

Supplement

Wheezing and bronchial hyperresponsiveness in the preschool years as predictors of newly diagnosed asthma in early adult life: a longitudinal birth cohort study

Debra A. Stern, Wayne J. Morgan, Marilyn Halonen, Anne L. Wright, and Fernando D. Martinez

Supplement Table 1. Proportion (%) of subjects in different categories for early life risk factors and smoking at age 22 who had active asthma, wheeze and shortness of breath with wheeze at age 22 years

Risk Factors	Categories	Age 22 Years											
		Total n	Neither (n)	Asthma and Wheeze*				total n	Neither (n)	Shortness of Breath with Wheeze*			
				Asthma % (n+)	p [†]	Wheeze Only % (n+)	p [†]			Infrequent % (n+)	p [†]	Frequent % (n+)	p [†]
Sex	Male	404	(240)	26.6 (87)		24.3 (77)		403	(328)	12.1 (45)		8.4 (30)	
	Female	445	(265)	26.2 (94)	0.9	24.5 (86)	0.9	447	(359)	13.7 (57)	0.4	7.9 (31)	0.8
Parental asthma	Neither	622	(407)	20.2 (103)		21.6 (112)		622	(523)	10.4 (61)		6.8 (38)	
	Either	179	(70)	48.5 (66)	<0.0001	38.1 (43)	0.003	179	(125)	21.4 (34)	0.0003	13.8 (20)	0.007
Parental smoking	No	565	(346)	25.1 (116)		22.9 (103)		566	(461)	12.9 (68)		7.4 (37)	
	Yes	273	(153)	28.5 (61)	0.4	27.8 (59)	0.2	273	(216)	13.3 (33)	0.9	10.0 (24)	0.2
Eczema 2yr	No	696	(411)	25.7 (143)		25.1 (139)		695	(571)	11.6 (75)		7.9 (49)	
	Yes	79	(48)	32.4 (23)	0.2	14.3 (8)	0.076	79	(61)	16.4 (12)	0.2	9.0 (6)	0.7
Early Wheezing Phenotypes	Never	354	(241)	13.6 (38)	ref	23.7 (75)	ref	353	(308)	8.6 (29)	ref	4.9 (16)	ref
	Transient	135	(84)	22.9 (25)	0.027	23.6 (26)	0.9	135	(115)	9.4 (12)	0.8	6.5 (8)	0.5
	Late Onset	107	(52)	44.7 (42)	<0.0001	20.0 (13)	0.5	107	(78)	18.8 (18)	0.006	12.4 (11)	0.015
	Persistent	86	(34)	55.3 (42)	<0.0001	22.7 (10)	0.9	86	(55)	24.7 (18)	0.0002	19.1 (13)	0.0002
<i>Alternaria</i> positive 6yr	No	546	(346)	22.4 (100)		22.4 (100)		545	(453)	12.0 (62)		6.2 (30)	
	Yes	113	(48)	49.5 (47)	<0.0001	27.3 (18)	0.4	113	(77)	18.9 (18)	0.069	18.9 (18)	<0.0001
CA-BHR 6yr	No	330	(217)	16.5 (43)		24.4 (70)		329	(284)	9.8 (31)		4.7 (14)	
	Yes	58	(25)	46.8 (22)	<0.0001	30.6 (11)	0.4	58	(40)	21.6 (11)	0.018	14.9 (7)	0.010
V'maxFRC Quartiles 6yr	High	132	(91)	15.0 (16)	ref	21.6 (25)	ref	132	(111)	11.2 (14)	ref	5.1 (6)	ref
	Med-high	132	(76)	26.9 (28)	0.005	26.9 (28)	0.3	132	(111)	9.0 (11)	0.6	8.3 (10)	0.3
	Med-low	132	(84)	22.9 (25)	0.031	21.5 (23)	0.8	132	(110)	14.1 (18)	0.5	3.5 (4)	0.5
	Low	132	(63)	41.1 (44)	<0.0001	28.4 (25)	0.3	131	(95)	17.4 (20)	0.17	15.2 (17)	0.016
Smoking 22yr	No	625	(409)	23.3 (124)		18.4 (92)		627	(517)	12.1 (71)		7.0 (39)	
	Yes	224	(96)	37.3 (57)	0.0006	42.5 (71)	<0.0001	223	(170)	15.4 (31)	0.2	11.5 (22)	0.055

* Percentages for each symptom group were calculated with respect to the symptom-negative group after excluding the other symptom group.

[†] p-values for the association between each risk factor and the symptom groups were estimated using multinomial logistic regression with the symptom-negative group as the reference group.

Supplement Table 2. Multinomial odds ratios for respiratory symptoms at age 22 years by different risk factors in early life

Risk Factors *	Categories	Age 22 Years							
		Asthma and Wheeze				Shortness of Breath with Wheeze			
		Diagnosed Asthma		Wheeze Only		Infrequent		Frequent	
		M-OR [†] (95%CI)	p	M-OR (95%CI)	p	M-OR (95%CI)	p	M-OR (95%CI)	p
Parental asthma	Yes	3.3 (2.2, 5.2)	<0.0001	2.1 (1.3, 3.3)	0.001	2.1 (1.3, 3.4)	0.002	2.0 (1.1, 3.6)	0.031
Eczema 2yr	Yes	1.0 (0.5, 1.9)	0.9	0.5 (0.2, 1.0)	0.052	-	-	-	-
Early Wheezing Phenotypes	Never	ref		ref		ref		ref	
	Transient	1.5 (0.8, 2.7)	0.2	0.9 (0.5, 1.6)	0.8	1.0 (0.5, 2.0)	0.9	1.0 (0.4, 2.5)	0.9
	Late Onset	4.6 (2.6, 8.3)	<0.0001	0.8 (0.4, 1.6)	0.5	2.2 (1.1, 4.3)	0.018	2.1 (0.9, 5.0)	0.081
	Persistent	6.5 (3.5, 12)	<0.0001	0.9 (0.4, 2.0)	0.8	3.0 (1.5, 6.0)	0.002	3.2 (1.4, 7.4)	0.008
<i>Alternaria</i> pos 6yr	Yes	2.4 (1.4, 4.1)	0.001	1.3 (0.7, 2.5)	0.3	1.3 (0.7, 2.4)	0.4	2.5 (1.3, 5.0)	0.007
CA-BHR 6yr	Yes	4.7 (2.2, 10)	0.001	1.5 (0.7, 3.3)	0.3	2.3 (1.1, 5.3)	0.030	3.1 (1.1, 8.8)	0.029
V'maxFRC 6yr	Low	2.3 (1.3, 4.0)	0.003	1.5 (0.8, 2.6)	0.2	1.5 (0.8, 2.7)	0.2	2.5 (1.2, 5.3)	0.015
Smoking 22yr	Yes	2.1 (1.4, 3.2)	0.001	3.3 (2.3, 5.0)	<0.0001	1.3 (0.8, 2.1)	0.3	1.8 (1.0, 3.3)	0.039

* Variables with p-values less than 0.1 in full models were retained for the best-fitting models

† M-OR multinomial odds ratio (estimated using multinomial logistic regression) with all risk factors listed in the table included in the model with the respective symptom-negative group as the reference group. Models were additionally adjusted for ethnicity and sex.

Supplement Table 3. Prevalence of respiratory symptoms and allergy skin test responses for asthma at age 22 years

Asthma Groups	Age 22 Years											
	SOB with Wheeze			Cough			Skin Test Positive			Alternaria Positive		
	%	n+/n	p*	%	n+/n	p*	%	n+/n	p*	%	n+/n	p*
No Asthma	8.8	52/593	ref	29.3	169/577	ref	76.6	255/333	ref	28.2	94/333	ref
Inactive	6.8	5/74	0.6	26.0	19/73	0.6	93.9	46/49	0.011	51.0	25/49	0.002
Newly Diagnosed	55.1	27/49	<0.0001	71.4	35/49	<0.0001	95.8	23/24	0.058	41.7	10/24	0.17
Chronic	59.1	78/132	<0.0001	48.4	61/126	<0.0001	91.3	63/69	0.009	55.1	38/69	<0.0001

* p-values computed using logistic regression with the *no asthma* group as the reference group

Supplement Table 4. Prevalence of respiratory symptoms and allergy skin test responses for asthma at age 22 and by prescription medication use for asthma

Asthma Groups	Age 22 Years											
	SOB with Wheeze			Cough			Skin Test Positive			Alternaria Positive		
	%	n+/n	p*	%	n+/n	p*	%	n+/n	p*	%	n+/n	p*
Newly Diagnosed												
No Meds [†]	45.8	11/24		70.8	17/24		92.9	13/14		42.9	6/14	
Yes Meds [†]	64.0	16/25	0.3	72.0	18/25	0.9	100	10/10	0.9	40.0	4/10	0.9
Chronic												
No Meds [†]	40.3	25/62		40.4	23/57		90.6	29/32		50.0	16/32	
Yes Meds [†]	75.7	53/70	<0.0001	55.1	38/69	0.110	91.9	34/37	0.9	59.5	22/37	0.5

* p-values computed with Fisher's exact test comparing medication use to no medication use for each asthma group

[†] Used any prescription medication for asthma or wheeze during the past year

Supplement Table 5. Pre- and post-bronchodilator FEV₁/FVC ratio and response to bronchodilator for asthma at age 22 and by prescription medication use for asthma

Asthma Groups	Age 22 Years						
	Pre-BD FEV ₁ /FVC ratio [*]			Post-BD FEV ₁ /FVC ratio [*]		Bronchodilator Response ^{*†}	
	(z-scores)			(z-scores)		(z-scores)	
	n	mean (sem)	p [‡]	mean (sem)	p [‡]	mean (sem)	p [‡]
Newly Diagnosed							
No Meds [§]	13	- 0.54 (0.33)		- 0.44 (0.22)		0.36 (0.51)	
Yes Meds [§]	11	- 0.42 (0.19)	0.7	- 0.52 (0.34)	0.8	0.03 (0.29)	0.6
Chronic							
No Meds [§]	35	- 0.03 (0.16)		- 0.01 (0.16)		- 0.05 (0.15)	
Yes Meds [§]	34	- 0.71 (0.24)	0.022	- 0.66 (0.23)	0.025	0.70 (0.26)	0.014

^{*} Each lung function outcome was adjusted for sex in a linear regression and the standardized residuals from the regression (z-scores) were saved and used as the outcome measures for this table.

[†] Bronchodilator response calculated using FEV₁ (ml) as ((post-pre)/(post+pre))*100

[‡] p-values computed with two-sample t-test with unequal variances comparing medication use to no medication use for each asthma group

[§] Used any prescription medication for asthma or wheeze during the past year

Supplement Figure 1. Early wheezing phenotype distribution for asthma at age 22 years. Sample sizes are limited to those with early wheezing phenotype information. For asthma at age 22 years: *inactive asthma* (n=65) is physician diagnosis of asthma between 2 and 16 years but no current symptoms at age 22, *newly diagnosed asthma* (n=35) is first diagnosis and active symptoms at age 22, *chronic asthma* (n=112) is a diagnosis between 2 and 16 years and active symptoms at age 22, and *no asthma* (n=470) is no diagnosis of asthma through age 22 years. For the early wheezing phenotypes: *persistent wheeze* includes children who wheeze during LRI before age 3 and were still wheezing at age 6, *late onset wheeze* includes children who did not have wheezing LRI but started wheezing by age 6, *transient early wheeze* includes children who wheezed with LRI but did not report wheezing at age 6 and *never wheeze* includes children with no wheezing LRIs and no wheeze at age 6.

