

Online Table O1 Baseline Characteristics of study sample and comparison with all eligible participants

Baseline Characteristic	I Methacholine test at follow-up, complete covariate data & no asthma medication (n=3005)	II Only baseline methacholine test, although eligible for testing at follow-up (n=3127)*	III Only baseline spirometry, but no methacholine test due to technical problems, refusal or medical exclusion (n=2084)*	p-Value comparing I and II**	p-Value comparing I and III**
Female sex (%)	49.1	50.7	55.9	0.219	<0.001
Age (mean/sd)	39.1 / 11	40.3 / 11.9	44.1 / 11.6	<0.001	<0.001
Phadiatop test (%)	29.4	28.7	28.2	0.564	0.397
Exposure to ETS never smoker (%)	13.2	13.3	12.5	0.993	0.415
Exposure to ETS ex-smoker (%)	6.9	7.6	7.9	0.292	0.192
BMI in kg/m ² (median/1st/3rd quartile)	23.0 / 21 / 25	23.4 / 21.2 / 26.2	23.8 / 21.4 / 26.8	0.01	<0.001
Current smoking (%)	28.3	37.5	34.1	<0.001	<0.001
Ex-smoking (%)	23.5	21.6	22.6	0.088	0.442
Packyears (median/1st/3rd quartile)	11.4 / 4 / 23	14 / 5.2 / 27.9	17.0 / 6.0 / 32.8	<0.001	<0.001
FEV1 in litres (median/1st/3rd quartile)	3.7 / 3.1 / 4.3	3.5 / 3 / 4.2	3.1 / 2.6 / 3.7	<0.001	<0.001
FEF ₂₅₋₇₅ in ml/sec(median/1st/3rd quartile)	3.5 / 2.7 / 4.4	3.4 / 2.7 / 4.3	2.9 / 2.0 / 3.8	<0.001	<0.001
FVC in litres (median/1st/3rd quartile)	4.6 / 3.9 / 5.4	4.4 / 3.7 / 5.2	4.1 / 3.5 / 4.9	<0.001	<0.001
Doctor's diagnosed asthma (%)	3.7	6.6	7.9	<0.001	<0.001
Being hyper-reactive (%)	12.9	18.2	24.9	<0.001	<0.001
Reactivity slope (median/1st/3rd quartile)	1.0 / 0.6 / 1.7	1.08 / 0.59 / 1.96		<0.001	
Wheezing without cold in the last year(%)	4.4	8.1	11.2	<0.001	<0.001
Chronic cough (%)	3.0	5.2	7.5	<0.001	<0.001

* smaller sample sizes for packyears because relating to ever-smokers (n=1794 in group II, n=1130 in group III)

** T-tests for means, Wilcoxon rank sum tests for medians, Chi-2 tests for proportions

Online table O2 Airway hyper-reactivity at baseline and follow-up examination

Baseline Examination	Follow-up Examination		
	normoreactive	hyper-reactive	Total
normoreactive n(%)	2684 (93.2)	195 (6.8)	2879
<i>% of total</i>	79.9	5.8	85.7
hyper-reactive n(%)	255 (53.2)	224 (46.8)	479
<i>% of total</i>	7.6	6.7	14.3
Total n(%)	2939 (87.5)	419 (12.5)	3358

p_{McNemar}=0.0054

Online table O3 Influence of adjustment for lung function on effect estimates for change in bronchial reactivity slope of other model covariates

Covariate	Main Model¹⁾ % change in b.r. slope (95%-CI)	Model with absolute change²⁾ %-change in b.r. slope (95%-CI)	Model without lung function variables³⁾ %-change in b.r. slope (95%-CI)	Model with %- predicted lung function and change⁴⁾ %-change in b.r. slope (95%-CI)
	-3.9	-10.9	-13.1*	-13.8*
Female sex	(-21.1 to 16.9)	(-27.8 to 9.9)	(-21.5 to -3.7)	(-22.4 to -4.2)
Age (centered at 40 years)	0.9* (0.4 to 1.5)	0.6 (-0.1 to 1.2)	0.8* (0.3 to 1.3)	0.7* (0.2 to 1.3)
Age(centered at 40 years) squared	0.05* (0.01 to 0.09)	0.05* (0.01 to 0.09)	0.04* (0.00 to 0.08)	0.04* (0.00 to 0.08)
ETS in never smokers	-1.0 (-16.0 to 16.7)	-0.3 (-15.5 to 17.6)	-1.0 (-16.0 to 16.7)	-1.0 (-16.0 to 16.7)
ETS in ex-smokers	10.7 (-10.1 to 36.3)	8.6 (-11.8 to 33.7)	10.3 (-10.4 to 35.8)	9.5 (-11.1 to 34.8)
Atopy	-6.3 (-15.8 to 4.2)	-6.7 (-16.1 to 3.8)	-6.5 (-16.0 to 4.1)	-7.2 (-16.6 to 3.2)
BMI (centered at 25 kg/m²)	-0.1 (-1.6 to 1.4)	-0.1 (-1.6 to 1.5)	-0.2 (-1.6 to 1.3)	-0.1 (-1.6 to 1.4)
Change** in centered BMI	2.7* (0.3 to 5.2)	2.4 (0.0 to 4.9)	2.7* (0.3 to 5.2)	2.5* (0.1 to 4.9)
Smoking	21.2* (7.5 to 36.7)	19.1* (5.4 to 34.6)	21.0* (7.3 to 36.5)	19.2* (5.5 to 34.6)
Ex-smoking	-5.1 (-18.2 to 10.1)	-4.7 (-17.9 to 10.6)	-4.8 (-17.9 to 10.4)	-5.3 (-18.4 to 9.8)
FEV1 percent predicted				-0.1 (-0.8 to 0.6)
Change** in FEV1 percent predicted				-1.2* (-2.1 to -0.4)
FVC percent predicted				0.2 (-0.4 to 0.9)
Change** FVC percent predicted				0.4 (-0.4 to 1.2)

b.r. slope: bronchial reactivity slope, defined as percent change in FEV1 per μmol methacholine

¹⁾ Estimates from a mixed linear model and adjusted for all covariates with estimates in the table plus baseline FEV1 (centered at 3.5L), baseline FVC (centered at 5L), baseline FEF₂₅₋₇₅ (adjusted for sex and FEV1 and centered at its mean). presence of concurrent colds at both examinations, seasonal terms, and random effects for area

²⁾ Model with all covariates from model 1 plus change in centered FEV1, FVC and FEF²⁵⁻⁷⁵ variables (calculated as follow-up minus baseline value)

³⁾ Model including just the covariates with estimates in the table

⁴⁾ Model including covariates as listed in the table and adjustment for FEV1 and FVC %-predicted (using ECTS prediction equations) and change in %-predicted values (calculated as follow-up minus baseline value)

* significant at 5% threshold

** change was calculated as follow-up minus baseline value