ONLINE DEPOSITORY

Figure S1. Flow diagram

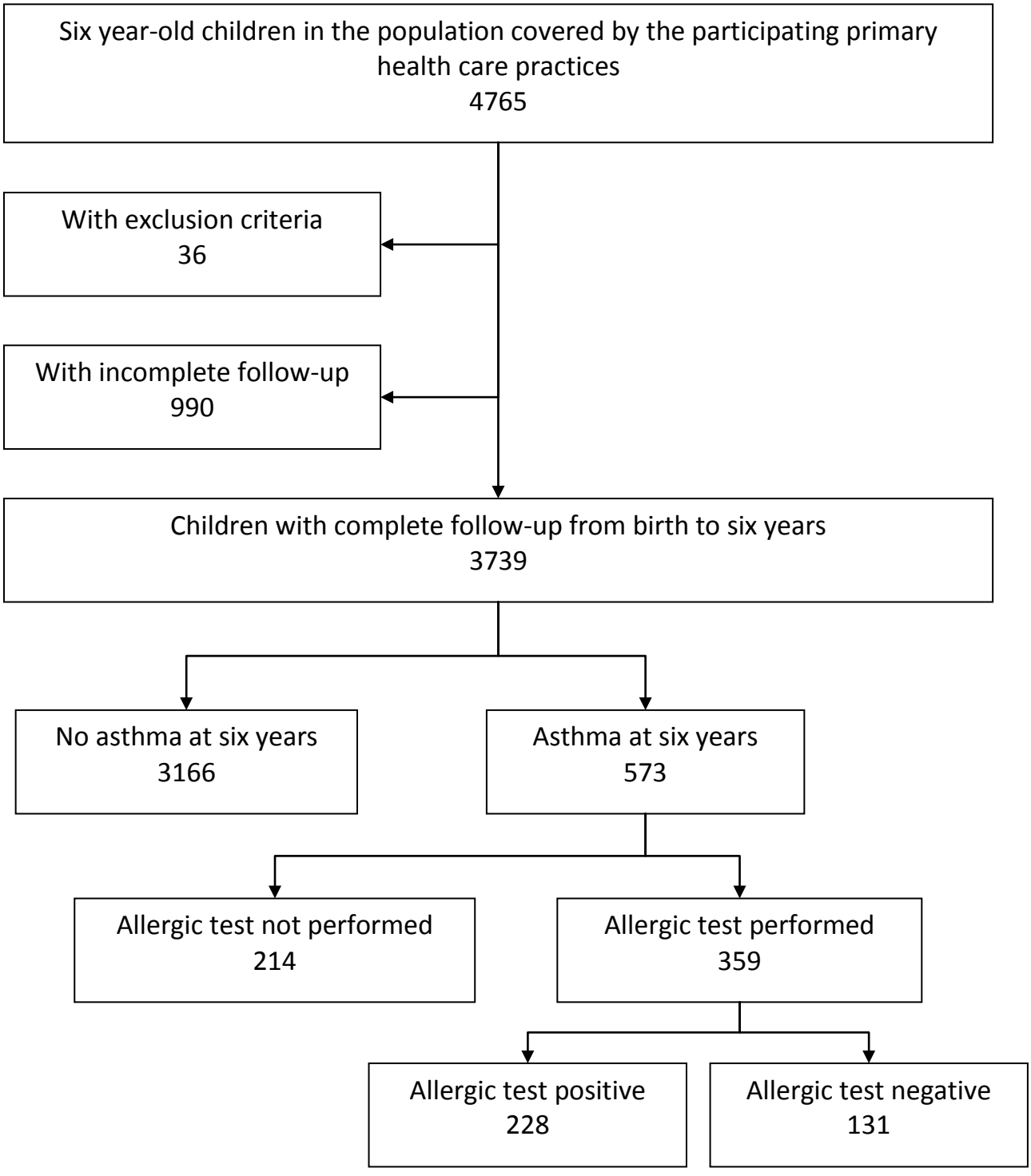


Table S1. Prespecified causes of exclusion and number of children excluded.

Causes of exclusion:	Nº of excluded
Tuberculosis.	3
Bronchopulmonary dysplasia/chronic neonatal lung disease.	2
α-1-antitrypsin deficiency.	1
Foreign body aspiration.	1
Pulmonary congenital anomalies: pulmonary secuestration, vascular rings, bronchial stenosis, cystic adenomatoid malformation, bronchogenic cysts, congenital pulmonary lymphangiectasia, congenital lobar amphysema.	2
Congenital heart disease, except mild non-complicated lesions as small patent ductus arteriosus, auricular septal defects and ventricular septal defects.	18
Neuromuscular disorders and cerebral palsy with Gross Motor Function Classification System ≥ 4 (children cannot sit on their own).	7
Chronic aspiration syndrome.	1
Interstitial lung diseases as pulmonary alveolar proteinosis, sarcoidosis, surfactant dysfunction disorders, hipersensitivity neumonitis, eosinophilic pneumonia, neuroendocrine cell hyperplasia of infancy, desquamative interstitial pneumonitis and others.	1
Other prespecified exclusion criteria not met for any children: Cystic fibrosis. Pulmonary hemosiderosis. Sickle cell disease. Bronchiectasis. Bronchiolitis obliterans, bronchitis follicular. Primary ciliary dyskinesia/Kartagener syndrome. Immunodeficiency, except selective IgA deficiency and IgG subclass deficiencies. Severe thoracic deformities. Primary or metastatic lung neoplasms.	

Table S2. Monthly incidence rates per 1000 and rate ratio of wheeze in asthmatic and non-asthmatic children from 0 to 36 months.

	Number of episodes		Mean monthly incidente rate (per 1000 children)		Rate ratio (95% CI)
Month (midpoint)	Non-asthmatic children (n_0 = 3166)	Asthmatic children (n_1 = 573)	Non-asthmatic children	Asthmatic children	
0.5	10	2	3.16	3.49	1.11 (0.24 – 5.24)
1.5	33	11	10.42	19.20	1.84 (0.93 – 3.64)
2.5	63	21	19.90	36.65	1.84 (1.12 – 3.02)
3.5	83	28	26.22	48.87	1.86 (1.21 – 2.86)
4.5	116	52	36.64	90.75	2.48 (1.79 – 3.44)
5.5	184	50	58.12	87.26	1.50 (1.10 – 2.05)
6.5	157	53	49.59	92.50	1.87 (1.37 – 2.55)
7.5	157	36	49.59	62.83	1.27 (0.88 – 1.82)
8.5	157	52	49.59	90.75	1.83 (1.34 – 2.50)
9.5	130	59	41.06	102.97	2.51 (1.84 – 3.41)
10.5	123	38	38.85	66.32	1.71 (1.19 – 2.46)
11.5	116	42	36.64	73.30	2.00 (1.41 – 2.85)
12.5	92	32	29.06	55.85	1.92 (1.29 – 2.87)
13.5	93	42	29.37	73.30	2.50 (1.73 – 3.59)
14.5	99	53	31.27	92.50	2.96 (2.12 – 4.13)
15.5	75	44	23.69	76.79	3.24 (2.23 – 4.70)
16.5	71	25	22.43	43.63	1.95 (1.23 – 3.07)
17.5	91	38	28.74	66.32	2.31 (1.58 – 3.37)
18.5	95	35	30.01	61.08	2.04 (1.38 – 3.00)
19.5	78	28	24.64	48.87	1.98 (1.29 – 3.05)
20.5	84	48	26.53	83.77	3.16 (2.21 – 4.50)
21.5	86	54	27.16	94.24	3.47 (2.47 – 4.88)
22.5	63	41	19.90	71.55	3.60 (2.43 – 5.33)
23.5	86	47	27.16	82.02	3.02 (2.12 – 4.31)
24.5	82	43	25.90	75.04	2.90 (2.00 – 4.19)
25.5	68	47	21.48	82.02	3.82 (2.63 – 5.54)
26.5	80	38	25.27	66.32	2.62 (1.78 – 3.86)
27.5	61	38	19.27	66.32	3.44 (2.30 – 5.16)
28.5	61	53	19.27	92.50	4.80 (3.32 – 6.94)
29.5	96	55	30.32	95.99	3.17 (2.27 – 4.41)
30.5	65	43	20.53	75.04	3.66 (2.49 – 5.37)
31.5	54	49	17.06	85.51	5.01 (3.41 – 7.38)
32.5	46	59	14.53	102.97	7.09 (4.82 – 10.42)
33.5	75	44	23.69	76.79	3.24 (2.23 – 4.70)
34.5	61	51	19.27	89.01	4.62 (3.18 – 6.70)
35.5	82	52	25.90	90.75	3.50 (2.48 – 4.96)
TOTAL	3173	1503	27.84	72.86	2.62 (1.81 – 3.78)

Table S3. Monthly incidence rates per 1000 and rate ratio of wheeze from 0 to 36 months in children with allergic and non-allergic asthma.

	Number of episodes		Mean monthly incidente rate (per 1000 children)	
Month (midpoint)	Non-allergic asthma (n_0 = 131)	Allergic asthma (n_1 = 228)	Non-allergic asthma	Allergic asthma
0.5	0	0	0.00	0.00
1.5	5	1	38.17	4.39
2.5	1	7	7.63	30.70
3.5	6	8	45.80	35.09
4.5	20	13	152.67	57.02
5.5	19	15	145.04	65.79
6.5	14	15	106.87	65.79
7.5	8	16	61.07	70.18
8.5	16	18	122.14	78.95
9.5	15	21	114.50	92.11
10.5	11	15	83.97	65.79
11.5	14	18	106.87	78.95
12.5	6	14	45.80	61.40
13.5	14	10	106.87	43.86
14.5	21	15	160.31	65.79
15.5	13	15	99.24	65.79
16.5	9	7	68.70	30.70
17.5	9	10	68.70	43.86
18.5	10	13	76.34	57.02
19.5	9	10	68.70	43.86
20.5	13	22	99.24	96.49
21.5	14	18	106.87	78.95
22.5	12	12	91.60	52.63
23.5	13	22	99.24	96.49
24.5	17	16	129.77	70.18
25.5	11	24	83.97	105.26
26.5	13	12	99.24	52.63
27.5	7	17	53.44	74.56
28.5	14	22	106.87	96.49
29.5	12	25	91.60	109.65
30.5	13	19	99.24	83.33
31.5	10	23	76.34	100.88
32.5	12	33	91.60	144.74
33.5	10	21	76.34	92.11
34.5	9	28	68.70	122.81
35.5	7	23	53.44	100.88
TOTAL	407	578	86.30	70.42

Table S4. Monthly incidence rates per 1000 of wheezing episodes in asthmatic and non-asthmatic children in the first three years of age, for calendar month.

Month	Non-asthmatic children			Asthmatic children		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Jul	9.48	14.21	6.95	17.45	24.43	31.41
Aug	6.32	6.95	6.00	10.47	20.94	45.38
Sep	19.27	16.42	13.58	26.18	80.28	102.97
Oct	26.53	32.53	23.06	68.06	85.51	80.28
Nov	43.27	27.48	38.22	76.79	76.79	102.97
Dec	63.49	48.01	32.22	120.42	83.77	134.38
Jan	64.75	37.59	31.59	95.99	104.71	85.51
Feb	45.48	28.11	18.64	76.79	62.83	95.99
Mar	49.91	36.01	26.85	90.75	99.48	94.24
Apr	37.59	29.06	24.32	83.77	75.04	73.30
May	33.80	25.58	24.01	61.08	89.01	94.24
Jun	19.90	18.00	17.06	47.12	47.12	57.59

Table S5. Joinpoint regression methodology.

Joinpoint regression is a least square lineal regression method that allows the building of regression models in which trend changes are permitted, that is, models in which the data are not fitted to a single regression line but a two or more segments joined in one or more joinpoints. The U.S. National Cancer Institute has developped a specific software for these models.

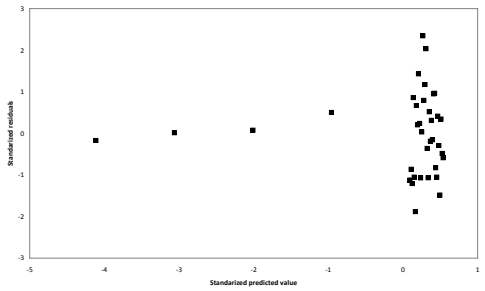
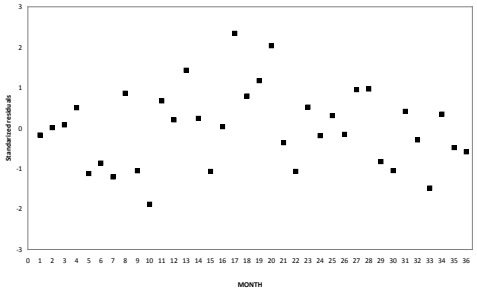
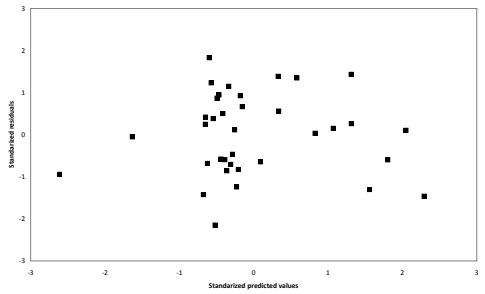
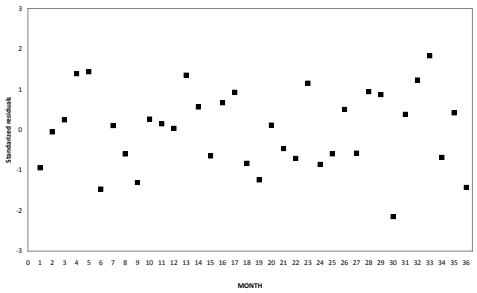
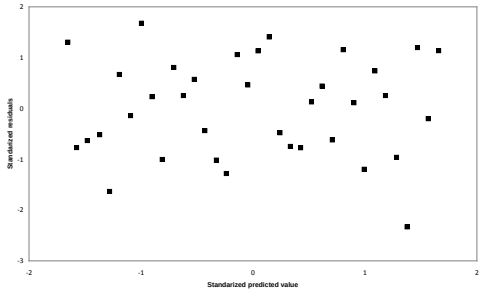
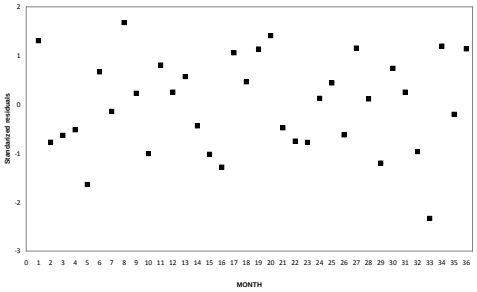
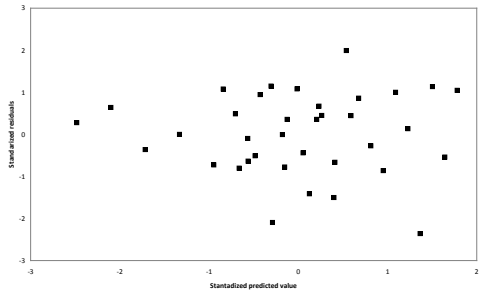
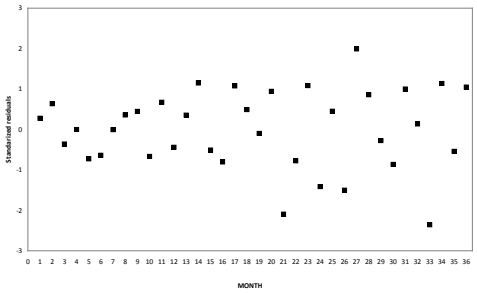
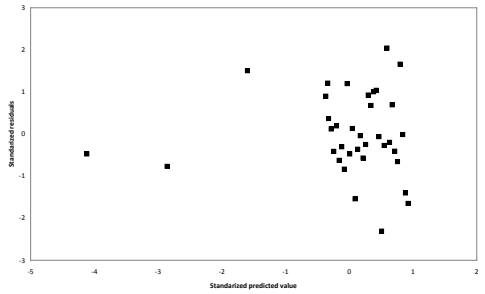
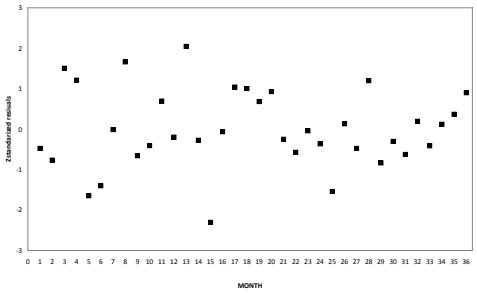
Models can be lineal or log-lineal. We used lineal models for IR but log-lineal for RR because using a non-transformed RR model caused a violation of normality assumption ($p = 0.001$ in Shapiro-Wilk test) . Durbin-Watson tests showed no evidence of autocorrelation in the models and in a graphic analysis of regression residuals there were not gross violations of the basic assumptions of lineality, homoscedasticity and independence (tables E6 and E7), so homoscedasticity was assumed and a model without autocorrelations was fitted.

Models with between zero and five joinpoints were tested. The method for joinpoint search was the "grid search", which creates a grid of possible joinpoint locations and uses the sum of squared errors (SSE) to identify which one best fit the data. A minimum of three observations from a joinponit to either end of the data and a minimum of four observations between two joinpoints were required, to avoid the joinpoints to be too much close and to allow each segment had a minimum of observations that would permit the calculation of standard errors.

Selection of the final model was based on a permutation test (results in table E8). Although the software can also use for this purpose the BIC (bayesian information criterion) that allows a faster analysis, permutation test was chosen because it is more parsimonious and lead to a model with less joinpoints. The permutation test compares two models, one with a lower number of joinpoints that is considered the "null hypothesis", and a second with more joinpoints which is considered the "alternative hypothesis". The comparison between them is made through a multiple permutation procedure[(1)], which for each comparison generates a Monte Carlo sample of 4500 randomly permuted data sets. The best fitted model in each comparison is selected according to a specified global significance level (p) stablished in 0.05, with a Bonferroni's correction for multiple comparisons.

(1) Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates [correction appears in *Stat Med* 2001;**20**:655]. *Stat Med* 2000;**19**:335-351.

Table S6. Residual plots.

A		
B		
C		
D		
E		

Standarized residuals as a function of standarized predicted value (left) and as a function of age (right). A) IR in asthmatic children; B) IR in non-asthmatic children; C) Log rate-ratio; D) IR in allergic asthma; E) IR in non-allergic asthma.

Table S7. Other regression diagnostics.

Model	R^2	Durbin-Watson test for autocorrelation*		Shapiro-Wilk test of standarized residuals for normality assumption (statistic and significance level)**	Breusch-Pagan test for homoscedasticity assumption (significance level)***
		d-value	(4-d) value		
IR in non-asthmatic children	0.898	2.04240	1.95760	0.978 (p = 0.674)	p=0.922
IR in asthmatic children	0.608	1.67331	2.32669	0.981 (p = 0.791)	p=0.239
Rate ratio (log-lineal model)	0.691	1.97274	2.02726	0.930 (p = 0.170)	p=0.596
IR in children with allergic asthma	0.742	2.63622	1.36378	0.970 (p = 0.419)	p=0.106
IR in children with non-allergic asthma	0.461	1.88224	2.11776	0.980 (p = 0.746)	p=0.371

*For a model with intercept, only one predictive variable and 36 point cases, autocorrelation (positive or negative) can be excluded at a significance level of 0.1 if both d-value and (4-d) value are > 1.31499[(2)].

** If p > 0.05, a normal distribution of residuals can be assumed.

*** If p > 0.05, homoscedasticity of residuals can be assumed.

(2) Savin NE, White KJ. The Durbin-Watson test for serial correlation with extreme sample sizes or many regressors. *Econometrica* 1977;**45**:1989-96

Table S8. Results of the permutation tests for each regression model.

Model	Test Number	Null Hypothesis	Alternate Hypothesis	P-Value	Significance Level
IR in asthmatic children	#1	0 Joinpoint(s)	5 Joinpoint(s) *	0.0004444	0.0100000
	#2	1 Joinpoint(s) *	5 Joinpoint(s)	0.2375556	0.0125000
	#3	1 Joinpoint(s) *	4 Joinpoint(s)	0.1691111	0.0125000
	#4	1 Joinpoint(s) *	3 Joinpoint(s)	0.0908889	0.0125000
	#5	1 Joinpoint(s) *	2 Joinpoint(s)	0.0224444	0.0125000
IR in non-asthmatic children	#1	0 Joinpoint(s)	5 Joinpoint(s) *	0.0002222	0.0100000
	#2	1 Joinpoint(s)	5 Joinpoint(s) *	0.0002222	0.0125000
	#3	2 Joinpoint(s) *	5 Joinpoint(s)	0.2857778	0.0166667
	#4	2 Joinpoint(s) *	4 Joinpoint(s)	0.3466667	0.0166667
	#5	2 Joinpoint(s) *	3 Joinpoint(s)	0.3911111	0.0166667
IR in children with allergic asthma	#1	0 Joinpoint(s) *	5 Joinpoint(s)	0.0111111	0.0100000
	#2	0 Joinpoint(s)	4 Joinpoint(s) *	0.0077778	0.0100000
	#3	1 Joinpoint(s) *	4 Joinpoint(s)	0.0266667	0.0125000
	#4	1 Joinpoint(s)	3 Joinpoint(s) *	0.0100000	0.0125000
	#5	2 Joinpoint(s) *	3 Joinpoint(s)	0.7937778	0.0166667
IR in children with non-allergic asthma	#1	0 Joinpoint(s)	5 Joinpoint(s) *	0.0073333	0.0100000
	#2	1 Joinpoint(s) *	5 Joinpoint(s)	0.6031111	0.0125000
	#3	1 Joinpoint(s) *	4 Joinpoint(s)	0.8584444	0.0125000
	#4	1 Joinpoint(s) *	3 Joinpoint(s)	0.8353333	0.0125000
	#5	1 Joinpoint(s) *	2 Joinpoint(s)	0.7655556	0.0125000
Log RR	#1	0 Joinpoint(s) *	5 Joinpoint(s)	0.5368889	0.0100000
	#2	0 Joinpoint(s) *	4 Joinpoint(s)	0.5913333	0.0100000
	#3	0 Joinpoint(s) *	3 Joinpoint(s)	0.6520000	0.0100000
	#4	0 Joinpoint(s) *	2 Joinpoint(s)	0.5184444	0.0100000
	#5	0 Joinpoint(s) *	1 Joinpoint(s)	0.6131111	0.0100000

* Selected model

Figure S2. Mean monthly incidence rates (per 1000) of wheeze from birth to thirty-six months of age in children with allergic (*closed squares*) and non-allergic (*open circles*) asthma.

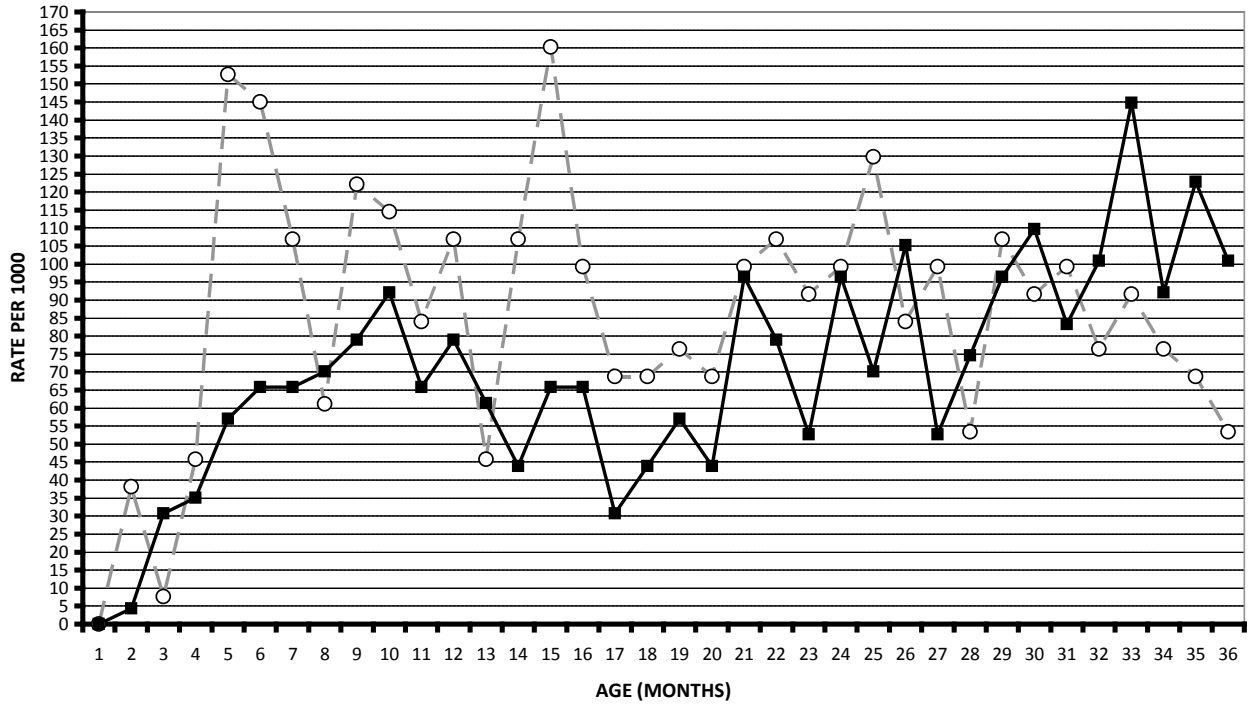


Figure S3. Monthly incidence rates of wheeze in children with non-allergic (left) and allergic (right) asthma, normalized for calendar month, in the first (*closed squares*), second (*open squares*) and third (*closed triangles*) years of age.