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Title: Predictors of completion and outcome of exercise challenge tests in childhood asthma

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Abbreviations: AUC=Area under the curve; BMI=Body Mass Index; EIB=Exercise Induced Bronchoconstriction; FeNO=Fraction of exhaled Nitric Oxide; FEV1=Forced Expiratory Volume in the first second; ppb=parts per billion; ICS=Inhaled corticosteroids; LABA=long acting β 2-agonist; LTRA=leukotriene receptor antagonist; NPV=negative predictive value; OR=Odds Ratio; PPV=positive predictive value; ROC=Receiver Operating Characteristics; SABA=short acting β 2-agonist.

MANUSCRIPT TEXT

To the Editor,

Exercise is a common trigger of bronchoconstriction in children with asthma(1). The gold standard for diagnosing exercise-induced bronchoconstriction (EIB) is a standardized exercise test on a treadmill(2). The test has high sensitivity and specificity(3), but requires considerable medical resources and child cooperation(4). Therefore, it is important to determine which children can complete the test procedure and to predict the test outcome, whereof the former has not previously been studied. Here, we aimed to identify predictors of exercise test completion and outcome to avoid frustrate and redundant tests.

The study is a retrospective, cross-sectional study of 5–18-year-old children, who performed an exercise challenge test to diagnose asthma in the pediatric asthma outpatient clinic at Herlev-Gentofte University Hospital from January to December 2015. The study was approved by the regional knowledge center of data reviews (IRB). All parents signed a consent form prior to exercise testing.

The exercise test was conducted by trained personnel using a motorized treadmill for 6min targeting a sub-maximal heart rate of $\geq 80\%$ of the maximum expected for age using a slope of 10% and a speed of 9 km/h, which was adjusted to reach the targeted heart rate. The child was wearing a nasal clip to ensure mouth breathing. Saturation and heart rate were monitored with an oximeter. Forced expiratory volume in the first second (FEV1) was measured at baseline and 1, 3, 5, 10 and 15 min post-exercise(2), but not 30 min post-exercise as a delayed drop in FEV1 is infrequently seen.

Non-completion was defined by the child not reaching the targeted heart rate for at least 4 min or not completing spirometry(5). EIB diagnosis was based on a FEV1-drop $\geq 10\%$ from baseline within 15 min post-exercise(2). Short-acting β_2 -agonists (SABA) were withheld 6 h, long-acting β_2 -agonists (LABA) 24 h, leukotriene receptor antagonists (LTRA) 5 days, and inhaled corticosteroids (ICS) 14 days before the test.

The following determinants were analyzed for association with test completion and outcome: sociodemographics (gender; age; BMI (WHO z-score); Caucasian origin; sports activity besides physical education in school), atopic predisposition (asthma; allergy; eczema; any predisposition), comorbidity (rhinitis; food allergy; eczema; any comorbidity), treatment (SABA; ICS; ICS+LABA; LTRA; any asthma controller; nasal corticosteroids), and fractional exhaled nitric oxide (FeNO) level.

Univariate analyses were done by logistic regression models adding cross-products to investigate for interaction. Multivariate logistic regression with backwards selection using Akaike information criterion were used for selection of the best model fit. Receiver operating characteristic (ROC) curve analyses were conducted to assess the predictive performance (area under the curve (AUC) with 95% CI) and to establish best cut-off values based on Youden index. Analyses were performed using R version 3.5.2 (**Online methods**).

In total, 228 children performed an exercise challenge test during 2015 of whom we obtained data from 110 children (**eFigure 1**). Of these, 61 (56%) were boys, mean (SD) age was 12.3 years (2.4), mean BMI z-score was 0.12 SD (1.04). Eighty two (83%) were sports active, with boys being more active than girls: 51 (93%) vs. 31 (71%); mean difference (MD) (95% CI), 22% (7–37), $p=0.01$ (**Table 1**).

Of the 110 children, 85 (77%) completed the test. Children not completing the test had higher BMI (0.54 vs. -0.003 SD; MD, 0.55 SD (0.02–1.07), $p=0.04$) and were less sports active (no. sports active/total, 12/20 (60%) vs. 70/79 (89%); MD, 29% (6–51), $p=0.002$) (**eTable 1**). Increasing BMI and not being sports active increased the risk of non-completion: adjusted odds ratio (aOR) per SD, 2.0 (1.2 to 3.5), $p=0.01$ and aOR 5.2 (1.3 to 21.6), $p=0.02$, respectively. The multivariate analysis showed that BMI, sports activity, age and FeNO were the best determinants of test completion. A ROC-curve analysis for BMI showed an AUC (95% CI) of 63% (52–79) with 1 SD as the optimal cut-off with negative predictive value (NPV) 86%, specificity 85%, positive predictive value (PPV) 50% and sensitivity 52%. Sports activity had an AUC of 64% (53–76), whereas AUC for FeNO and age were insignificant. A ROC-curve analysis including both BMI and sports activity showed an AUC of 77% (66–89) (**Figure 1**).

Of the 85 children completing the test, 30 (35%) had a post-exercise FEV1-drop $\geq$ 10%. Children with a post-exercise FEV1-drop $\geq$ 10% were less sports active (22/29 (76%) vs. 48/50 (96%), MD, 20% (4–37), $p=0.01$), had higher FeNO (25.1 vs 15.8ppb; geometric MD, 1.6ppb (1.1–2.3), $p=0.01$) and were less often males (13/30 (43%) vs. 38/55 (69%); MD, 26% (4–47), $p=0.02$) (**eTable 2**). Not being sports active increased the risk of a FEV1-drop $\geq$ 10% (aOR 6.0 (1.2 to 44.7), $p=0.04$), whereas male gender was not significant: aOR 2.2 (0.8 to 6.1), $p=0.14$ (p -interaction=0.99). FeNO and maximum post-exercise FEV1-drop were linearly associated with every 10ppb increase in FeNO resulting in a post-exercise FEV1-drop of 7% (0–14), $p=0.04$. The multivariate analysis confirmed that not being sports active (OR 12.1 (1.8–243.9), $p=0.03$) and FeNO (OR per 10ppb, 6.8 (1.3–42.2), $p=0.03$) increased the risk of a FEV1-drop $\geq$ 10%. A ROC-curve analysis of FeNO showed an AUC of 67% (54–79) with 20.4ppb as the best cut-off for predicting FEV1-drop $\geq$ 10% with NPV 75%, specificity 68%, PPV 51% and sensitivity 60%. A combined ROC-curve analysis of FeNO and sports activity showed an AUC of 71% (59–84) (**Figure 2**).

We found an association between higher BMI and non-completion, aligning a study investigating the relationship between physical activity and post-exercise FEV1-drop showing 90% of children not completing the test were overweight(6), which may be due to the known association between higher BMI and reduced motor competencies in children(7). A z-score BMI above 1 SD showed a high NPV of 86%, but a poor PPV of 50%, suggesting that BMI is better at predicting completion than non-completion. Not participating in sports activities outside school was also associated with non-completion, which remained significant adjusted for BMI and gender. The ROC analysis of BMI and sports activity showed a fair accuracy, which warrants replication to assess true test performance.

Not being sports active outside school was associated with post-exercise FEV1-drop $\geq$ 10%, which is in line with a study showing that increasing bronchial hyperresponsiveness was correlated to reduced level of physical activity(8), possibly caused by undertreated asthma. We also found that elevated FeNO was associated with FEV1-drop $\geq$ 10%, which remained significant after adjusting for rhinitis and ICS treatment. The ROC analysis of FeNO for predicting EIB showed a poor accuracy and low NPV of 75% and PPV of 51%, which is congruent with previous studies(9) and

might be due to EIB also occurring in individuals without asthma and type 2 inflammation(10), who have lower FeNO.

The primary limitation of our study is the retrospective design, that some medical records could not be retrieved and lack of further information on type, duration and intensity of sports activities, whereas it is a strength that the exercise tests were conducted by trained staff assuring consistency in the procedure.

Our findings of association between BMI, sports activity and test completion and sports activity, FeNO level and test outcome may be useful to guide the clinician for selecting an appropriate bronchial hyperresponsiveness test.

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TABLES

Table 1: Baseline characteristics of the study group

Baseline characteristics	Missing data	Study population N=110
Sociodemographic variables		
Gender, male, N (%)	0	61 (56%)
Age (years), mean (SD)	0	12.3 (2,4)
BMI (kg/m ²), mean (SD)	1	18.7 (3.2)
BMI z-score (SD), mean (SD)	1	0.12 (1.04)
Caucasian origin, yes, N (%)	0	74 (67%)
Sports active, yes, N (%)	11	82 (83%)
Atopic comorbidity		
Rhinitis, yes, N (%)	0	72 (66%)
Eczema, yes, N (%)	0	48 (44%)
Dust mite allergy, yes, N (%)	0	51 (46%)
Pet allergy, yes, N (%)	0	61 (56%)
Pollen allergy, yes, N (%)	3	44 (41%)
Food allergy, yes, N (%)	2	9 (8%)
Any atopic comorbidities, yes, N (%)	0	93 (85%)
Treatment		
SABA monotherapy, yes, N (%)	0	17 (16%)
ICS, yes, N (%)	0	70 (64%)
ICS + LABA, yes, N (%)	0	15 (14%)
LTRA, yes, N (%)	1	27 (25%)
Nasal steroids, yes, N (%)	2	69 (64%)
Antihistamine, yes, N (%)	3	65 (61%)
Any controller, yes, N (%)	0	86 (78%)
No treatment, yes, N (%)	0	7 (6%)
Atopic predispositions (first degree relatives)		
Asthma, yes, N (%)	9	43 (43%)
Allergy, yes, N (%)	9	60 (59%)
Eczema, yes, N (%)	9	19 (19%)
Any atopic predispositions, yes, N (%)	9	75 (74%)
Pre-exercise characteristics		
Baseline FEV1 (L), mean (SD)	0	2.6 (0.8)

Baseline FEV1 (%-predicted), mean (SD)	0	89.8 (11.4)
Baseline FeNO (ppb), median (IQR)	3	19.1 (3.2)

SD, standard deviation; BMI, Body Mass Index; Any atopic comorbidities includes rhinitis, eczema or food-allergy; SABA, Short-acting β 2-agonist; LABA, Long-acting β 2-agonist; ICS, Inhaled corticosteroids; LTRA, Leukotriene receptor antagonist; Any controller includes ICS, ICS+LABA, LTRA; FEV, Forced expiratory volume in 1 s; FeNO, Fractional exhaled nitric oxide; ppb, parts per billion.

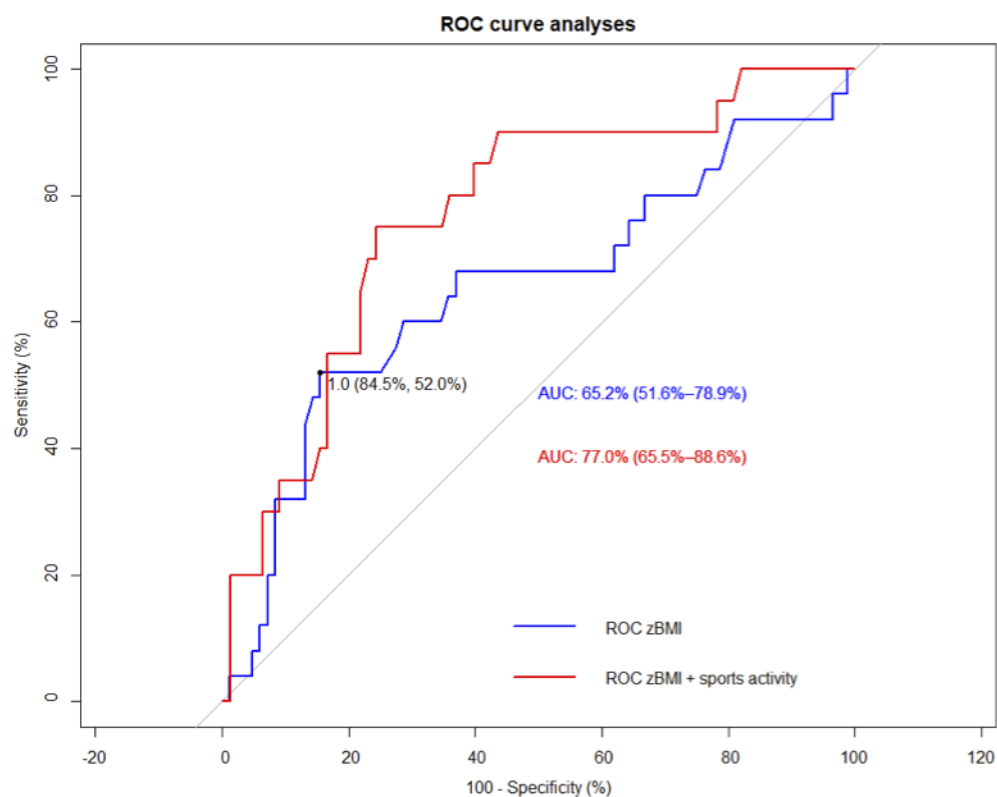
FIGURE LEGENDS

Figure 1: Receiver operation characteristic (ROC)-curve analyses for BMI z-score and the combined value of BMI z-score and sports activity status for predicting exercise test completion.

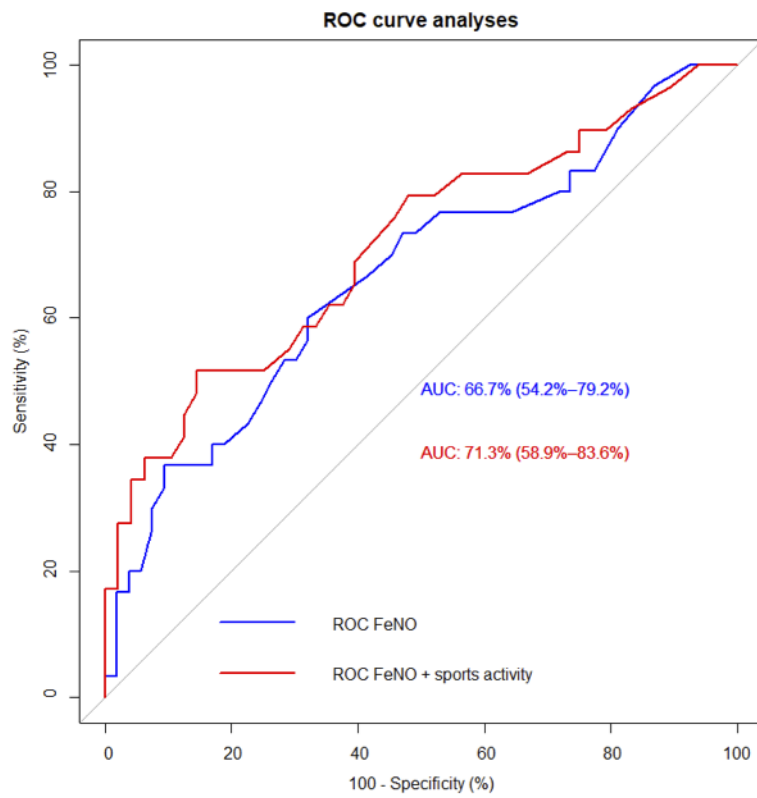
The blue curve shows the ROC-curve analysis for the predictive value of body mass index (BMI) z-score and the best cut-off value for BMI-z-score with area under the curve (AUC (95% CI)) for predicting exercise test completion. The red curve shows the ROC-curve analysis for the predictive value of the combined effect of BMI z-score and sports activity.

Figure 2: Receiver operation characteristic (ROC)-curve analyses for FeNO and the combined value of FeNO and sports activity status for predicting an exercise challenge with a maximum FEV1-drop $\geq 10\%$.

The blue curve shows the ROC-curve analysis for the predictive value of FeNO with area under the curve (AUC (95% CI)) for predicting a maximum post-exercise FEV1-drop $\geq 10\%$. The red curve shows the ROC-curve analysis for the predictive value of the combined effect of FeNO and sports activity status.



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pai_13224_f2.tiff

1 **ONLINE REPOSITORY**

2 **ONLINE METHODS**

3 **Exercise test methods**

4 Spirometry was performed as per ATS standards using a MasterScope spirometer (Jaeger,
5 Würzburg, Germany) with the child sitting and wearing a nose clip. Spirometry was performed in
6 triplicates with a maximum of 5% difference between the highest FEV1 values and only children
7 with baseline FEV1 above 70% of predicted normal value were enrolled. A post-exercise
8 reversibility test was conducted measuring the change in FEV1 from baseline 15-20 minutes after
9 administration of 4 puffs of inhaled salbutamol (Ventoline®, pMDI, 0.1 mg/dose (GlaxoSmithKline
10 Pharma).

11 **Exercise test characteristics**

12 Minutes on treadmill (continues), Maximum heart rate (continues), Max drop in FEV1 from
13 baseline in L (continues), Max drop in FEV1 from baseline in %-predicted (continues), $\geq 10\%$ drop
14 in FEV1 from baseline (yes/no), Reversibility in L (continues), Reversibility in %-change
15 (continues), Significant reversibility ($>12\%$ increase in post- β_2 -agonist-FEV1 – yes/no), Significant
16 SAT-drop ($>10\%$ -drop in >2 min - yes/no), Asthma symptoms (yes/no).

17 **FeNO measurement**

18 FeNO was measured before performing the baseline spirometry and the exercise challenge test
19 using a Niox Vero gas analyzer (Aerocrine AB, Solna, Sweden). The test was conducted in
20 accordance with ATS and ERS recommendations(1). The child was instructed to empty the lungs,
21 then inhale to total lung capacity through the filter and immediately after exhale at a constant flow

22 of 50 ml/s, until reaching a FeNO plateau of ≥ 2 s. The exhalation was guided by an animated flow-
23 driven computer program, helping the child obtain the targeted flow.

24 **Rhinitis**

25 The diagnosis of rhinitis was made according to ARIA guidelines(2) based on allergic symptoms
26 including: Sneezing, rhinorrhea, nasal obstruction and pruritus, accompanied by allergen-specific
27 sensitization diagnosed by skin prick test or serum-specific IgE.

28 **Eczema**

29 Atopic dermatitis was diagnosed according to the guidelines from the American Academy of
30 Dermatology (AAD)(3). The diagnosis included the presence of the following 4 criteria: 1: pruritus,
31 2: eczema, 3: typical morphology and age-specific patterns (facial, neck and extensor involvement
32 in infant and children; current or previous flexural lesions in any age group; sparing of the groin
33 and axillary regions) and 4: chronic or relapsing history.

34 **Food allergy**

35 The food allergy diagnosis was based on dietary history, a clinical examination, typical skin-,
36 gastrointestinal-, respiratory- or circulatory symptoms, a positive skin prick test and serum-specific
37 IgE, and either a convincing history or a positive oral food challenge in accordance with the
38 European Academy of Allergy and Clinical Immunology (EAACI) guidelines(4).

39 **STATISTICAL ANALYSIS**

40 **Data preparation**

41 FeNO values were log10-transformed before analysis to obtain normal distribution of the data.

42 **Univariate analyses**

43 Differences between completion and non-completion of the exercise test, test outcome and
44 differences between gender were analyzed using Pearson’s chi-square, Fishers exact test and
45 students t-test.

46 The association between test completion, BMI z-score and sports activity level were investigated
47 using logistic regression analysis with test completion (yes/no) as the dependent dichotomous
48 variable, BMI z-score as a numerical variable and sports activity as dichotomous categorical
49 variable. Results are reported crude and adjusted for sports activity, BMI z-score and Caucasian
50 origin. For further investigation of the relationship between BMI z-score and sports activity level an
51 interaction analysis was performed. The effect of sports activity on test completion was additionally
52 investigated using logistic regression analysis stratified for gender.

53 The effect of sports activity and gender on the outcome of the test (EIB, yes/no) was examined
54 using logistic regression analysis, with outcome of the test as the dependent dichotomous
55 categorical variable. Results are reported crude and adjusted for BMI z-score, sports activity and
56 Caucasian origin.

57 The influence of FeNO on the test outcome was analyzed using logistic regression and general
58 linear model analyses. Test outcome was a dependent dichotomous categorical variable, post-
59 exercise percentage drop in FEV1 was a continuous dependent variable and FeNO a continuous
60 explanatory variable. Result are reported crude and adjusted for age, gender, rhinitis and ICS.

61 **Multivariate analyses**

62 The multivariate analyses for the best determinants of test completion and test outcome were
63 performed using multivariate logistic regression with backwards selection, and AIC as the method,

64 for selection the best model. The dependent variables were respectively test completion (yes/no)
65 and test outcome (post-exercise-FEV1 drop $\geq 10\%$, yes/no) both dichotomous categorical variables.
66 Predictor variables included: gender, age, BMI z-score, Caucasian origin, sports activity, rhinitis,
67 eczema, food allergy, SABA monotherapy, any controller, any dispositions, pre-exercise-FEV1(%-
68 predicted) and pre-exercise-FeNO.

69 **ROC analyses**

70 After performing the multivariate analyses, ROC analyses of the best determinants for respectively
71 test completion and test outcomes were conducted. Cut-off values for predicting a completed
72 exercise test and an exercise challenge test with an FEV1-drop $\geq 10\%$, were also investigated.

73 All analyses on the outcome of the exercise challenge, were only performed on the group of
74 children who completed the test.

75 Results of the logistic regression analyses are presented as ORs with 95%-confidence intervals and
76 p-values. General linear models are presented with β -coefficients, 95%-confidence intervals and p-
77 value. A p-value ≤ 0.05 was considered significant. ROC-curve analyses are represented with AUC
78 and 95%-confidence intervals. The best cut-off values are based on Youdens-index, and presented
79 with specificity, sensitivity, negative predictive value and positive predictive value.

80 All statistical analyses were performed using R version 3.5.2 for Windows.

Baseline characteristics	Test completion N=85	Test non-completion N=25	Difference in % or mean (95% CI)	p-value
Sociodemographics				
Gender (male), N (%)	51 (60%)	10 (40%)	20% (-1,8;41,8%)	0,08
Age (years), mean (SD)	12,0 (2,3)	13,0 (2,9)	0,99 (-0,28; 2,26)	0,12
BMI (kg/m ²), mean (SD)	18,2 (3,0)	20,5 (2,3)	2,28 (0,78; 3,77)	0,004
BMI z-score (SD), mean (SD)	-0,003 (0,96)	0,54 (1,18)	0,55(0,02;1,07)	0,04
Caucasian origin, yes, N (%)	60 (70,6%)	14 (56%)	14,6% (-7,1;36,3%)	0,17
Sports active, yes, N (%)	70 (88,6%)	12 (60%)	28,6% (6,0;51,2%)	0,002
Comorbidity				
Rhinitis, yes, N (%)	54 (63,5)	18 (72%)	8,5% (-11,9;28,8%)	0,43
Eczema, yes, N (%)	40 (47,1%)	8 (32,0%)	15,1% (-6,1;36,2%)	0,18
Dust mite allergy, yes, N (%)	42 (49,4%)	9 (36,0%)	13,4% (-8,2;35,0%)	0,24
Pet allergy, yes, N (%)	46 (54,1%)	15 (60,0%)	5,9% (-16,0;27,8%)	0,60
Pollen allergy, yes, N (%)	36 (43,9%)	8 (32,0%)	11,9% (-9,3;33,1%)	0,29
Food allergy, yes, N (%)	9 (10,8%)	0 (0,0%)	10,8% (4,2;17,5%)	0,11
Any comorbidities, yes, N (%)	73 (85,9%)	20 (80,0%)	5,9% (-11,5;23,2%)	0,47
Treatment				
SABA monotherapy, yes, N (%)	14 (16,5%)	3 (12,0%)	4,5% (-10,5;19,5%)	0,76
ICS, yes, N (%)	56 (65,9%)	14 (56,0%)	9,9% (-12,0;31,8%)	0,37
ICS + LABA, yes, N (%)	9 (10,6%)	6 (24,0%)	13,4 (-4,6;31,4%)	0,09
LTRA, yes, N (%)	21 (25,0%)	6 (24,0%)	1,0% (-18,1;20,1%)	0,92
Nasal steroids, yes, N (%)	51 (61,4%)	18 (72,0%)	10,6% (-9,9;31,0%)	0,34
Antihistamine, yes, N (%)	51 (62,2%)	14 (56,0%)	6,2% (-15,9;28,3%)	0,58
Any controller, yes, N(%)	65 (76,5%)	21 (84,0%)	7,5% (-9,4;24,5%)	0,58
Predispositions				
Asthma, yes, N (%)	31 (39,2%)	12 (54,5%)	15,3% (-8,1;38,7%)	0,20
Allergy, yes, N (%)	46 (58,2%)	14 (63,6%)	5,4% (-17,4;28,3%)	0,65
Eczema, yes, N (%)	12 (15,2%)	7 (31,8%)	16,6% (-4,4;37,6%)	0,08
Any predispositions, yes, N (%)	58 (73,4%)	17 (77,3%)	3,9% (-16,2;23,9%)	0,71
Pre-exercise characteristics				
Pre-exercise FEV1 (L), mean (SD)	2,6 (0,78)	2,8 (0,77)	0,26 (-1,00; 0,61)	0,15
Pre-exercise FEV1 (%-predicted), mean (SD)	89,6 (12,14)	90,2 (8,86)	0,57 (-3,86;5,00)	0,80
Pre-exercise FeNO (ppb), mean (SD)	18,6 (2,14)	13,8 (2,40)	1,34 (-0,91;1,99)	0,14
Exercise test characteristic				
Minutes on treadmill (min), mean (SD)	5,8 (1,44)	2,3 (1,35)	3,04 (2,41; 3,67)	<0,001
Maximum heart rate (beats/min), mean (SD)	188,5 (9,67)	181,0 (17,27)	7,52 (-0,57;15,62)	0,07
Max drop in FEV1 from baseline (L), mean (SD)	0,20 (0,21)	0,17 (0,20)	0,04(-0,13;0,06)	0,45
Max drop in FEV1 from baseline (%), mean (SD)	8,20 (8,63)	5,4 (6,32)	2,9 (-0,3;6,0%)	0,08
Significant drop in FEV1 from baseline (≥10%), N (%)	30 (35,3%)	4 (16,0%)	19,3% (-1,7;36,9%)	0,09
Reversibility (L), mean (SD)	0,11 (0,15)	0,06 (0,18)	0,05 (-0,04;0,13)	0,25
Reversibility (%), mean (SD)	0,05 (0,06)	0,03 (0,07)	0,01 (-0,02; 0,05)	0,32
Significant Reversibility (post-β2-FEV1-increase ≥ 12%), N (%)	10 (12,7%)	2 (8,7%)	4,0% (-9,7;17,6%%)	1
Significant saturation-drop (>10% in > 2min), N (%)	13 (15,9%)	7 (31,8%)	15,9% (-5,0;37,0%)	0,9

Asthma symptoms, yes, N (%)	40 (47,6%)	15 (60,0%)	12,4% (-9,6;34,3%)	0,28
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83 *SD, standard deviation; CI, confidence interval; MD, missing data; BMI, Body Mass Index; Any comorbidities, rhinitis,*
84 *eczema, food-allergy; SABA, Short acting β 2-agonist; LABA, Long acting β 2-agonist; ICS, Inhaled corticosteroids;*
85 *LTRA, Leukotriene receptor antagonist; Any controller, LABA, ICS, ICS+LABA,LTRA; FEV1. Forced expiratory*
86 *volume in 1 s; FeNO, Fraction of exhaled nitric oxide; ppb, parts per billion. Pearsons chi-square-test are performed*
87 *for categorial variables, Students t-test are performed for numerical variables.*

No of completed exercise tests, N=85	Maximum FEV1-drop ñ10%, N=30	Maximum FEV1-drop <10%, N=55	Difference in % or mean (95% CI)	p-value
Sociodemographic				
Gender (male), N(%)	13 (43,3%)	38 (69,1%)	25,8% (4,2;47,3%)	0,02
Age (years), mean (SD)	12,0 (2,32)	12,0 (2,26)	0 (-1,1;1,0)	1
BMI (kg/m ²), mean (SD)	18,3 (2,52)	18,2 (3,17)	0,06 (-1,3;1,2)	0,92
BMI z-score (SD), mean (SD)	0,02 (0,98)	-0,02 (0,96)	0 (-0,49;0,40)	0,84
Caucasian origin, yes, N(%)	19 (63,3%)	41 (74,5%)	11,2% (-9,5;31,9%)	0,28
Sports active, yes, N (%)	22 (75,9%)	48 (96,0%)	20,1% (3,6;36,6%)	0,01
Comorbidity				
Rhinitis, yes, N (%)	23 (76,7%)	31 (56,4%)	20,3% (0,3;40,3%)	0,06
Eczema, yes, N (%)	15 (50%)	25 (45,5%)	4,5% (-17,7;26,8%)	0,69
Dust mite allergy, yes, N (%)	15 (50%)	27 (49,1%)	0,9% (-21,3;23,2%)	0,94
Pet allergy, yes, N (%)	18 (60%)	28 (50,9%)	9,1% (-12,9;31,0%)	0,42
Pollen allergy, yes, N (%)	13 (44,8%)	23 (43,4%)	1,4% (-21,1;23,9%)	0,90
Food allergy, yes, N (%)	2 (6,9%)	7 (13,0%)	6,1% (-6,8;18,9%)	0,48
Any comorbidities, yes, N (%)	26 (86,7%)	47 (85,5%)	1,2% (-14,1;16,5%)	1
Treatment				
SABA monotherapy, yes, N (%)	4 (13,3%)	10 (18,2%)	4,9% (-11,0;13,3%)	0,76
ICS, yes, N (%)	20 (66,7%)	36 (65,5%)	1,2% (-19,8;22,2%)	0,91
ICS + LABA, yes, N (%)	3 (10%)	6 (10,9%)	0,9% (-12,6;14,4%)	1
LTRA, yes, N (%)	10 (33,3%)	11 (20,4%)	12,9% (-7,0;33,0%)	0,19
Nasal steroids, yes, N (%)	17 (56,7%)	34 (64,2%)	7,5% (-14,5;29,4%)	0,50
Antihistamine, yes, N (%)	18 (60%)	33 (63,5%)	3,5% (-18,4;25,3%)	0,76
Any controller, yes, N (%)	23 (76,7%)	42 (76,4%)	0,3% (-18,5;19,1%)	0,97
Predispositions				
Asthma, yes, N (%)	10 (35,7%)	21 (41,2%)	5,5% (-16,8;27,8%)	0,63
Allergy, yes, N (%)	16 (57,1%)	30 (58,8%)	1,7% (-21,1;24,4%)	0,88
Eczema, yes, N (%)	5 (17,9%)	7 (13,7%)	4,2% (-12,9;21,2%)	0,62
Any predispositions, yes, N (%)	22 (78,6%)	36 (70,6%)	8,0% (-11,7;27,7%)	0,44
Pre-exercise characteristics				
Pre-exercise FEV1 (L), mean (SD)	2,47 (0,77)	2,60 (0,80)	0,13 (-0,22;0,49)	0,46
Pre-exercise FEV1 (%-predicted), mean (SD)	87,3 (11,82)	91,0 (12,23)	3,7 (-1,78;9,08)	0,18
Pre-exercise FeNO (ppb), mean (SD)	25,1 (2,34)	15,8(2,00)	1,58 (1,10;2,29)	0,01
Exercise test characteristic				
Minutes on treadmill (min), mean (SD)	5,35 (1,46)	6,08 (1,37)	0,73 (0,08;1,38)	0,03
Maximum heart beat (beats/min), mean (SD)	189,3 (11,60)	188,0 (8,53)	1,3 (-3,7;6,2)	0,62
Max drop in FEV1 from baseline (L), mean (SD)	0,42 (0,17)	0,08 (0,10)	0,34 (0,27;0,40)	<0,001
Max drop in FEV1 from baseline (%), mean (SD)	18,0 (0,07)	3,0 (0,04)	15,0 (12,0;17,0)	<0,001
Reversibility (L), mean (SD)	0,08 (0,16)	0,13 (0,15)	0,05 (-0,03;0,12)	0,22
Reversibility (%), mean (SD)	0,04 (0,07)	0,05 (0,06)	0,01 (-0,02;0,05)	0,34
Significant Reversibility (post-β2-FEV1-increase ≥12%), N (%)	4 (13,8%)	6 (12,0%)	1,8% (-17,2;13,7%)	1
Significant SAT-drop (>10% in >2 min), N (%)	6 (21,4%)	7 (13,0%)	8,4% (-9,2;26,1%)	0,32

91 *Inhaled corticosteroids; LTRA, Leukotriene receptor antagonist; Any controller, LABA, ICS, ICS+LABA,LTRA; FEV1.*
92 *Forced expiratory volume in 1 s; FeNO, Fraction of exhaled nitric oxide; ppb, parts per billion.*
93 *Pearsons chi-square-test are performed for categorial variables, Students t-test are performed for numerical variables.*
94

95 **ONLINE FIGURE LEGENDS**

96 ***eFigure 1:*** *Study group flow chart.*

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