ONLINE SUPPLEMENT ADDED INFORMATION

METHODS (Additional description of dry air hyperventilation challenge)

Isocapnic dry air hyperventilation challenge (DACh) was performed after baseline spirometry at age 13 and 18 years. Dry air containing 5% CO_2 was breathed at a rate corresponding to resting FEV_1 x 26 (L/min) for four minutes. An adult size Hans-Rudolph two-way valve was used for the provocations to ensure that no flow limitation would occur. FEV_1 was measured in triplicate at baseline and in duplicate at 2, 5, and 10 minutes after challenge, and the highest value at each point in time was noted. The maximum fall in FEV_1, from the baseline value, was calculated. After challenge 400 μg of salbutamol was inhaled, via a dry powder inhaler, (800 μg if fall in FEV_1 was ≥10%) and followed by spirometry (in triplicate) 15 minutes later.

Table E1. Background factors from age 1 to 18 in the RSV and control cohorts.

Variable		RSV					Controls				
Age, yr		1	3	7	13	18	1	3	7	13	18
Family history											
Family history of Atopy	Total		57	70	74	74		56	65	74	74
	Parent		49	62	61	65		46	48	54	56
Family history of Asthma	Total		23	45	50	52		24	29	35	35
	Parent		21	34	37	39		18	20	27	28
Current smoking in family		45	45	43	35	42	45	45	39	42	43
Own smoking						22					15
Current indoor furred animals		30	26	45	63	52	38	39	44	74	61

Data displayed as percentage (%)

Table E2. Proportion of tested subjects in the RSV and control cohorts with positive skin prick tests, Phadiatop® tests or raised specific serum IgE antibodies to inhalant allergens at age 18 years. HDM = house dust mite.

	RSV (n=46)	Control (n=92)	p-value
Skin prick test			
Any pollen	16/41 (39%)	22/85 (26%)	0.194
Any animal dander	13/40 (33%)	9/85 (11%)	0.006
Any HDM	10/40 (25%)	9/85 (11%)	0.068
Any perennial	16/40 (40%)	12/85 (14%)	0.003
Any positive test	19/41 (46%)	26/85 (31%)	0.126
Blood samples			
Phadiatop® test	23/41 (56%)	24/85 (28%)	0.005

Table E3. Airway function and inflammatory markers in subjects with vs without current asthma/RW at age 18 years.

	Current asthma/RW (n=26)	No current asthma/RW (n=112)	95% CI for difference
Resting			
FEV_1 (z-score)	-0.43 (0.87)	0.09 (1.06)	0.07; 0.96 *
FEV_1/FVC (z-score)	-0.59 (1.09)	-0.20 (0.98)	-0.04; 0.83
FEF_{25-75} (z-score)	-0.64 (0.84)	-0.13 (0.84)	0.14; 0.87 **
LCI	6.88 (0.53)	6.53 (0.41)	-0.54; -0.16 ***
Challenge (DACh)			
Fall in FEV_1 (%)	8.5 (0.0; 42.8)	3.1 (0.0; 22.1)	2.5; 8.7 ***
Post-bronchodilation			
Rise in FEV_1 (%)	5.6 (0.0; 10.2)	3.7 (0.0; 10.4)	0.0; 3.1
FEV1 (z-score)	-0.05 (0.88)	0.40 (1.08)	-0.01; 0.88
FEV1/FVC (z-score)	-0.01 (0.94)	0.34 (0.94)	-0.05; 0.76
FEF25-75 (z-score)	-0.05 (0.82)	0.33 (0.82)	0.02; 0.73 *
Inflammatory markers			
FENO (ppb)	18 (7; 84)	13 (5; 74)	1; 5 **
Blood eosinophil counts ($x10^9/L$)	0.24 (0.04; 0.57)	0.14 (0.01; 0.79)	0.04; 0.15 **

Definition of abbreviations: LCI= lung clearance index; FENO = fraction exhaled nitric oxide; ppb = parts per billion; DACh = Isocapnic dry air hyperventilation challenge. Data are displayed as mean (SD) or median (range). For normally distributed data differences between the two groups are shown with 95% CI for the mean values and for non-normally distributed data as the 95% CI for the medians. * p<0.05, ** p<0.01, *** p<0.001.

Table E4. Airway function and inflammatory markers RW at age 18 years in RSV subjects with vs without current asthma/RW and in control subjects with vs without current asthma/RW.

	RSV			Controls		
	Asthma/RW (N= 18)	No asthma/RW (N= 24)	95% CI for difference	Asthma/RW (N= 8)	No asthma/RW (N= 78)	95% CI for difference
Resting						
FEV_1 (z-score)	-0.64 (0.85)	0.00 (0.91)	0.09;1.20 *	0.05 (0.77)	0.11 (1.11)	-0.74; 0.86
FEV_1/FVC (z-score)	-0.89 (0.82)	-0.53 (0.86)	-0.17; 0.90	0.08 (1.37)	-0.10 (1.00)	-0.94; 0.59
FEF_{25-75} (z-score)	-0.89 (0.71)	-0.38 (0.75)	0.04; 0.97 *	-0.06 (0.86)	-0.05 (0.85)	-0.62; 0.64
LCI	6.88 (0.63)	6.44 (0.31)	-0.74; -0.14 **	6.89 (0.25)	6.56 (0.43)	-0.64; -0.03 *
Challenge (DACh)						
Fall in FEV_1 (%)	8.5 (0.0; 37.8)	3.6 (0.0; 9.3)	1.0; 12.8 **	7.5 (0.3; 42.8)	3.1 (0.0; 22.1)	0.5; 8.8
Post broncho-dilation						
Rise in FEV_1 (%)	6.5 (0.0; 10.2)	5.4 (0.0; 10.5)	-1.1; 3.4	2.5 (0.0; 9.9)	3.1 (0.0; 10.4)	-2.9; 2.3
FEV_1 (z-score)	-0.18(0.79)	0.41 (0.81)	0.09; 1.10 *	0.25 (1.05)	0.39 (1.15)	-0.71; 0.99
FEV_1/FVC (z-score)	-0.23 (0.83)	0.11 (0.90)	-0.21; 0.88	0.48 (1.06)	0.41 (0.95)	-0.77; 0.65
FEF_{25-75} (z-score)	-0.29 (0.76)	0.19 (0.74)	0.10; 0.95 *	0.48 (0.72)	0.37 (0.84)	-0.73; 0.50
Inflammatory markers						
FENO (ppb)	22 (6; 84)	13 (6; 54)	1; 25 *	15 (7; 51)	12 (5; 74)	-3; 17
Blood eosinophils ($x10^9$/L)	0.33 (0.06; 0.57)	0.16 (0.04; 0.37)	0.04; 0.23**	0.16 (0.04; 0.31)	0.14 (0.01; 0.79)	-0.04; 0.08

Definition of abbreviations: LCI= lung clearance index; FENO = fraction exhaled nitric oxide; ppb = parts per billion; DACh = Isocapnic dry air hyperventilation challenge. Data are displayed as mean (SD) or median (range). For normally distributed data differences between the two groups are shown with 95% CI for the mean values and for non-normally distributed data as the 95% CI for the medians. * $p < 0.05$, ** $p < 0.01$.

Table E5. Associations between bronchial hyperresponsiveness (maximum % fall in FEV_1 after dry air hyperventilation challenge) and inflammatory variables and resting airway function assessed by regression analysis in the RSV cohort.

Group assessed	N	Dependent variable	Independent variable(s)	R^2 adj	p-value	Beta value(s)
RSV cohort	39	Max % fall in FEV_1	Eosinophil count	0.123	0.0106	0.382
RSV cohort	41	Max % fall in FEV_1	FENO	0.260	0.0004	0.528
RSV cohort	40	Max % fall in FEV_1	LCI	0.436	0.000002	0.672
RSV cohort	41	Max % fall in FEV_1	FEV_1 (z-score)	0.021	0.665	-0.007
RSV cohort	38	Max % fall in FEV_1	Eosinophil count FENO LCI	0.489	0.000009	0.091 (n.s.) 0.247 (n.s.) 0.540

Table E6. Results from conditional (case- control) logistic regression tests with one index subject matched to two controls of the same sex from the same health care centre, and allocation (RSV or control), sex, parental smoking in the first year of life, domestic pets in the first year of life, own smoking at age 18, and a history of physician diagnosed parental asthma at the last follow-up as independent factors.

Dependent variable	Significant independent variables	p-value	OR	95% CI
Asthma/RW at age 18	RSV allocation	0.004	3.41	1.47; 7.95
Asthma at age 18	RSV allocation	0.002	5.74	1.87; 17.64
ARC at age 18	RSV allocation	0.014	2.54	1.21; 5.36

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