	0.16 (0.02, 0.30)	207	-0.35 (-0.49, -0.22)	209	-0.25 (-0.39, -0.11)
School-age onset persisting	129	-0.16 (-0.33, 0.02)	131	0.08 (-0.10, 0.25)	129	-0.45 (-0.62, -0.28)	131	-0.40 (-0.57, -0.22)
Late-childhood onset persisting	135	-0.20 (-0.36, -0.03)	135	-0.04 (-0.21, 0.13)	135	-0.29 (-0.45, -0.13)	135	-0.33 (-0.50, -0.17)
Continuous wheeze	128	-0.23 (-0.41, -0.04)	130	0.04 (-0.14, 0.22)	128	-0.54 (-0.72, -0.37)	130	-0.53 (-0.71, -0.35)

\* Adjusted for gender, parity, maternal history of asthma or allergy, maternal smoking and anxiety during pregnancy, preterm delivery, low birth weight and daycare attendance during first year.

N: Number of participants with data available (approximated from modal assignment)

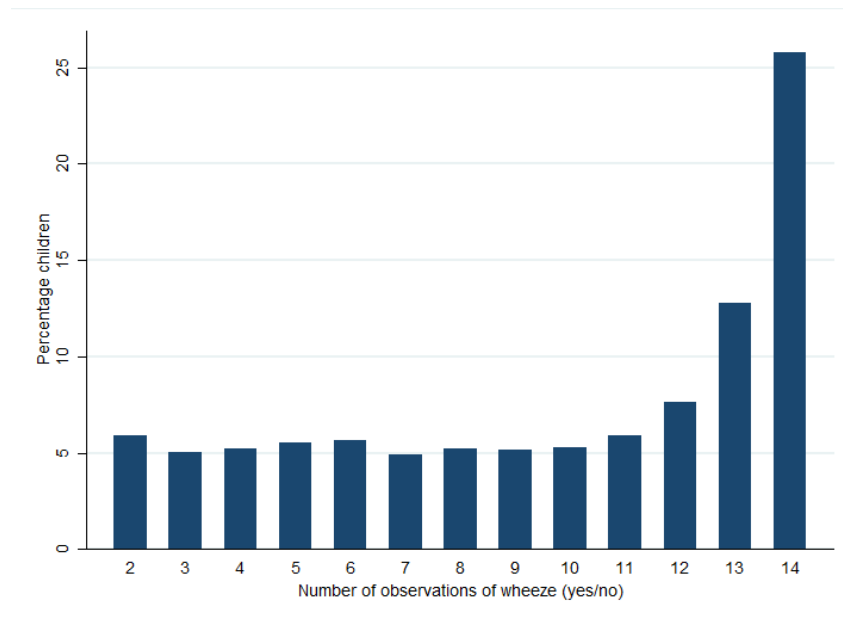
**Table E7** Adjusted associations of wheezing phenotypes 0 to 16½ years with **lung function measures at 15 years (pre-salbutamol z-scores) further adjusted by lung function measures at 8 years (pre-salbutamol z-scores)**, in participants with at least 2 observations of wheeze.

Wheezing phenotype 0 to 16½ years	FEV <sub>1</sub> (SDU) at 15 years		FVC (SDU) at 15 years		FEV <sub>1</sub> /FVC (SDU) at 15 years		FEF <sub>25-75</sub> (SDU) at 15 years	
	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *	N	Adjusted Mean diff. (95% CI) *
Never/Infrequent	1784	0 (ref)	1826	0 (ref)	1743	0 (ref)	1825	0 (ref)
Pre-school onset remitting	415	0.02 (-0.08, 0.11)	422	0.08 (-0.01, 0.17)	407	-0.16 (-0.25, -0.07)	421	-0.03 (-0.12, 0.06)
Mid-childhood onset remitting	183	0.08 (-0.05, 0.22)	187	0.17 (0.04, 0.31)	179	-0.22 (-0.36, -0.09)	187	-0.02 (-0.15, 0.11)
School-age onset persisting	110	-0.05 (-0.22, 0.13)	113	0.11 (-0.06, 0.28)	110	-0.33 (-0.50, -0.16)	113	-0.19 (-0.36, -0.03)
Late-childhood onset persisting	117	-0.07 (-0.24, 0.09)	118	0.02 (-0.14, 0.18)	117	-0.21 (-0.37, -0.05)	118	-0.17 (-0.32, -0.01)
Continuous wheeze	106	-0.04 (-0.22, 0.14)	110	0.06 (-0.12, 0.23)	103	-0.25 (-0.42, -0.07)	110	-0.14 (-0.31, 0.03)

\* Adjusted for gender, parity, maternal history of asthma or allergy, maternal smoking and anxiety during pregnancy, preterm delivery, low birth weight, daycare attendance during first year and additionally for lung function at 8 years.

N: Number of participants with data available (approximated from modal assignment)

**Figure E1** Distribution of 12,303 children with 2 to 14 (complete data) observations of wheeze



**Figure E2** Estimated prevalence of wheezing at each time point from birth to 16½ years for each of the six wheezing phenotypes identified by latent class analysis in 12,303 children with at least 2 observations of wheeze including atopic status as a covariate in the model.

