Novel Approaches to Asthma Evaluation
: IOS and FENO

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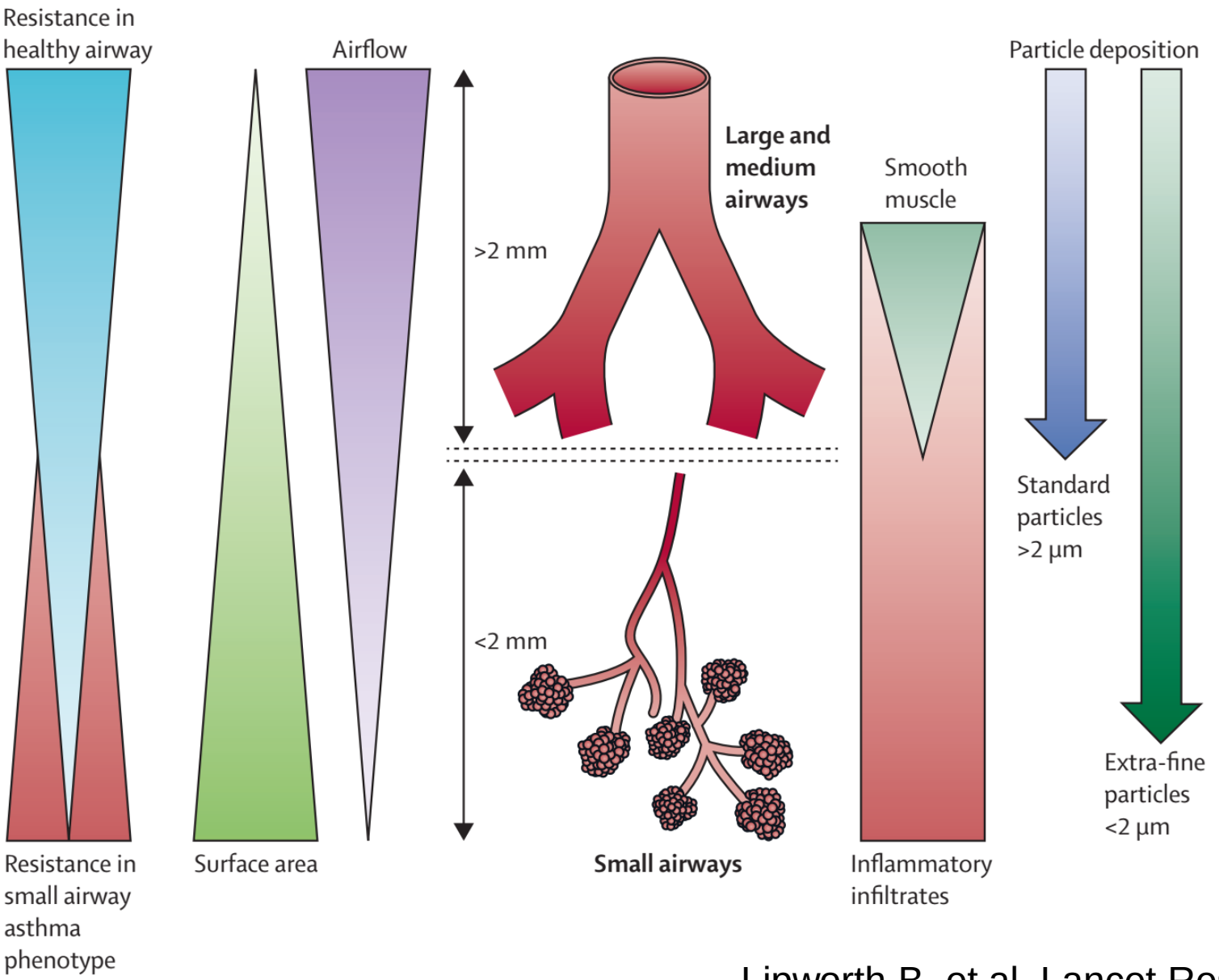
Impulse oscillometry (IOS)

Small airway disease in asthma



Lipworth B, et al. Lancet Respir Med 2014;2(6):497-506.

SAD and clinical outcome of asthma

	Modest SAD	Relevant SAD
Asthma treatment steps GINA 1-2 GINA 3 GINA 4-5	 + + +	 +/- + +++
Duration of disease	-	Longer
Asthma control	-	Worse
Health status	-	Worse
Exacerbation risk (prior and future)	Increases with SAD severity	
Severe exacerbations	-	More frequent

Baraldi F, et al. Arch Bronconeumol 2022;58(6):471-473.

충격진동법 (Impulse Oscillometry System)

- 저주파를 이용해 반사되어 돌아오는 신호를 측정

  → 비침습적으로 기관지의 성질과 저항을 평가

- 5~30Hz의 저주파를 사용

  ✓성인과 같이 기도의 직경이 클 경우 기도의 특성을 제한적으로 반영

  ✓주로 spirometry를 시행하기 어려운 소아에게 적용

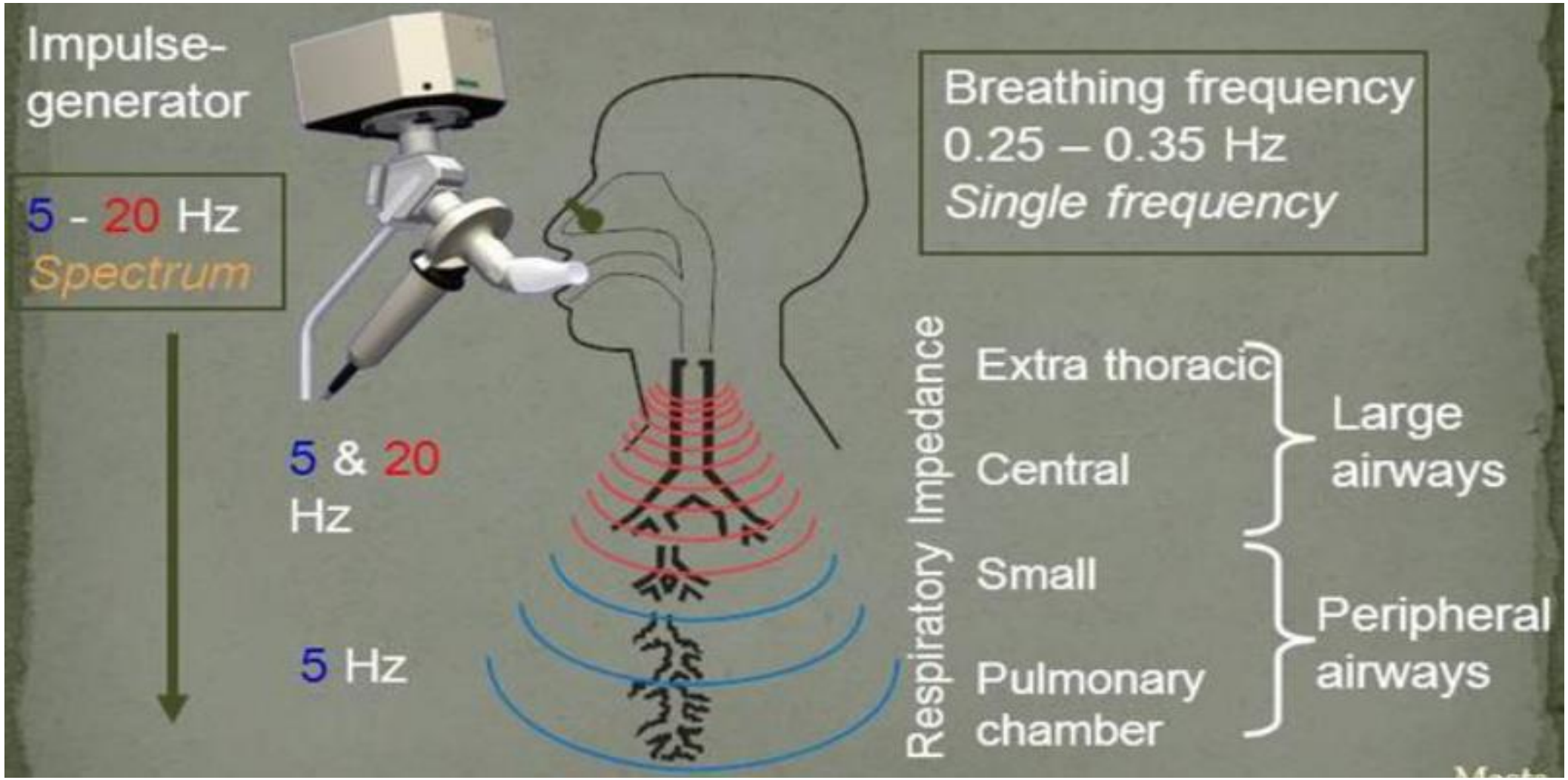
Testing procedure

- Tidal breathing for 30-45 secs
  - ✓ Effortless examination
  - ✓ No breathing maneuver
  - ✓ No box
  - ✓ No foreign- or calibration gases

- Nearly all patients can be examined, independent on age or disease

Impedance measurement according to frequency

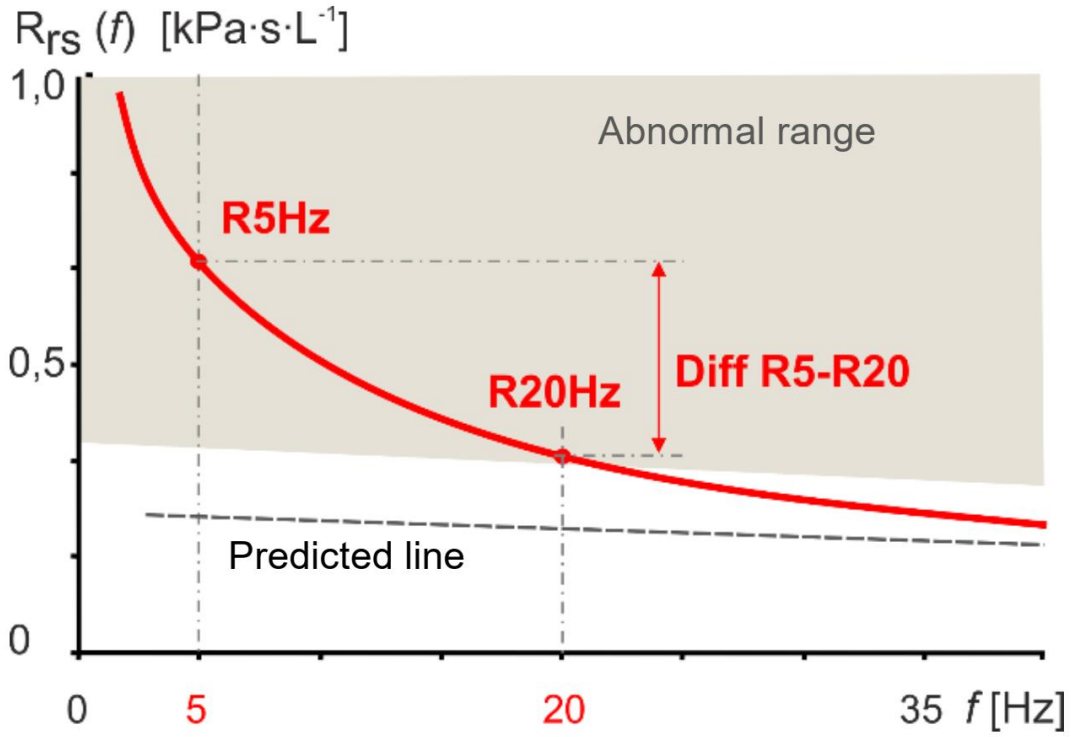
Pulsatile stimulus through the adapter



Pressure waves get into airways with the airflow

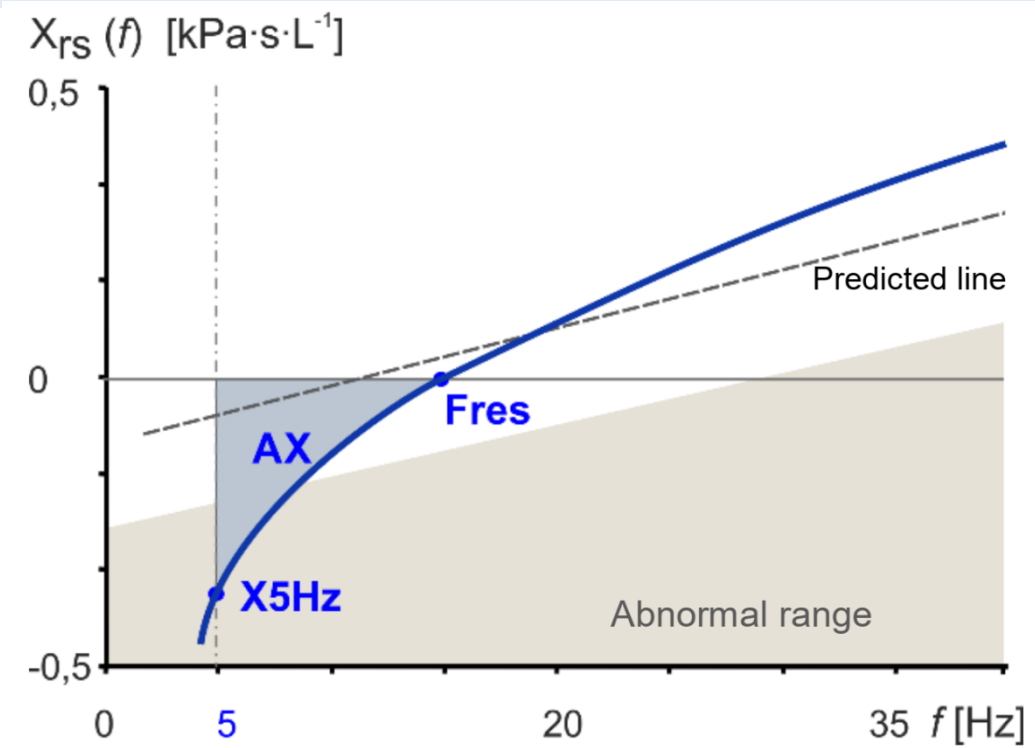
Important parameters

- **R5** (R at 5Hz): Total airway resistance
  - ✓ Extra-thoracic, central and peripheral airways
  - ✓ Abnormal, if >150% predicted
- **R20** (R at 20Hz): Proximal airway resistance
  - ✓ Extrathoracic and first of all central airways
- **R5-R20:** Distal airway resistance
- **X5** (X at 5Hz): Distal capacitive reactance
  - ✓ Elastic and interstitial property of lung
  - ✓ Abnormal, if < X5 predicted-0.15 kPa/L/s
    or X5 predicted-1.53cmH_2O/L/s



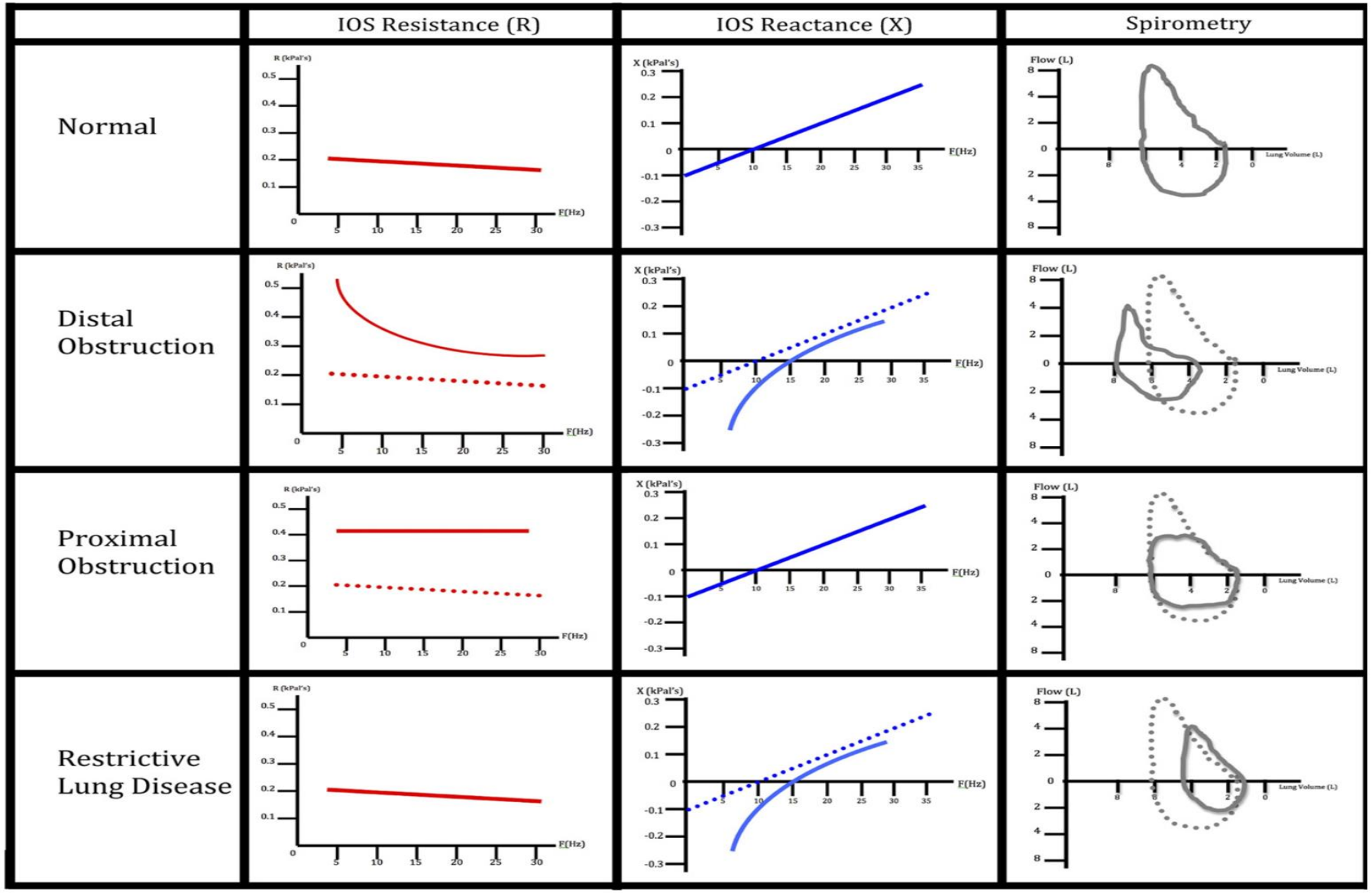
❖1 kPa/L/sec = 10.1971626 cmH_2O/L/sec
≈ 10.2 cmH_2O/L/sec

Measured parameters



- **Resonant frequency (Fres, 공진주파수)**
  - ✓ Frequency at which the strength of capacitance and inertance of the respiratory system is balanced, and the reactance is zero
- **Area of reactance (AX, 리액턴스 지역)**
  - ✓ Total area of capacitance reflecting the elastic properties of the respiratory system being sensitive to peripheral lungs pathology

Patterns of IOS results

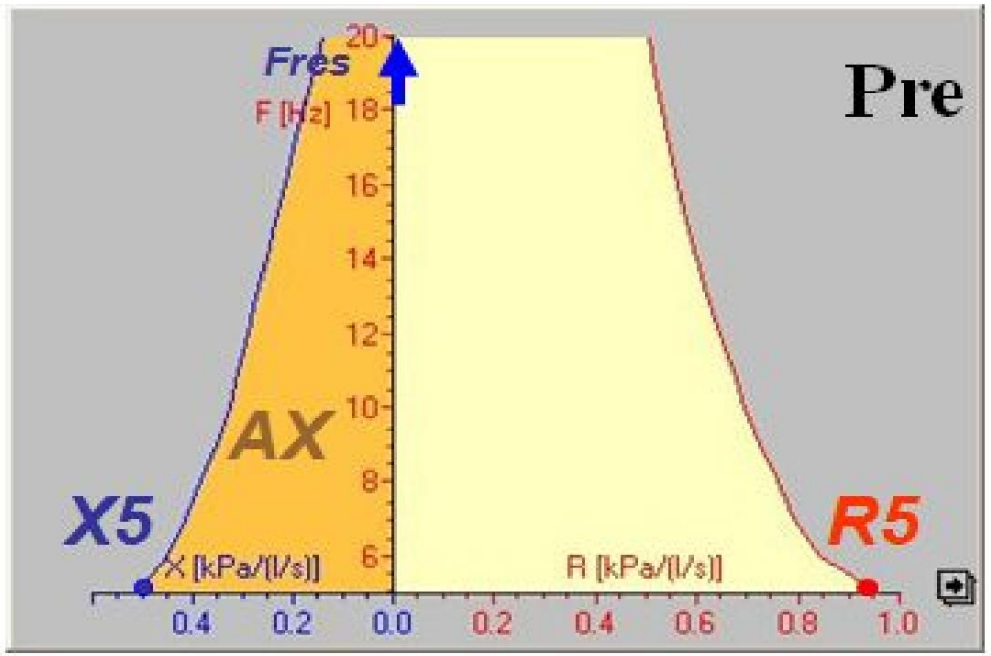


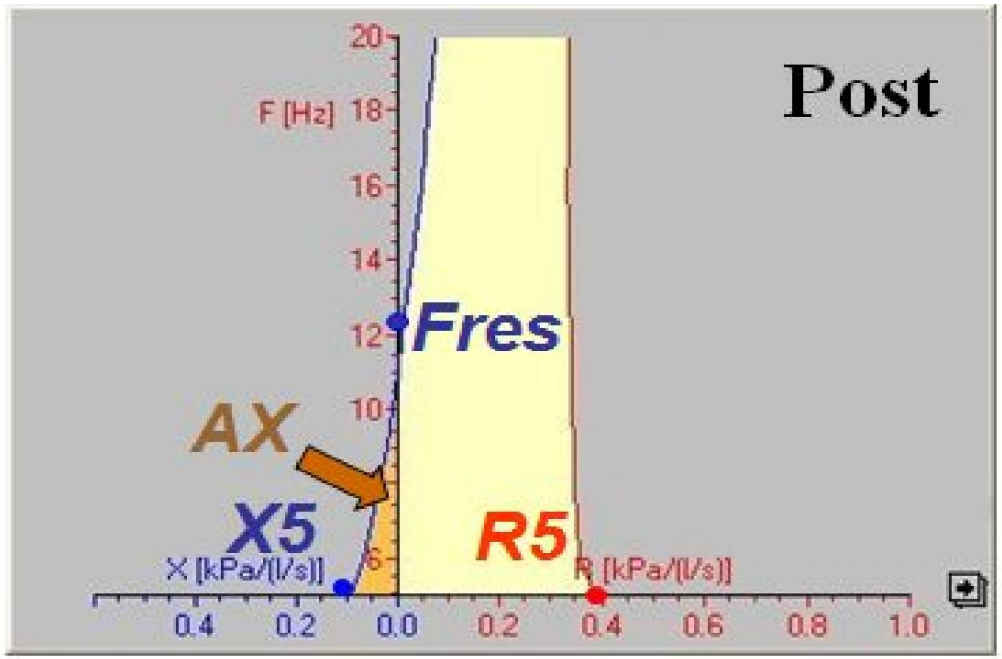
Komarow HD, et al. Ann Allergy Asthma Immunol 2011;106(3):191-9.

Main advantages of IOS

- Requirement of only passive cooperation (natural breathing)
- Fast, easy to perform and reproducible
- Useful especially in children, elderly patients, and patients unable to perform spirometry
- Standardized method
- Allows analysis of respiratory resistance in real time
- Useful in bronchodilator and provocation tests

Criteria for bronchodilator response test





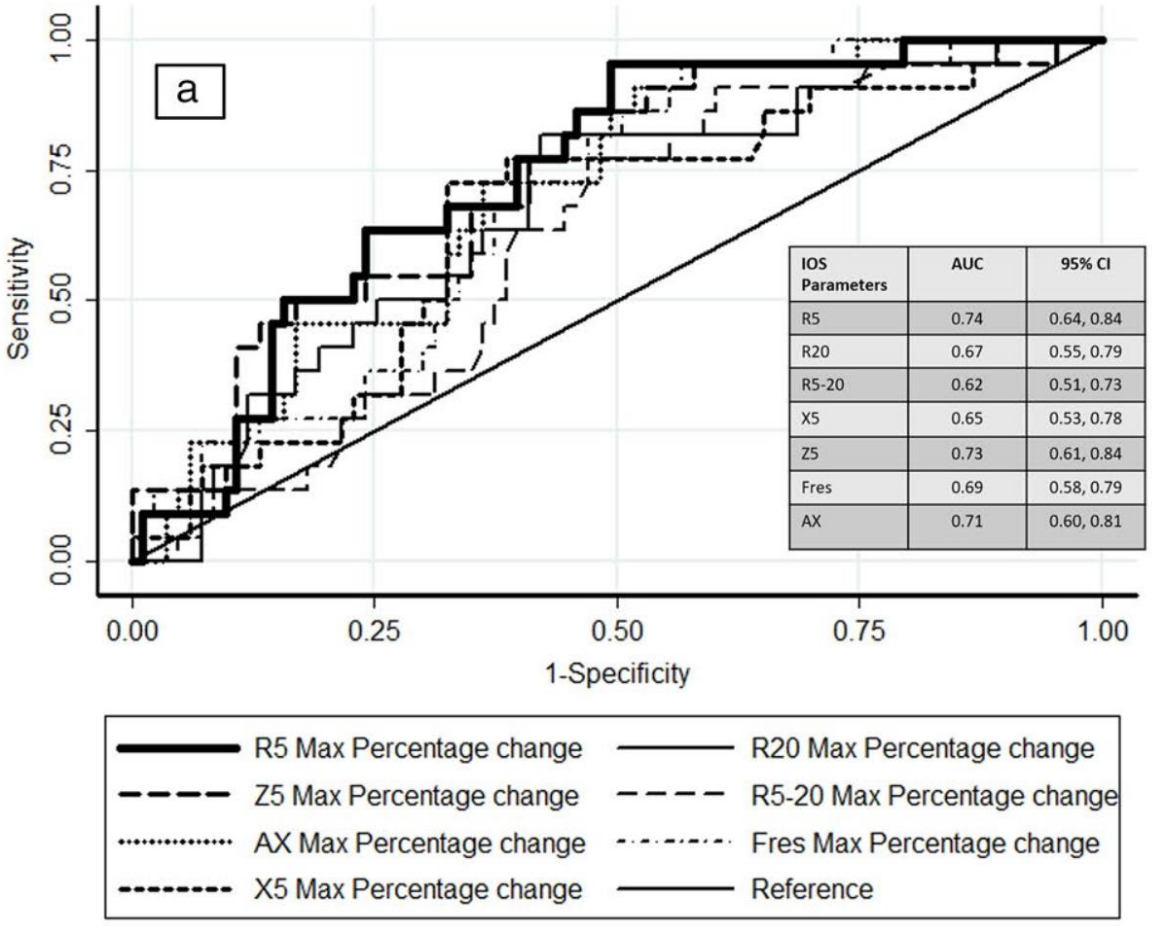
Observation parameter	Significant reversibility
Respiratory resistance, R5	-20% to -25%
Small airway index, Diff R5-R20	-0.04 kPa/L/s or -0.408 cmH_2O/L/s
Resonant frequency, Fres	-20%
Reactance area, AX	-40%

Criteria for provocation test

Observation parameter	Baseline measurement	Determmination value
R5	R5 < 140% predicted	+40% (+50%?)
X5	X5 > X5predicted – 0.15 (kPa/L/s) or X5predicted – 1.53 (cmH_2O/L/s)	-
Fres	-	+35% (+40%?)

IOS as exercise provocation test

- 105 children with asthma, ages 6-15 years
- Pre- and post (10/20/30min)-exercise IOS and spirometry (free running treadmill test)
- Exercise-induced bronchoconstriction: FEV1 decline ≥ 10% within 30 min of exercise



IOS Parameters	AUC	95% CI
R5	0.74	0.64, 0.84
R20	0.67	0.55, 0.79
R5-20	0.62	0.51, 0.73
X5	0.65	0.53, 0.78
Z5	0.73	0.61, 0.84
Fres	0.69	0.58, 0.79
AX	0.71	0.60, 0.81

∆R5 max percentage withing 30 min post-exercise

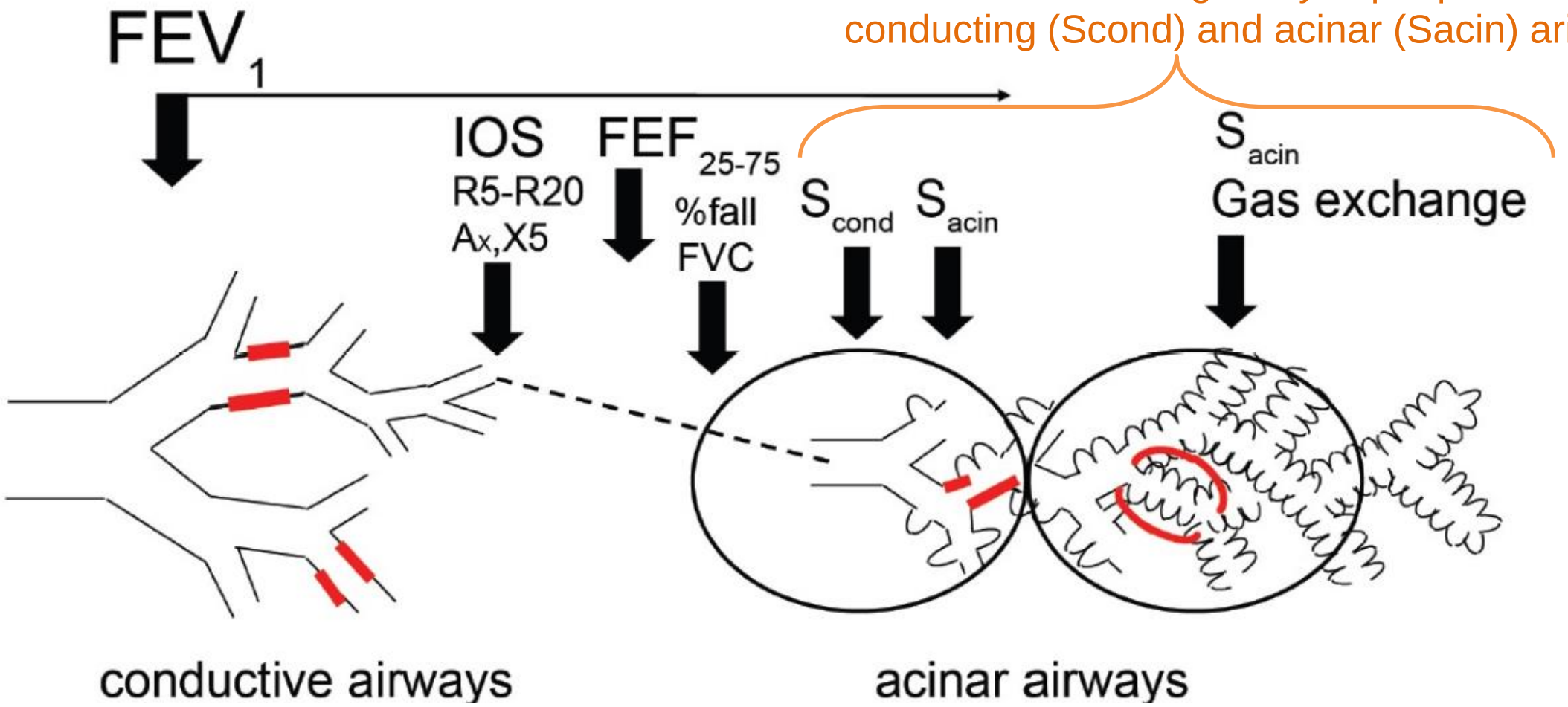
- ✓ AUC 0.74 (95% CI 0.64-0.84)
- ✓ Cutoff value of 14.1% increase: sensitivity 95.5%, specificity 50.6%

Gupta S, et al. J Asthma 2023;60(7):1336-1346.

Physiologic and imaging tests for SAD in ATLANTIS study

- Adults patients with stable asthma, regular treatment vs. healthy control, multinaitional prospective cohort study (ATLANTIS)

Mutiple breath nitrogen washout
→Ventilation heterogeneity in peripheral conducting (Scond) and acinar (Sacin) ariways



CT imaging (airway geometry and densitometry)

Kraft M, et al. Lancet Respir Med 2022;10(7):661-668.

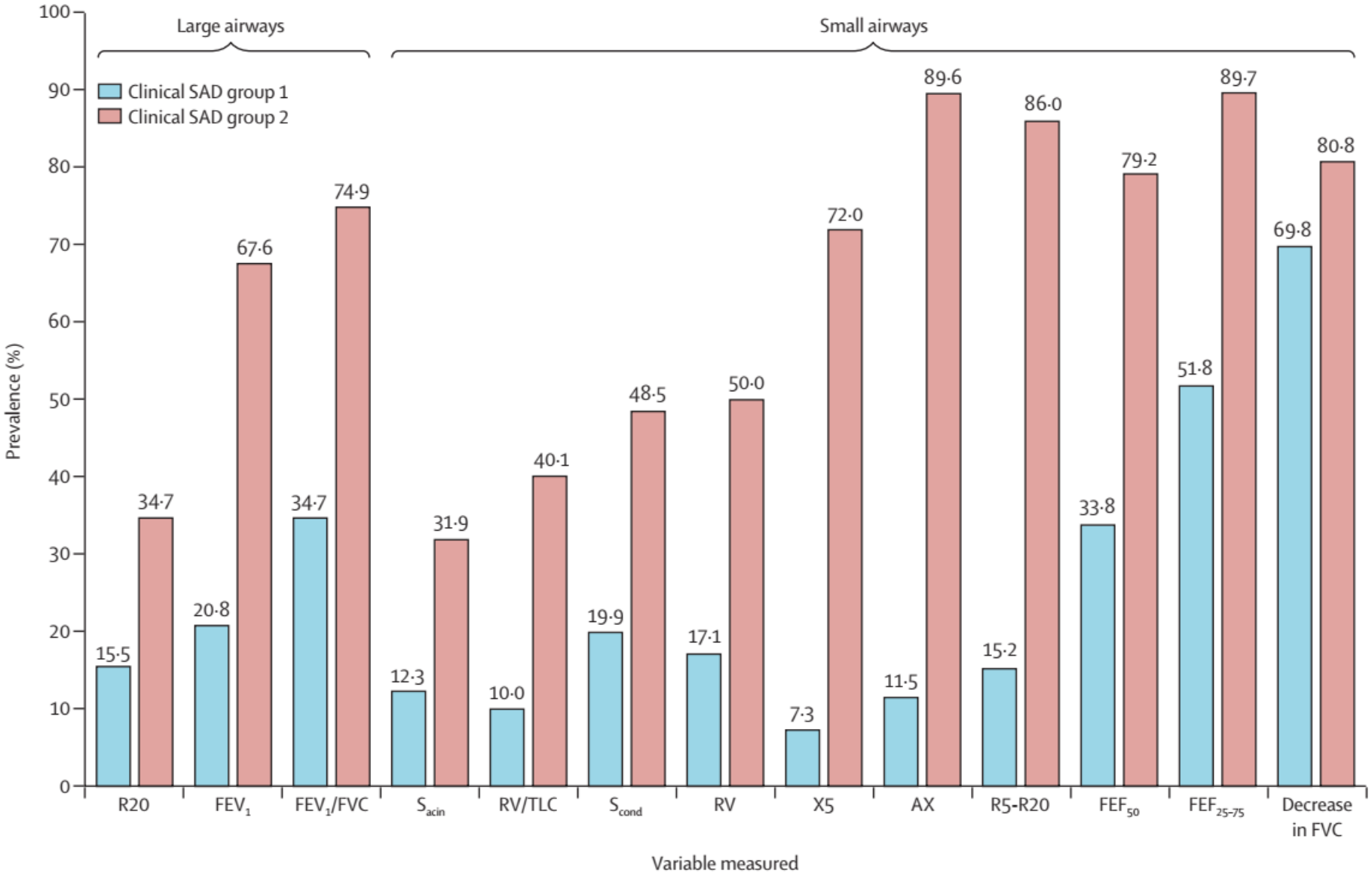
IOS and asthma severity

SAD prevalence according to lung physiology variables

	GINA1 (n=135)	GINA2 (n=85)	GINA3 (n=207)	GINA4 (n=300)	GINA5 (n=46)
Spirometry					
FEF_{25-75}	41%	43%	51%	55%	80%
FEF_{50}	37%	49%	54%	55%	75%
Decrease in FVC	72%	68%	75%	73%	84%
Body plethysmography					
Residual volume/total lung capacity	14%	16%	19%	28%	31%
Functional residual capacity	16%	23%	19%	25%	27%
Impulse oscillometry					
R5–R20	30%	40%	37%	51%	71%
AX	32%	34%	35%	49%	68%
X5	23%	32%	29%	33%	53%
Multiple breath nitrogen washout					
S_{cond}	21%	20%	30%	33%	64%
S_{acin}	12%	18%	19%	21%	41%

Postma DS, et al. Lancet Respir Med 2019;7:402-16.

IOS and other parameters in SAD subgroups



Postma DS, et al. Lancet Respir Med 2019;7:402-16.

Characterization of IOS-defined SAD in asthma

- 400 adult patients with physician-diagnosed asthma
- IOS-defined SAD (R5-R20 > 0.07 kPa/L/s): 62%

Variables	Predictors of SAD	
	aOR (95% CI)	P-value
Age ≥ 50 years	3.08 (1.77-5.49)	<0.0001
Female sex	2.27 (1.29-4.06)	0.0046
Overweight, BMI>25kg/m^2	3.64 (1.99-6.85)	<0.0001
Smoking, former or current	2.05 (1.14-3.70)	0.0006
FENO > 25ppb	2.05 (1.14-3.70)	0.0164
Night awakening due to asthma	3.34 (1.85-6.17)	<0.0001
Exercise-induced asthma symptoms	6.39 (3.65-11.45)	<0.0001

Cottini M, et al. J Allergy Clin Immunol Pract 2020;8:997-1004.

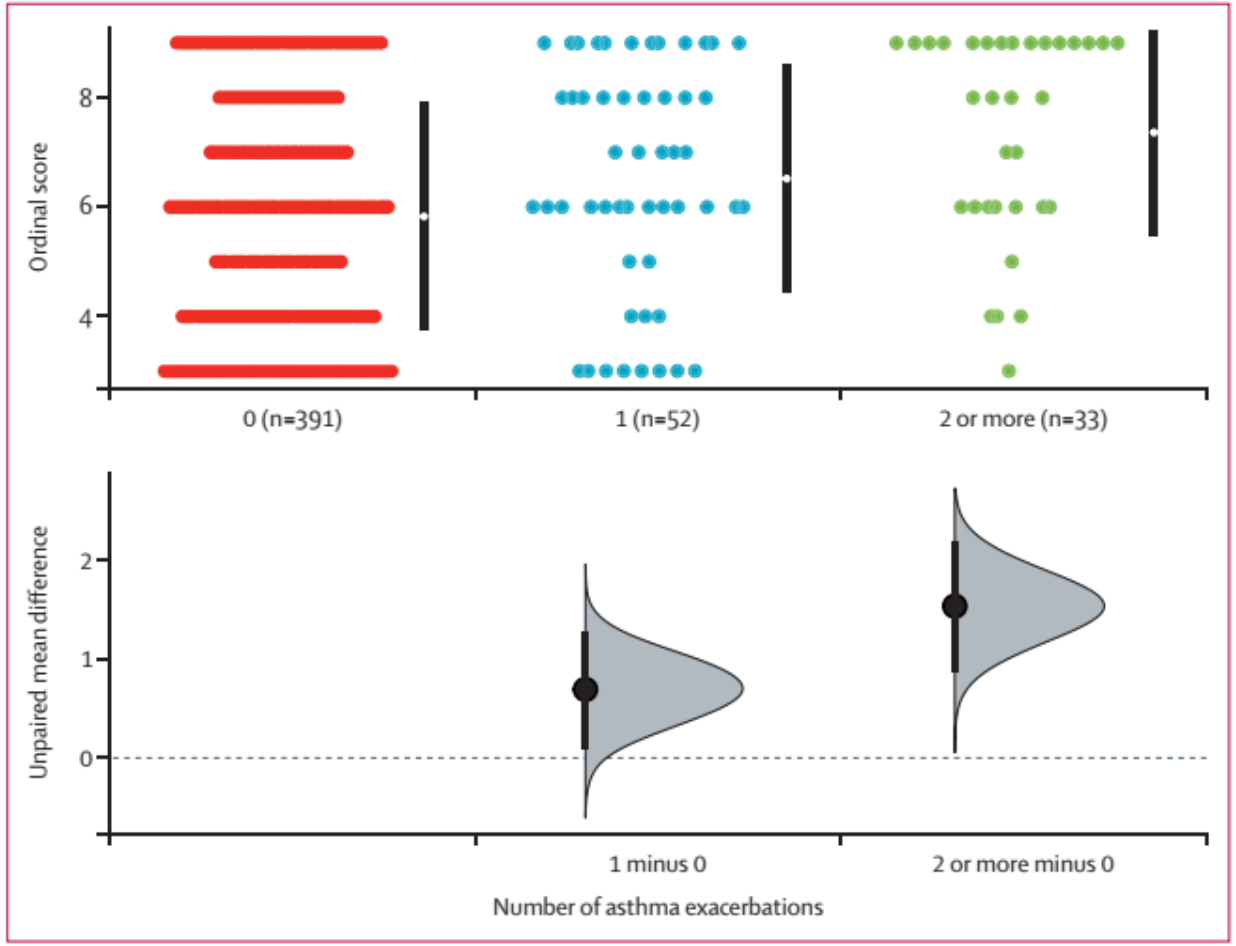
Prediction of asthma control and exacerbation

- 773 stable asthma, median 46 years, 1 year follow-up, ATLANTIS
- **Ordinal score** = AX %predicted + R5-R20 %predicted + X5 %predicted

Exacerbations

Physiology Variables at Baseline	Correlation	P. Value
SCOND	0.25	2.9E-06
AX	0.23	2.8E-07
R5-R20	0.23	4.9E-08
RV/TLC	0.18	1.8E-06
SACIN	0.14	1.0E-02
FVCFALL	0.08	9.5E-02
FRC	0.01	8.6E-01
X5	-0.17	7.3E-05
F2575	-0.20	1.5E-07
F50	-0.21	3.1E-08
FEV1	-0.24	1.2E-10

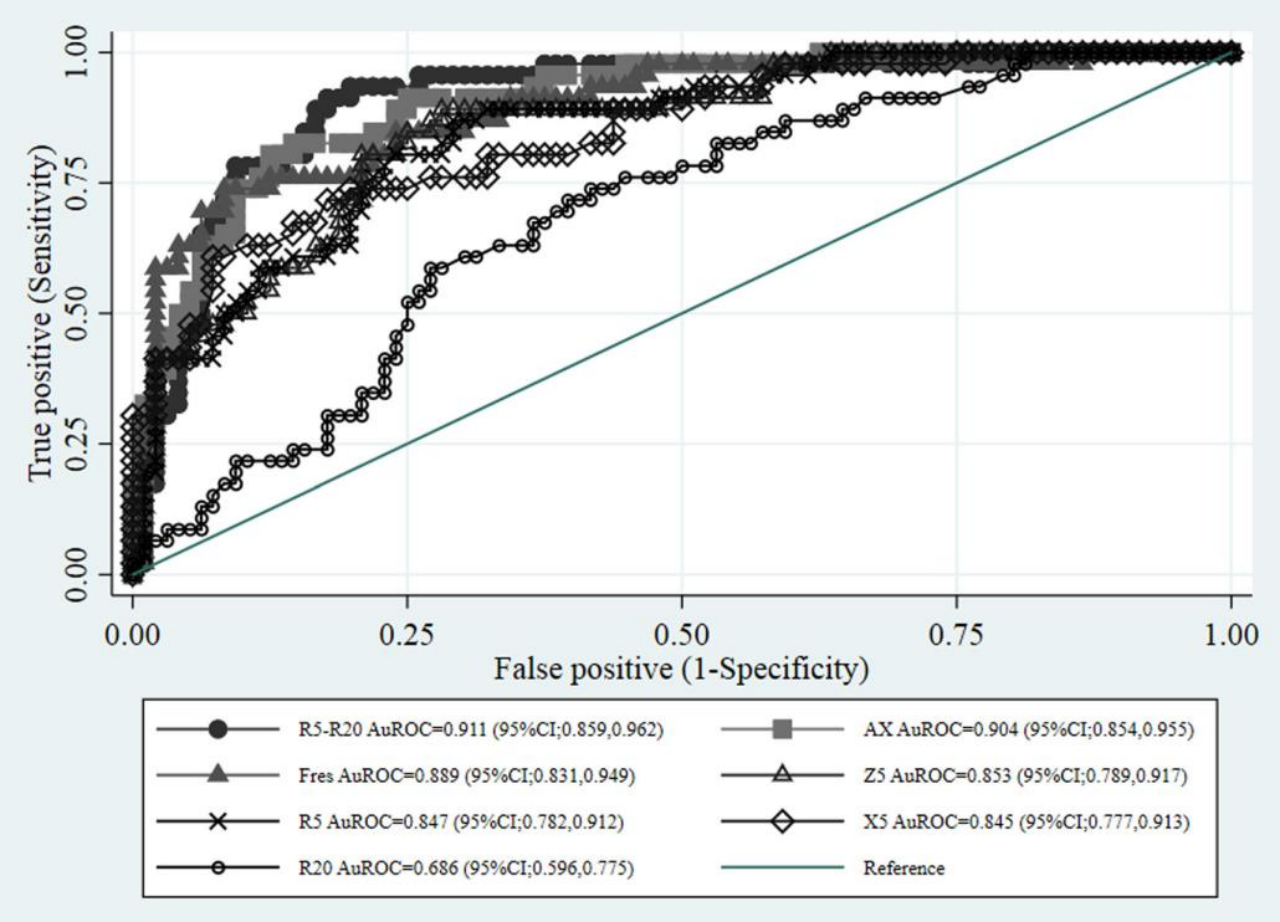
Physiology Variables at Baseline	ACT Visit 3	
	Correlation	P. Value
FEV1	0.23	1.2E-09
F50	0.17	2.3E-05
X5	0.17	1.0E-04
F2575	0.14	2.2E-04
FRC	0.09	1.7E-02
FVCFALL	-0.03	5.5E-01
SACIN	-0.12	3.1E-02
RV/TLC	-0.12	1.9E-03
SCOND	-0.15	4.9E-03
R5-R20	-0.20	1.3E-06
AX	-0.21	2.2E-06



Kraft M, et al. Lancet Respir Med 2022;10(7):661-668.

Prediction of uncontrolled asthma with normal spirometry

- 142 adult asthma with normal spirometry
- Prediction of poorly controlled asthma: ACT score ≤19 with pulmonologists' rating as uncontrolled or partially controlled according to GINA



R5-R20 : AUC = 0.911
AX : AUC = 0.904

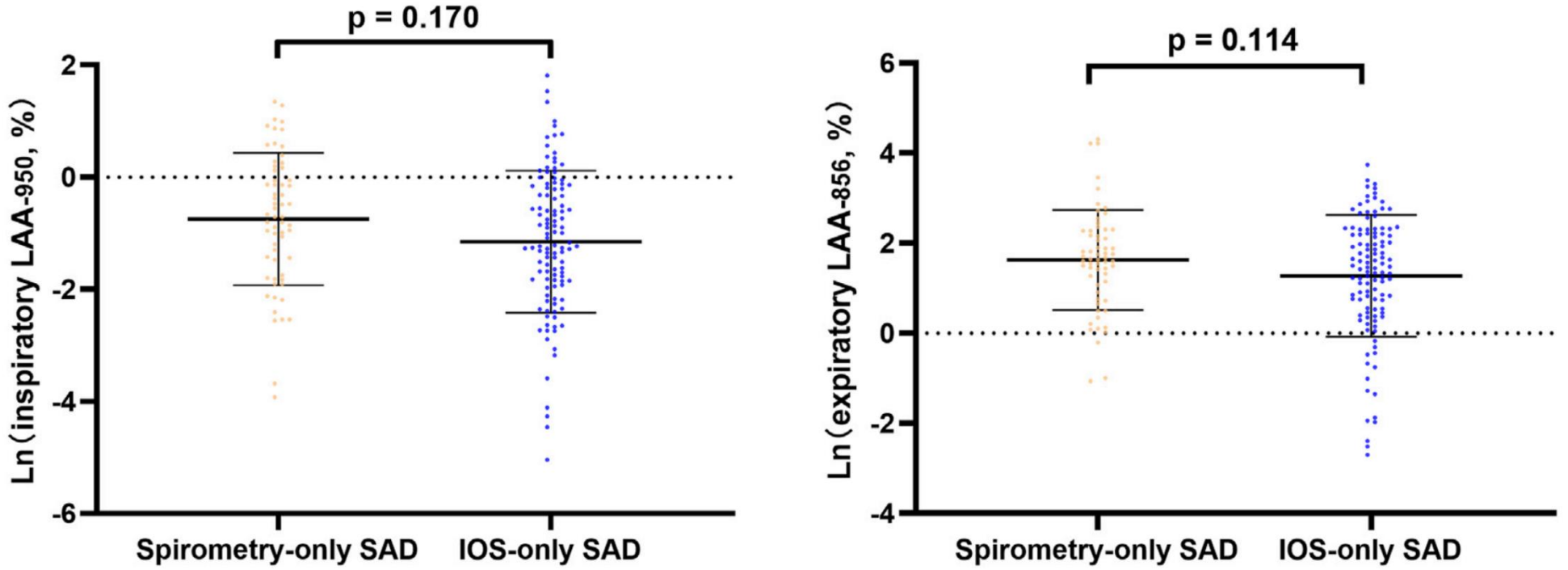
R5-R20 ≥ 1.0 $cmH_2O/L/s$
AUC 0.86;
sensitivity 89.1%, specificity 82.3%

Chaiqond W, et al. J Asthma 2022;59(3):561-571.

Discordant spirometry and IOS assessments

- 1836 patients with COPD, 40-80 years old, from ECOPD cohort, China
- IOS-defined SAD: R5-R20 > upper limit of normal
- Spirometry-defined SAD: 2 of $FEF_{25-75\%}$, $FEF_{50\%}$ and $FEF_{75\%}$ < 65% predicted

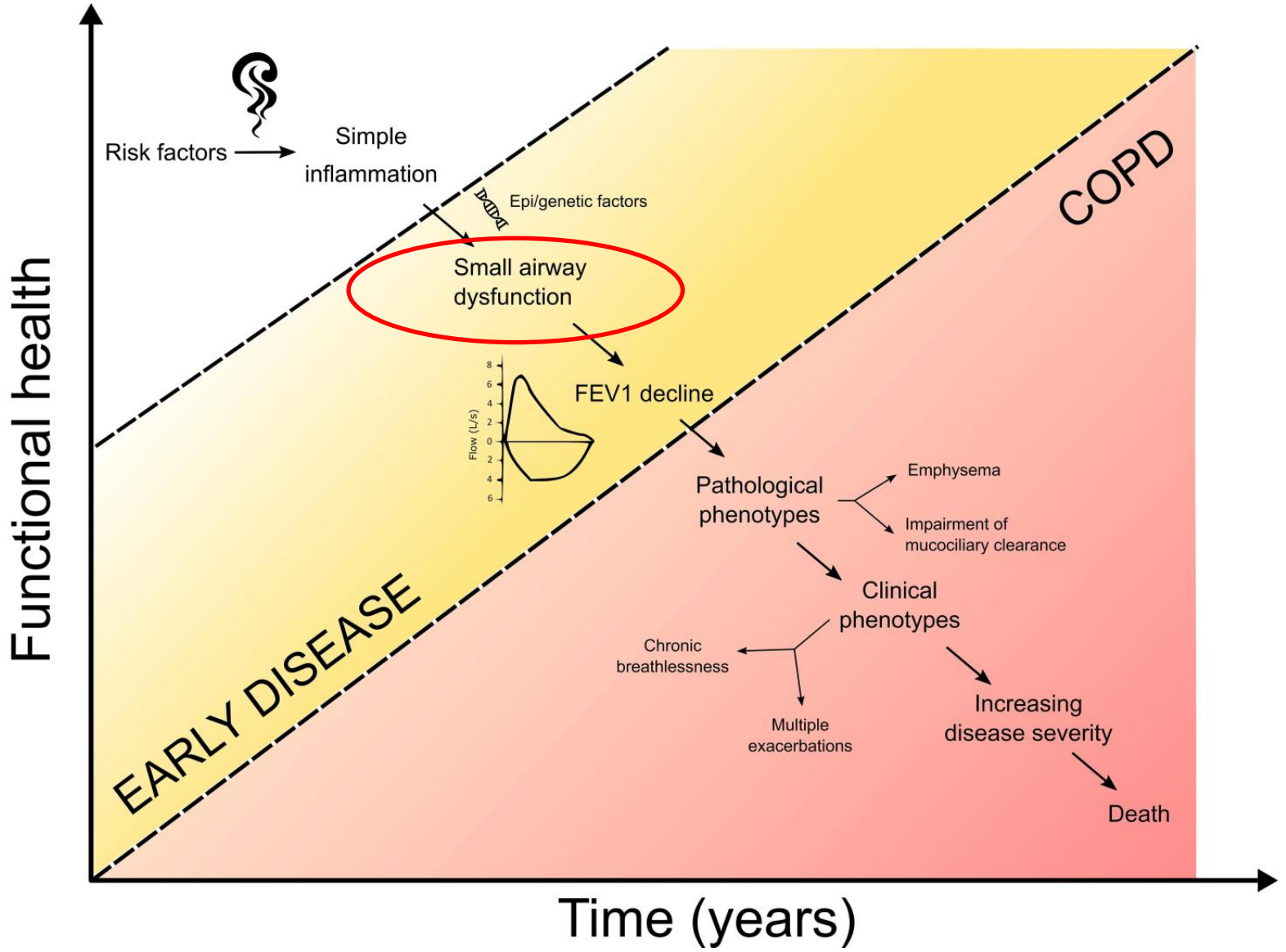
CT-emphysema and gas trapping difference in normal lung function



Spirometry-only SAD vs. IOS-only SAD: 61 vs. 113 patients

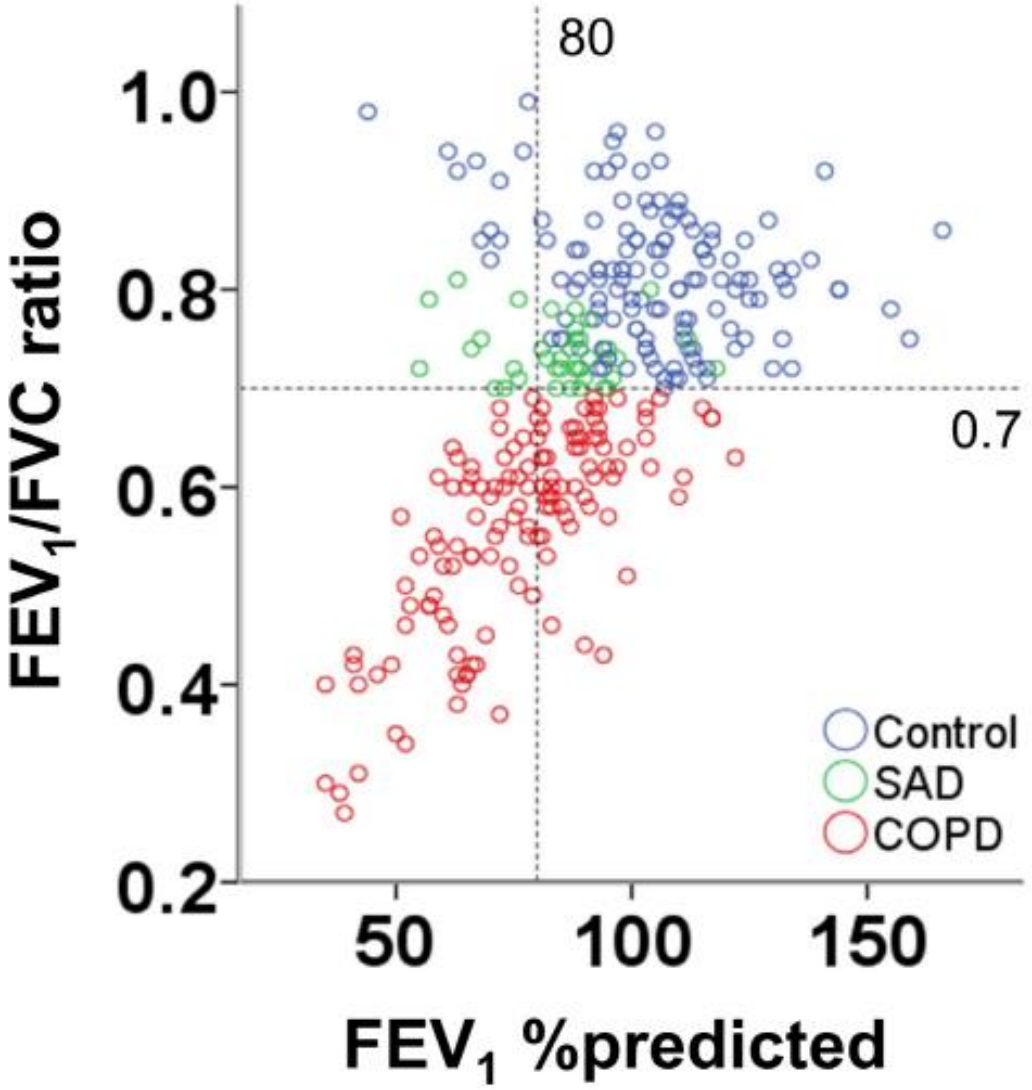
Lu L, et al. Front Physiol 2022;13:892448.

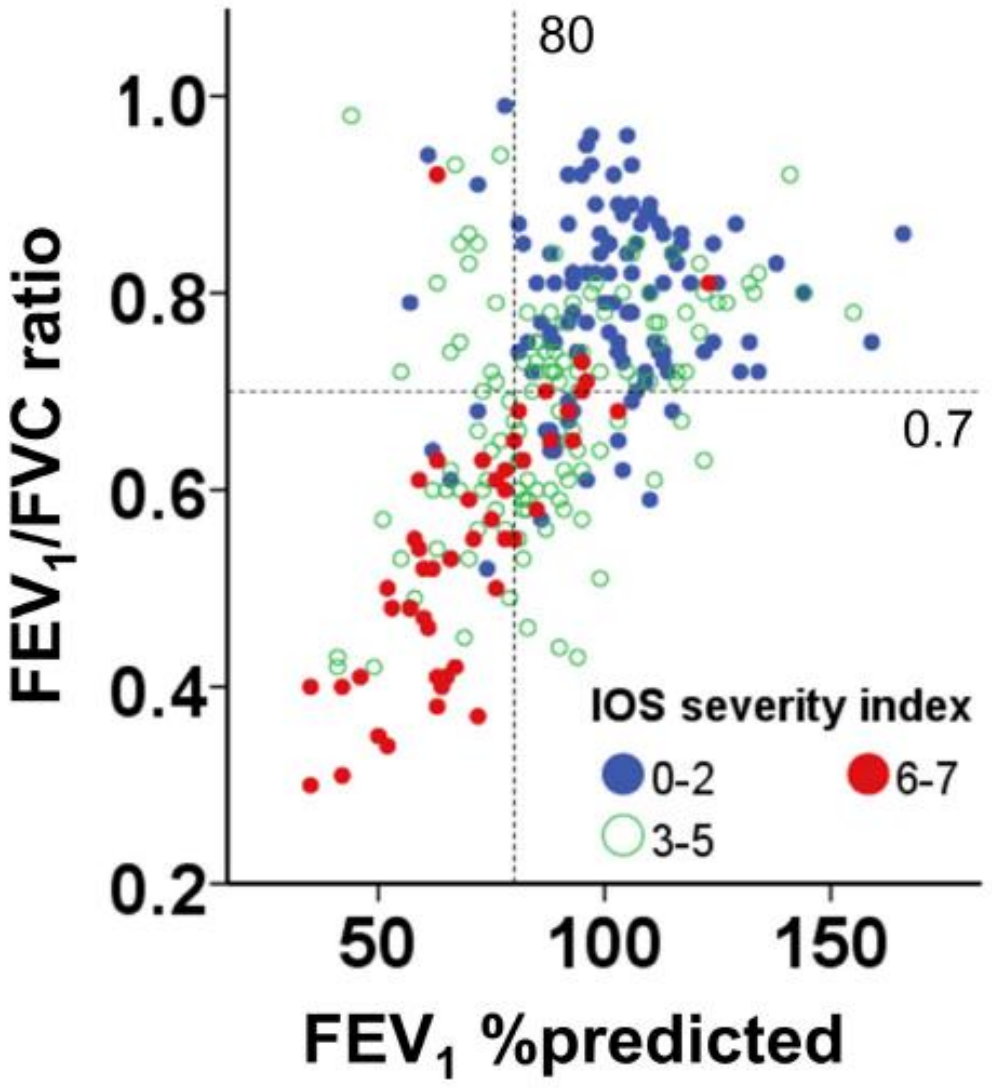
Timeline of disease progression in smokers



Yip KP, et al. Int J Chron Obstruct Pulmon Dis 2021;16:957-968.

Prediction of progression to airflow limitation





(Unpublished)

IOS and FENO in diagnosis of cough variant asthma

- 197 preschool-aged children with chronic cough
- CVA vs. non-CVA group, differentiated by pediatric respiratory specialists

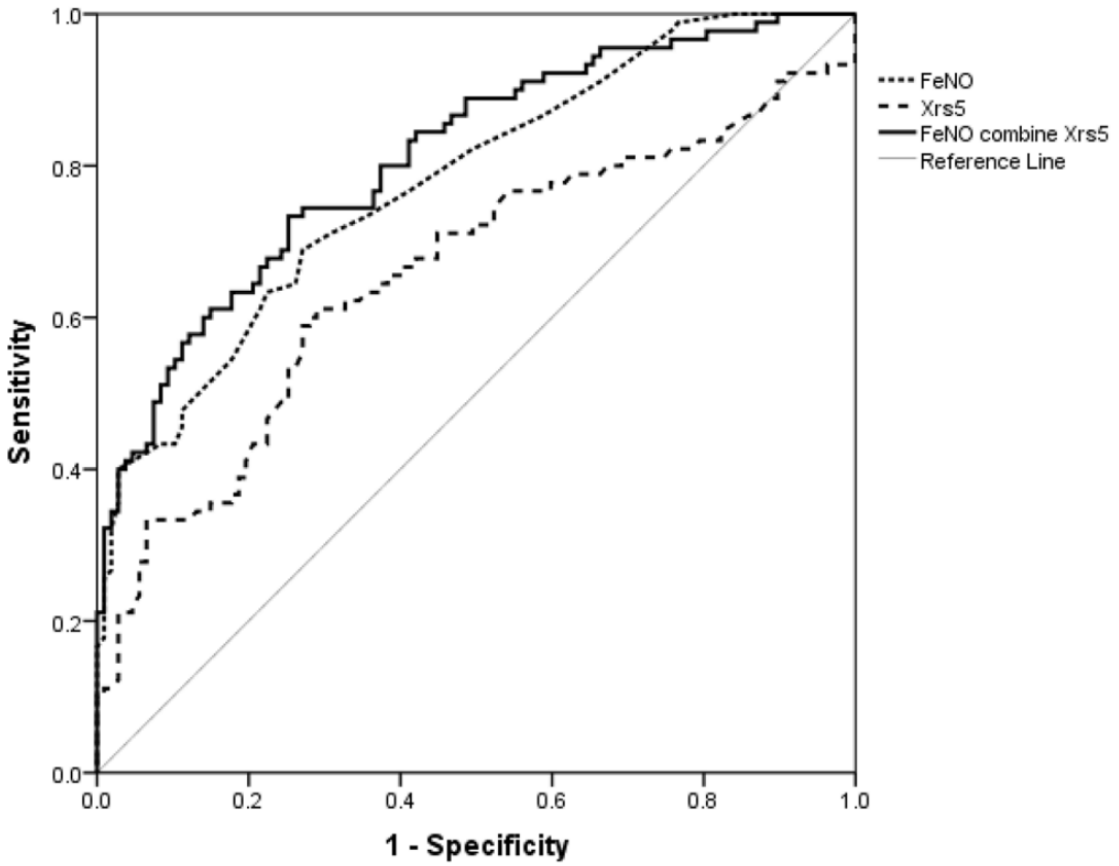


Fig. 2 Comparison of the AUCs of X5 alone, FeNO alone and FeNO plus X5

Table 3 AUCs of IOS indices alone, FeNO alone and FeNO + X5

Variables	AUC
FeNO	0.779
X5	0.657
FeNO + X5	0.809

Table 4 Comparison of the AUC of X5 alone, FeNO alone and FeNO + X5

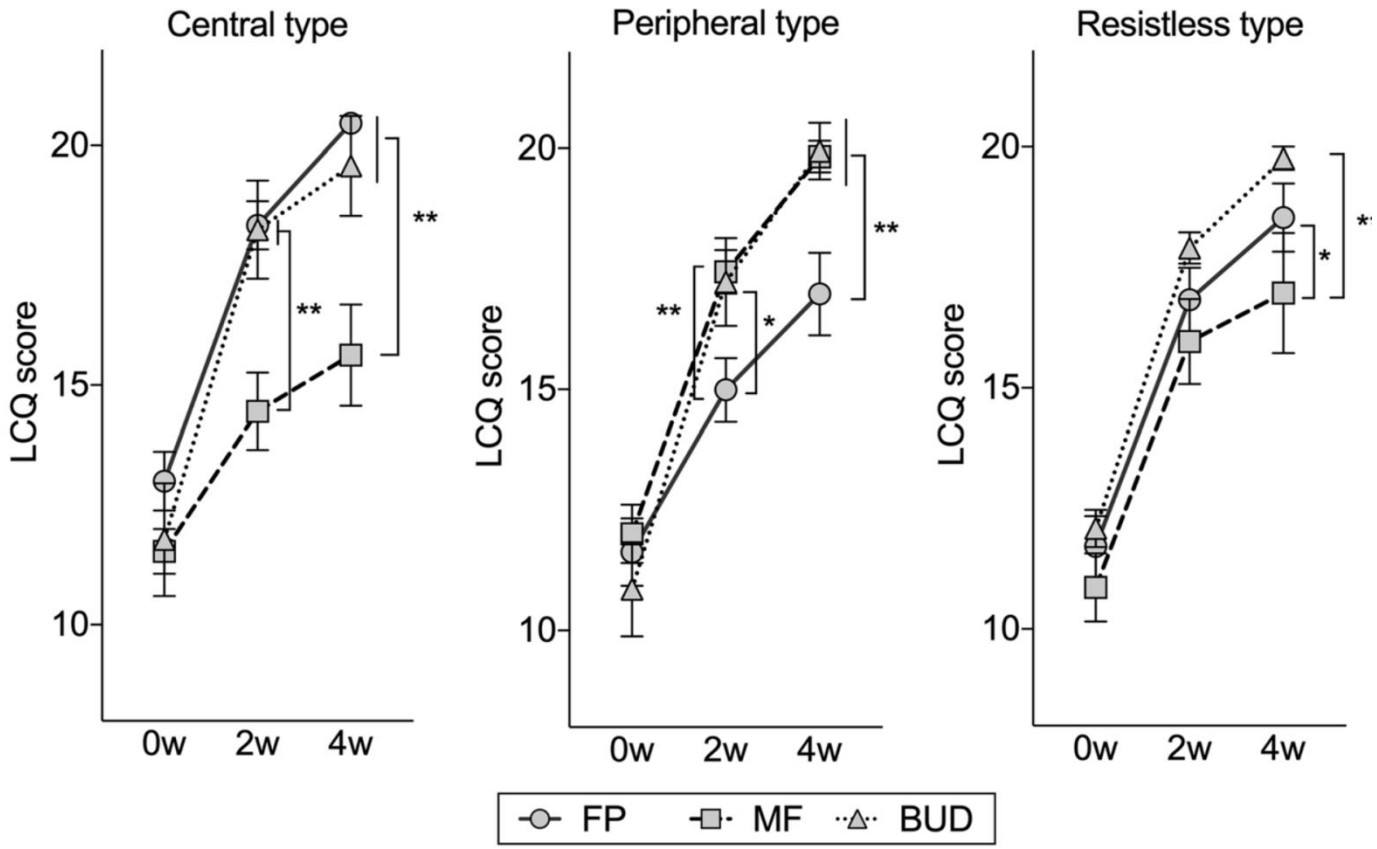
	Cut-off value(s)	Sensitivity	Specificity	Youden index
X5 [cmH_2O/(l/s)]	− 3.30	0.611	0.710	0.321
FeNO (ppb)	19.50	0.689	0.729	0.418
X5 [cmH_2O/(l/s)] + FeNO (ppb)	− 4.15, 18.00	0.733	0.748	0.481

Hu Y, et al. Allergy Asthma Clin Immunol 2023;19(1):83.

Prediction of ICS response on cough variant asthma

- 127 patients with cough variant asthma
- Randomly prescribed ICS: coarse-particle (fluticasone propionate), fine-particle (mometasone furoate), moderate-particle (budesonide)

Relationship between IOS subtype classification and ICS particle size in terms of therapeutic efficiency



◆ Subtyping based on IOS measurement
- ✓ Central: R20 ≥100% and R5-R20 <100%
- ✓ Peripheral: R20 <100% and R5-R20 ≥100%
- ✓ Resistless: R20 <100% and R5-R20 <100%

Sugawara H, et al. Respir Res 2019;20(1):41.

Minimal clinically important difference of IOS measures

- Adult patients with mild-to-severe asthma, 1 year follow-up, ALLIANCE cohort
- Distribution-based method to statistically determine the MCID

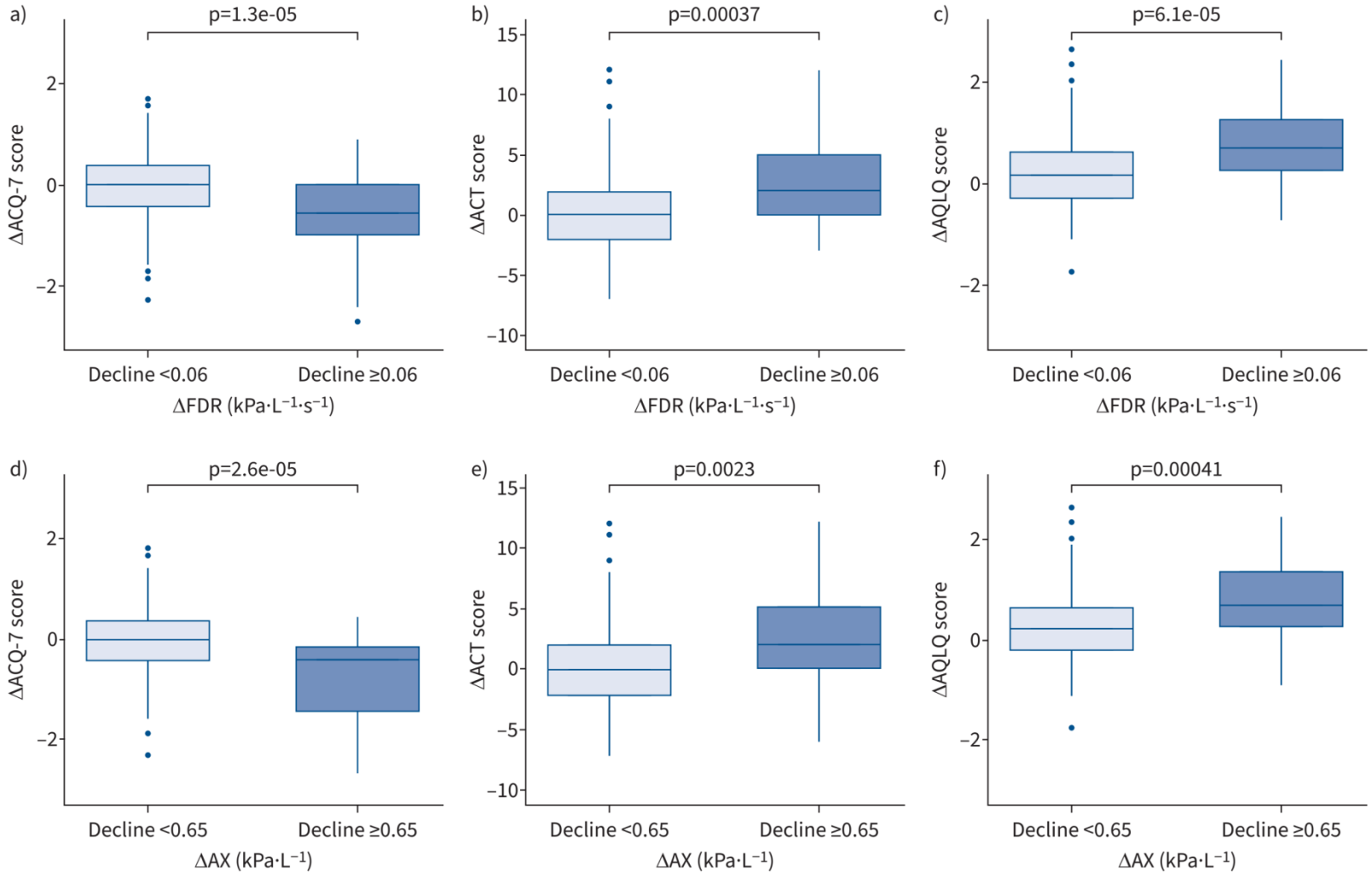
TABLE 2 Change in patient-reported outcome measures according to the effect size of impulse oscillometry

	Relative size							p-value
	Large improvement	Moderate improvement	Small improvement	No change	Small worsening	Moderate worsening	Large worsening	
Effect size of FDR								
Patients	22	16	45	74	42	17	19	
ΔFDR (kPa·L^{-1}·s^{-1})	−0.19±0.12	−0.08±0.01[#]	−0.04±0.02[#,¶]	0±0.01[#,¶]	0.04±0.01[#,¶]	0.08±0.01[#,¶]	0.17±0.07[#,¶]	<0.001
ΔACT score	3.82±4.27	1.5±2.83	0.61±3.29[#]	0.45±3.24[#]	0.63 3.67[#]	0.29±0.84[#]	0.2±0.7[#]	<0.01
ΔACQ-7 score	−1.1±0.93	−0.25±0.72[#]	−0.17±0.75[#]	−0.07±0.7[#]	−0.1±0.68[#]	0.08±1.03[#]	0.06±0.56[#]	<0.001
ΔAQLQ score	1.11±0.79	0.41±0.51	0.22±0.7[#]	0.17±0.64[#]	0.36±0.76[#]	0.29±0.84[#]	0.2±0.76[#]	<0.001
Effect size of AX								
Patients	21	12	27	114	28	12	17	
ΔAX (kPa·L^{-1})	−3.0±1.20	−1.05±0.14[#]	−0.52±0.16[#]	−0.03±0.14[#,¶]	0.54±0.14[#,¶]	1.03±0.16[#,¶]	2.13±0.93[#,¶]	<0.001
ΔACT score	4.0±4.2	0.34±2.0	1.3±4.0	0.53±3.18[#]	0.0±3.95[#]	2.91±3.7	−0.71±3.1[#]	<0.01
ΔACQ-7 score	−1.12±0.9	−0.41±0.59	−0.32±0.80[#]	−0.11±0.69[#]	0.05±0.83[#]	−0.03±0.8[#]	0.22±0.66[#]	<0.001
ΔAQLQ score	1.11±0.72	0.3±0.81	0.26±0.70[#]	0.22±0.63[#]	0.39±0.92[#]	0.47±0.93	0.08±0.63[#]	<0.001

Abdo M, et al. Eur Repir J 2023;61(5):2201793.

Validation of MCID

- Validation the proposed MCID according to patient-reported outcome measures



ΔR5-R20, 0.06 kPa/L/s

ΔAX, 0.65 kPa/L

Abdo M, et al. Eur Repir J 2023;61(5):2201793.

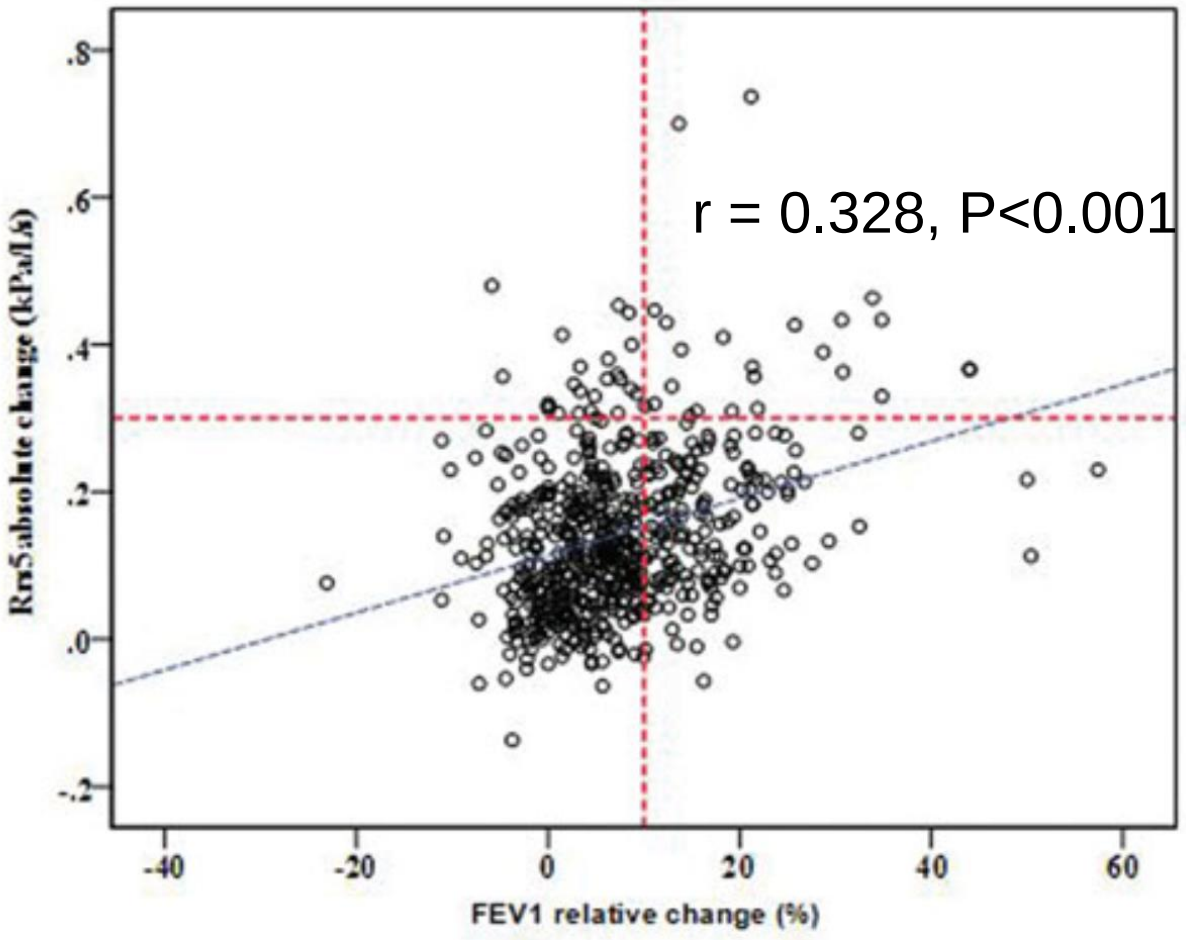
Predictive equation in different adult population

Study, Population, Participants (n)	Age	R5	R20	X5
Shiota et al. [22], Japanese, n = 299	20–83 years	−3.841167*LogH+8.67158	−2.546561*LogH+5.841867	−0.000097*A+1.018597*logH-2.343672
Newbury et al. [23], Australian, n = 100	25–74 years	Males: 1.1672–0.0017*A+0.0043*W-0.007*H Females: 0.768+0.00064*A-0.00276*H	Males: 0.9216–0.0013*A+0.0027*W-0.0049*H Females: 0.4821+0.00034*A-0.00125*H	Males: −0.3593+0.00013*A+0.0016*H Females: −0.4689–0.00092*A+0.00245*H
Ostveen et al. [24], Caucasian, n = 386	18–80 years	Males: 5.327–3.032*H-0.00381*A+0.01390*W Females: 2.591–1.461*H+0.00279*A+0.01221*W	Males: 3.540–1.824*H-0.00330*A+0.00888*W Females: 2.482–1.122*H+0.00135*A+0.00695*W	Males: 2.683–0.703*H++0.00190*W Females: 2.373–0.607*H+0.00150*A+0.00312*W
Schulz et al. [25], (equations for median) Caucasian, n = 387	45–91 years	Males: 0.9861137–0.0001490*A-0.0001223*H+0.0029891*W Females: 0.7887960+0.0015118*A-0.0046594*H+0.0029768*W	Males: 0.7722257–0.0006446*A-0.0037120*H+0.0029891*W Females: 0.4505645+0.0001251*A-0.0020488*H+0.0017939*W	Males: −0.4670275–0.0003344*A+0.0027755*H-0.00010424*W Females: −0.3313017–0.0007541*A+0.0022090*H-0.0014132*W

Bednarek M, et al. Respir Med 2020;170:105952.

Low concordance between spirometric and osciilometric BDRs

- 592 children with asthma or suspected asthma
- Oscillometric BDR: relative or absolute changes of R5 or X5 ≥ 2 standard deviations
  vs. spirometric BDR: absolute change of FEV_1 ≥ 12%



Correlation between relative changes in FEV1 and absolute changes in Rrs5 before and after administration of a bronchodilator

- ✓ Positive for spirometric BDR only: 17.6%
- ✓ Positive for oscillometric BDR only: 8.5%
- ✓ Positive for both BDRs: 8.3%
- ✓ Negative for both BDRs: 65.6%

Sheen YH, et al. J Asthma 2018;55(12):1343-1351.

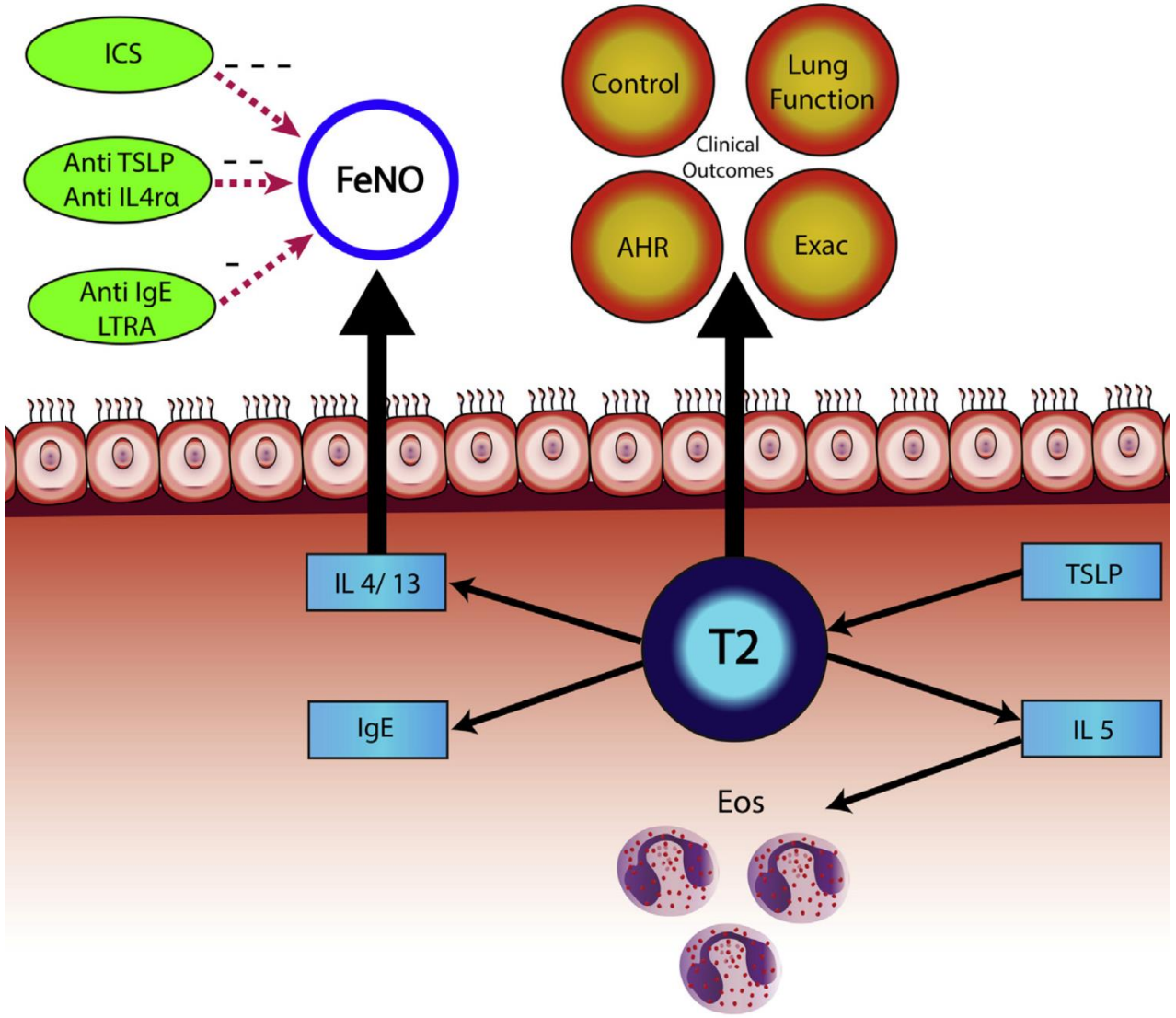
Fractional exhaled nitric oxide (FENO)

FENO in asthma

- **Nitric oxide (NO)**
  - ✓ Gas normally found in exhaled breath
  - ✓ Produced at low levels in the upper and lower airways by NO synthases

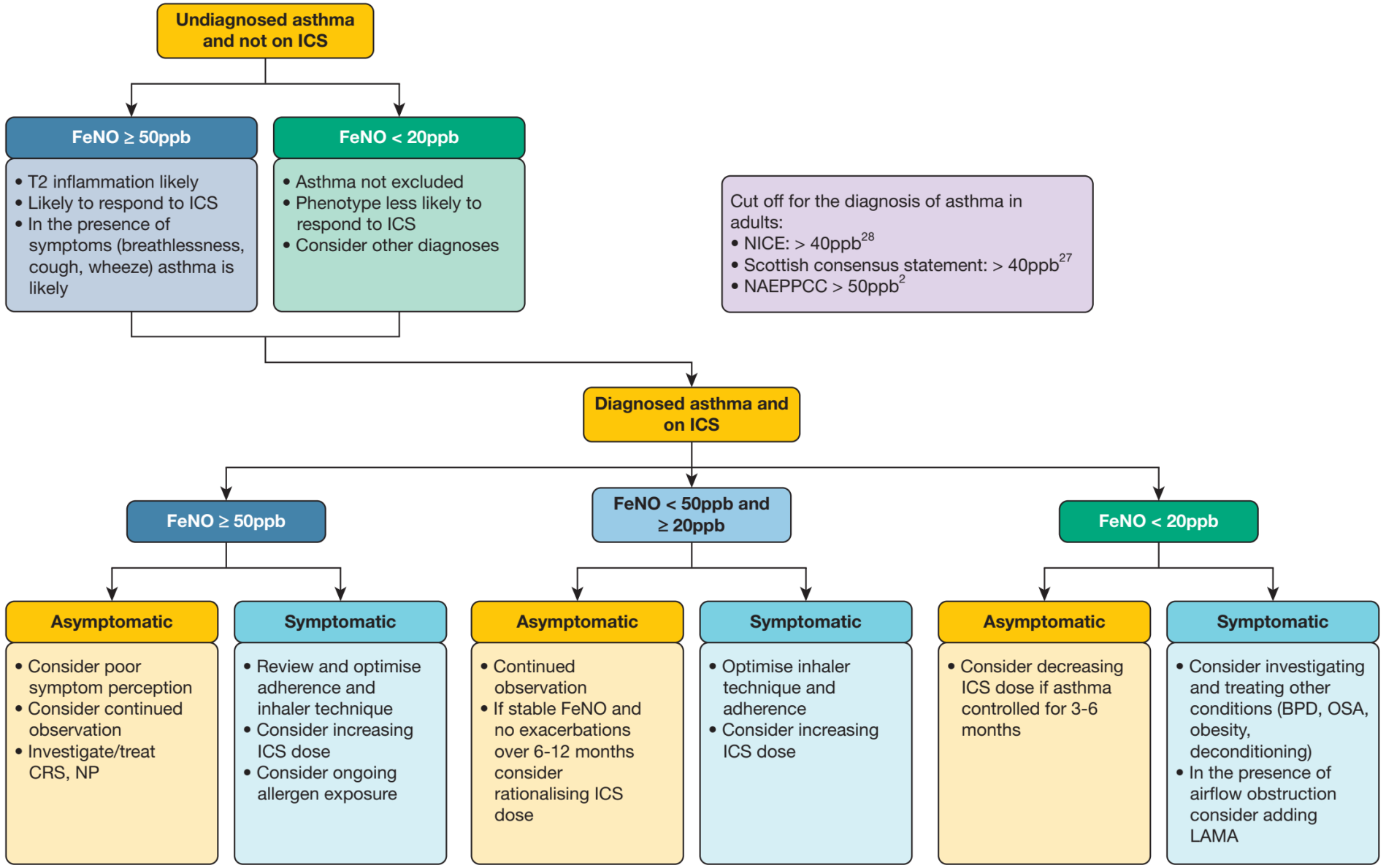
- Within the asthmatic airway, type 2 cytokine IL-4/13 upregulates inducible NO synthases
  → resulting in increased production of NO by airway epithelial and inflammatory cells

Index of eosinophilic airway inflammation



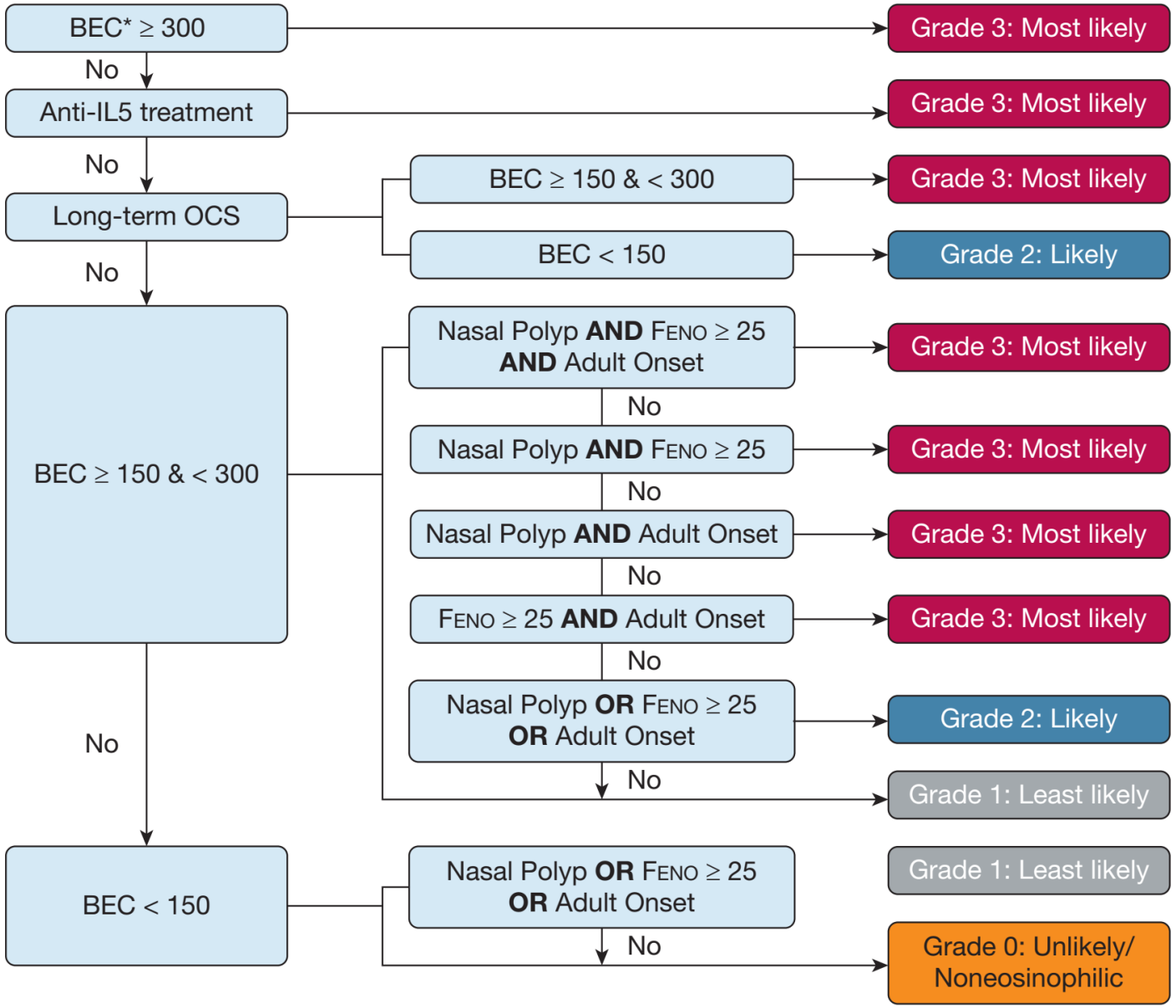
Lipworth B, et al. J Allergy Clin Immunol 2020;146(6):1281-1282.

Usefullness of FENO in diagnotic algorithm



Rupani H, et al. Chest 2022;161(4):906-917.

Eosinophilic and non-eosinophilic asthma



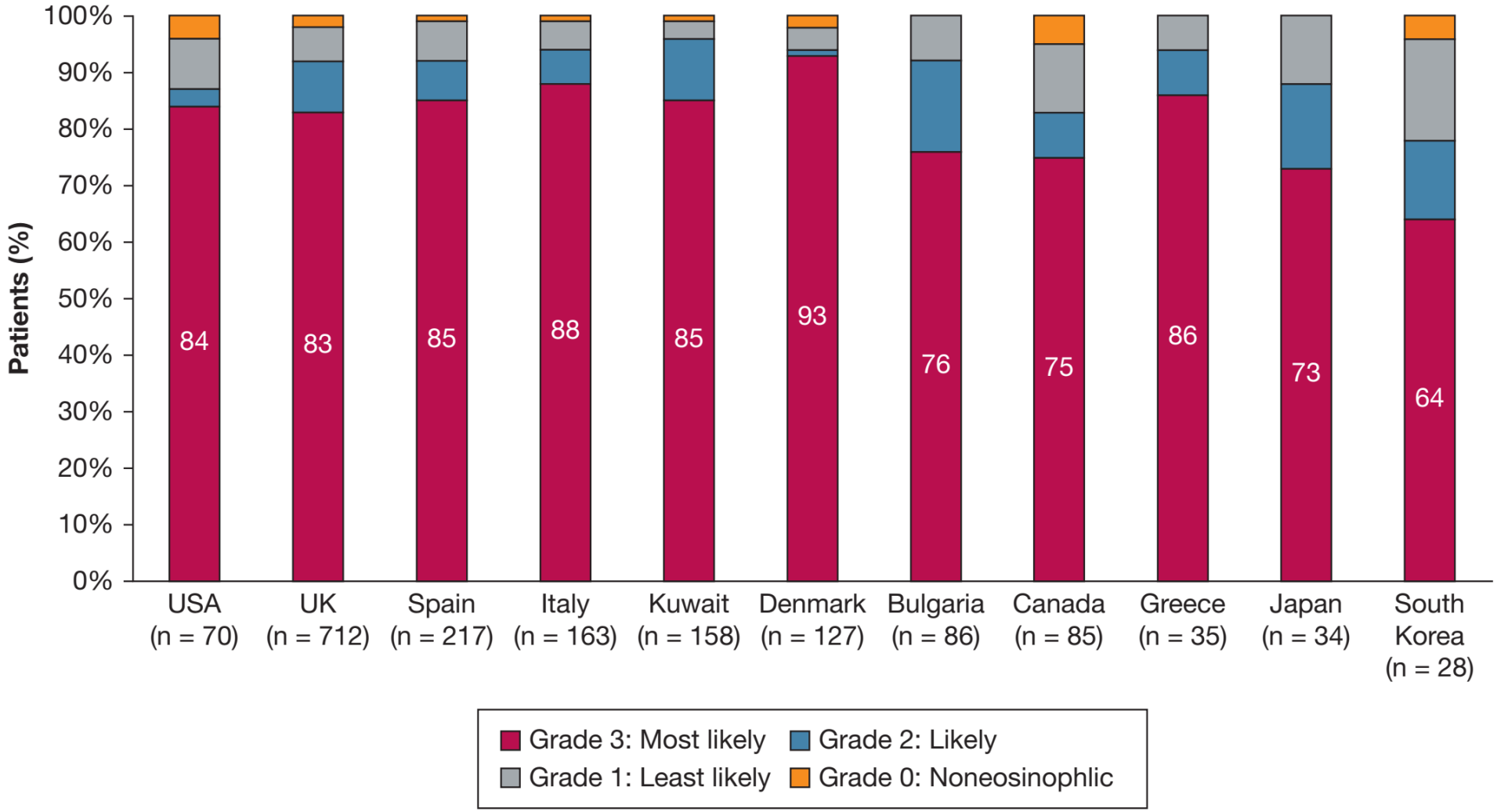
- 1,716 adult patients with severe asthma from 11 countries enrolled in the International Severe Asthma Registry (ISAR)

- **Eosinophilic phenotype**
  - ✓ Using a predefined eosinophil gradient algorithm

Heaney LG, et al. CHEST 2021;160(3):814-830.

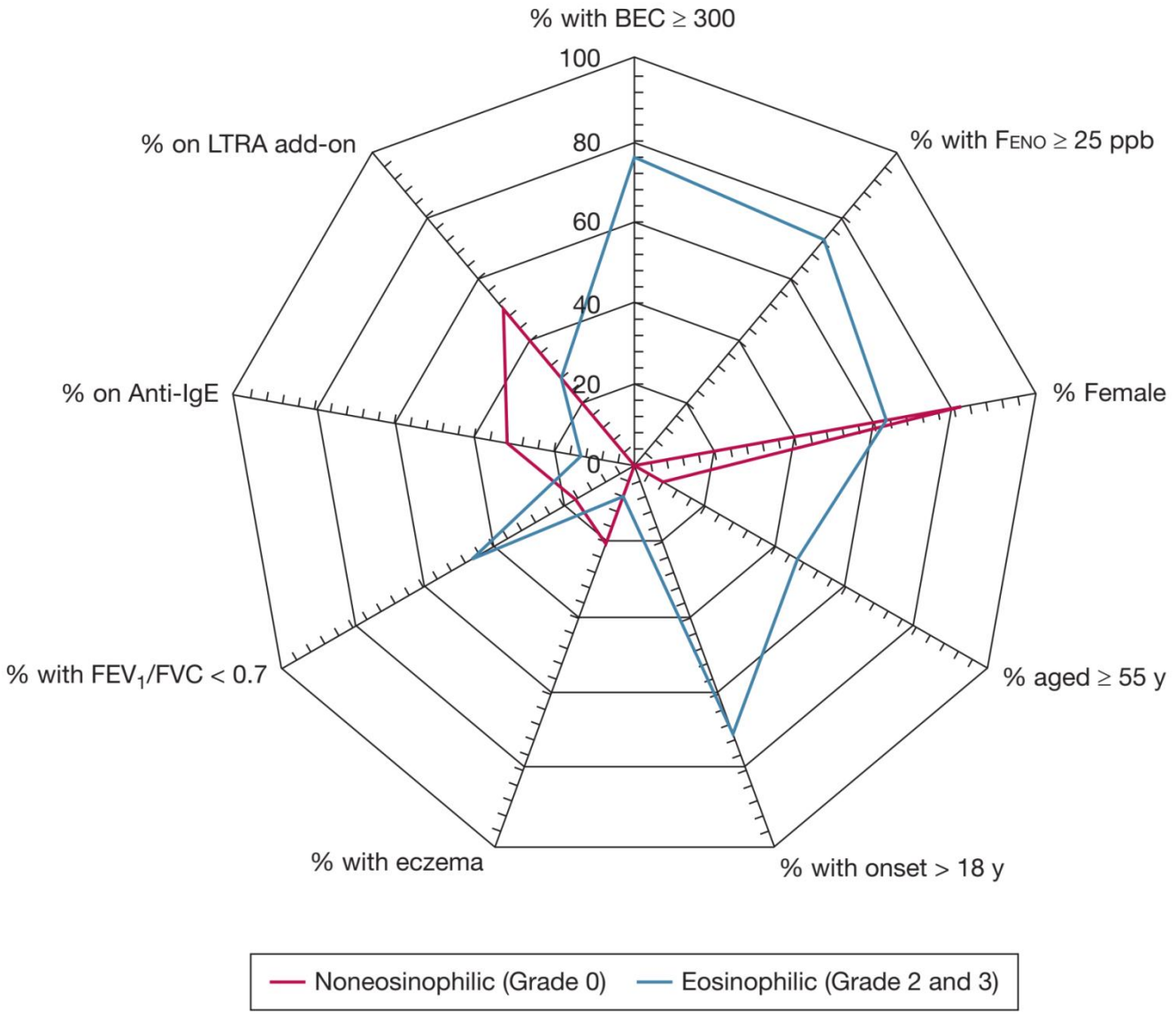
Phenotype distribution by country

- 83.8%, most likely had an eosinophilic phenotype



Heaney LG, et al. CHEST 2021;160(3):814-830.

Clinical and biomarker distribution according to phenotype



Heaney LG, et al. CHEST 2021;160(3):814-830.

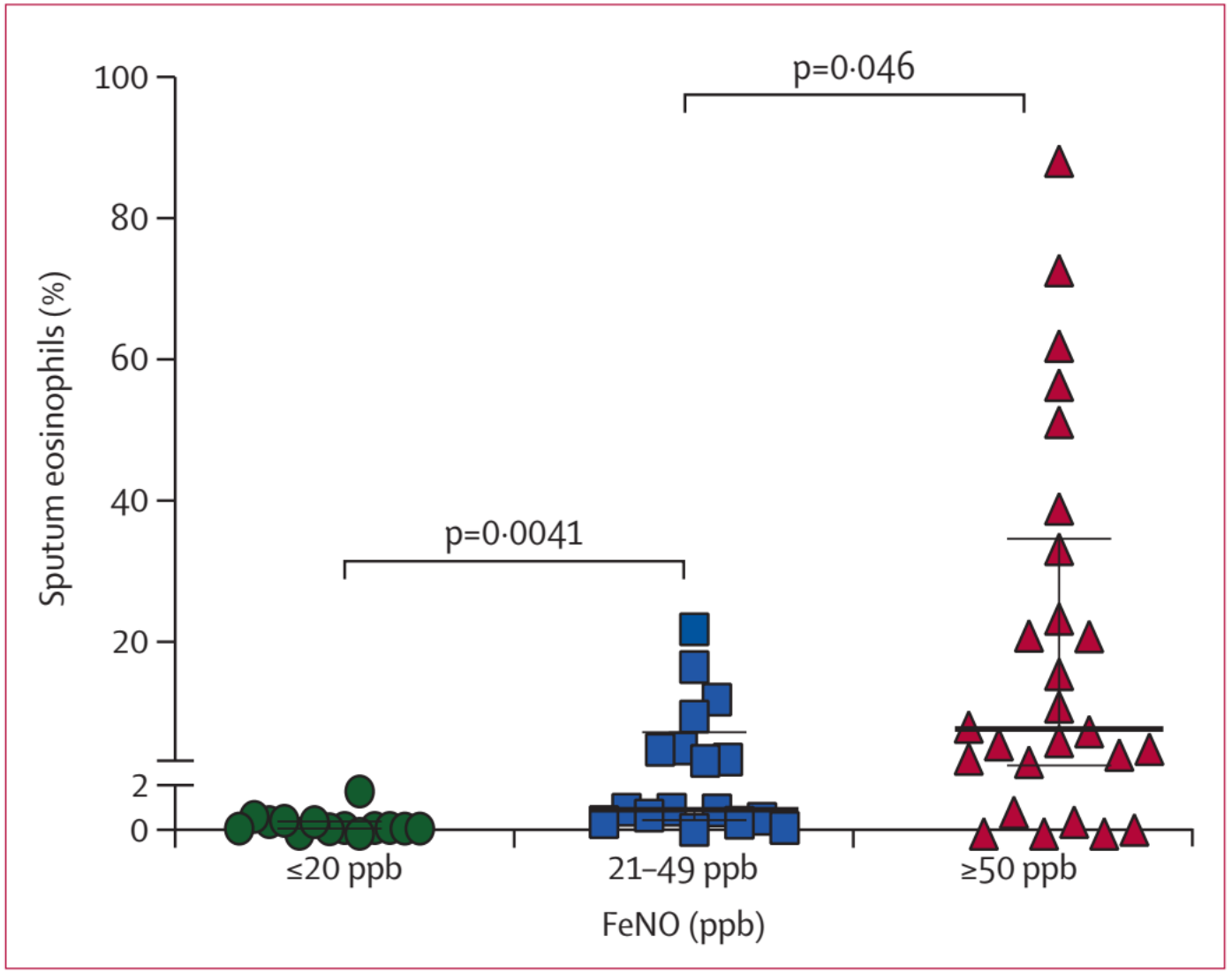
Inflammatory profile of exacerbation with mepolizumab

- 140 severe eosinophilic asthma patients of GINA step 4-5, MEX study
- Mepolizumab 100mg SC, q4wk, at least 3 months

	Low sputum eosinophil (<2%)	High sputum eosinophil (≥2%)	P-value
FeNO, ppb	24 (16.0-45.0)	57.0 (30.0-111.0)	0.0004
FEV1, %predicted	71.5% (21.4)	55.6% (15.3)	0.00075
FEV1/FVC	67.8 (9.0)	57.5 (13.5)	0.0043
Clinical diagnosis			0.040
Non-infective exacerbation	3 (12.5%)	10 (50%)	
Infective exacerbation	21 (87.5%)	8 (40%)	
Blood eosinophils, cells/uL	30 (10-50)	70 (50-90)	0.0009
C-reactive protein, mg/L	15.0 (5.0-24.0)	2.3 (1.5-4.9)	<0.0001
Sputum neutrophils, %	89.8 (71.6-94.9)	37.1 (28.6-544.2)	<0.0001
Sputum eosinophilis, %	0.4 (0.2-0.8)	10.4 (4.5-20.6)	<0.0001

McDowell PJ, et al. Lancet Respir Med 2021;9:1174-84.

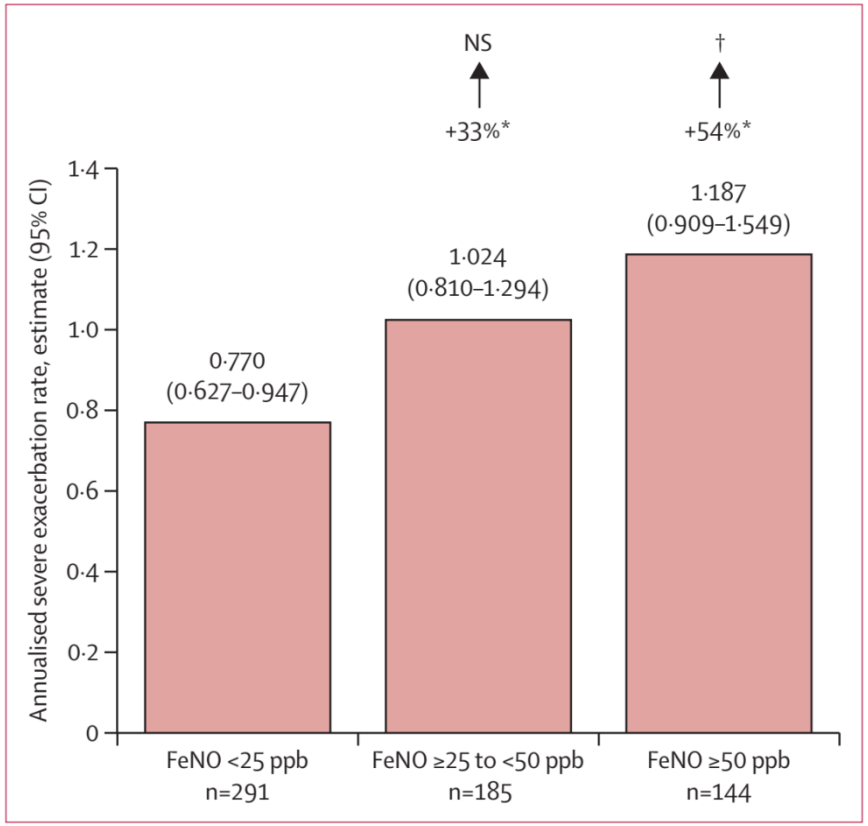
FENO as a predictor of sputum eosinophilia in exacerbation



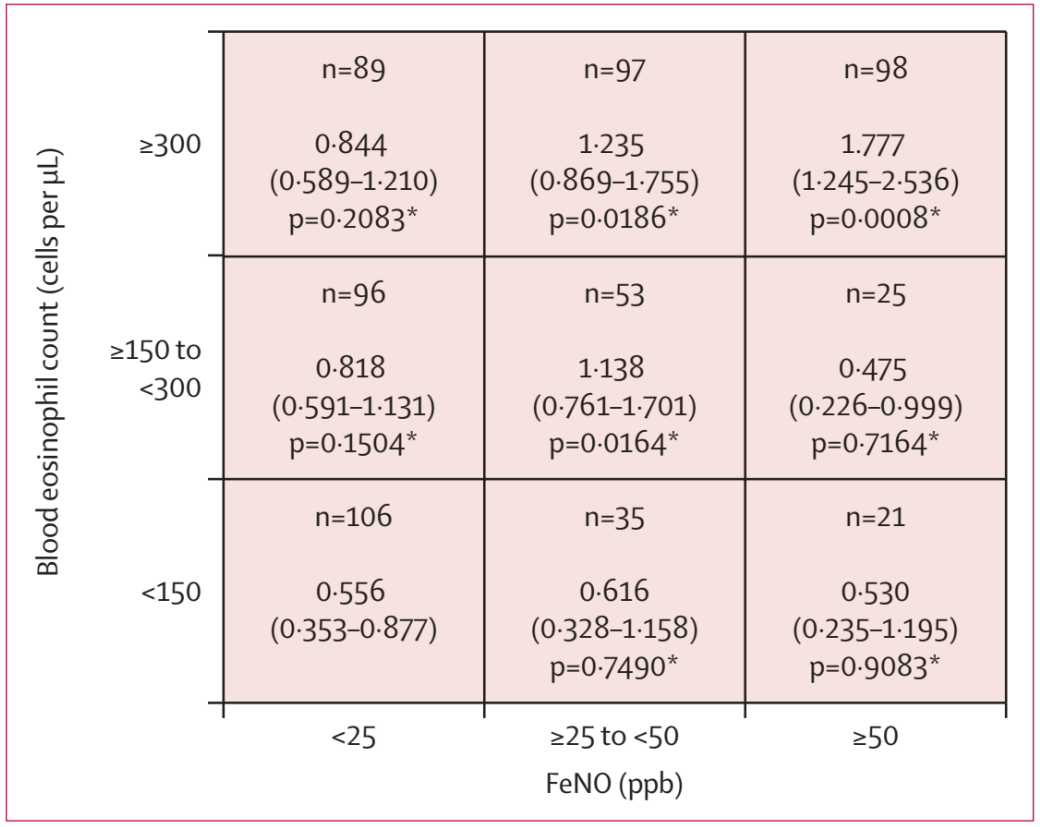
McDowell PJ, et al. Lancet Respir Med 2021;9:1174-84.

FENO as a prognostic biomarker

- Post-hoc analysis of phase 3 LIBERTY ASTHMA QUEST study
- 620 patients with uncontrolled moderate-to-severe asthma receving placebo, 52wk



Annualized severe exacerbation rate stratified by baseline FENO

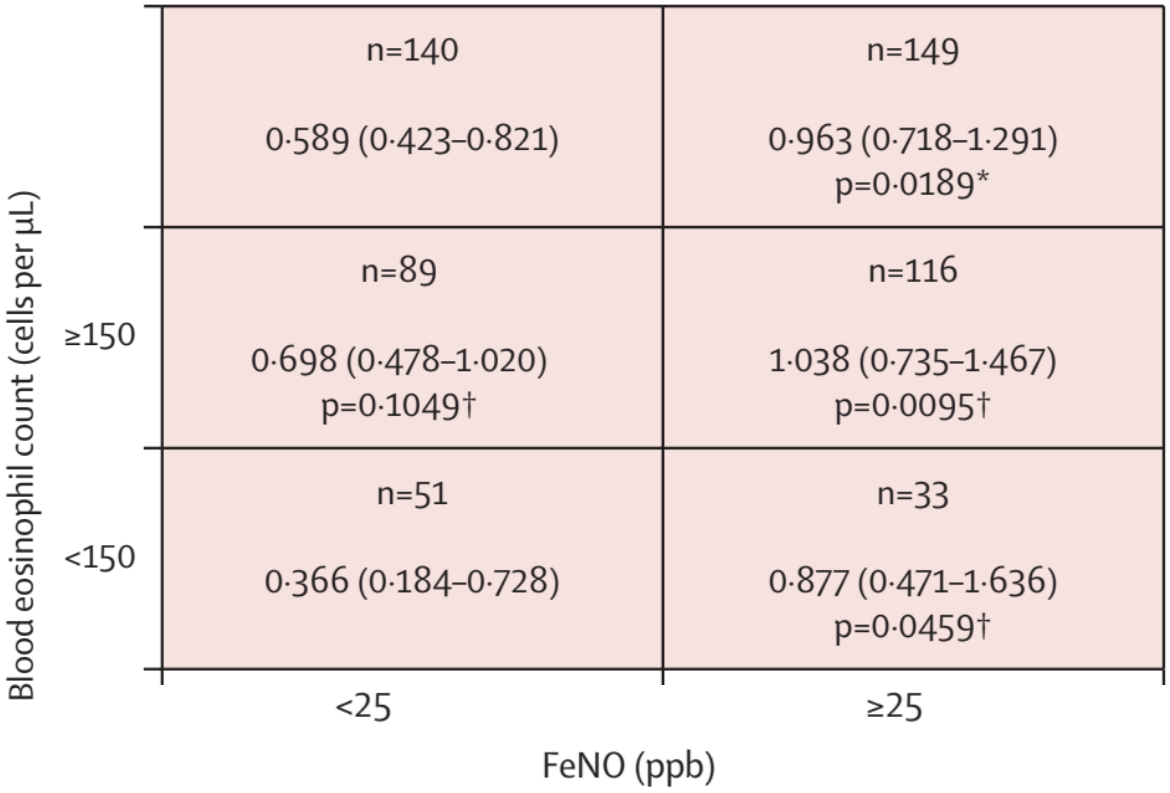


Annualized severe exacerbation rate stratified by baseline FENO and BEC

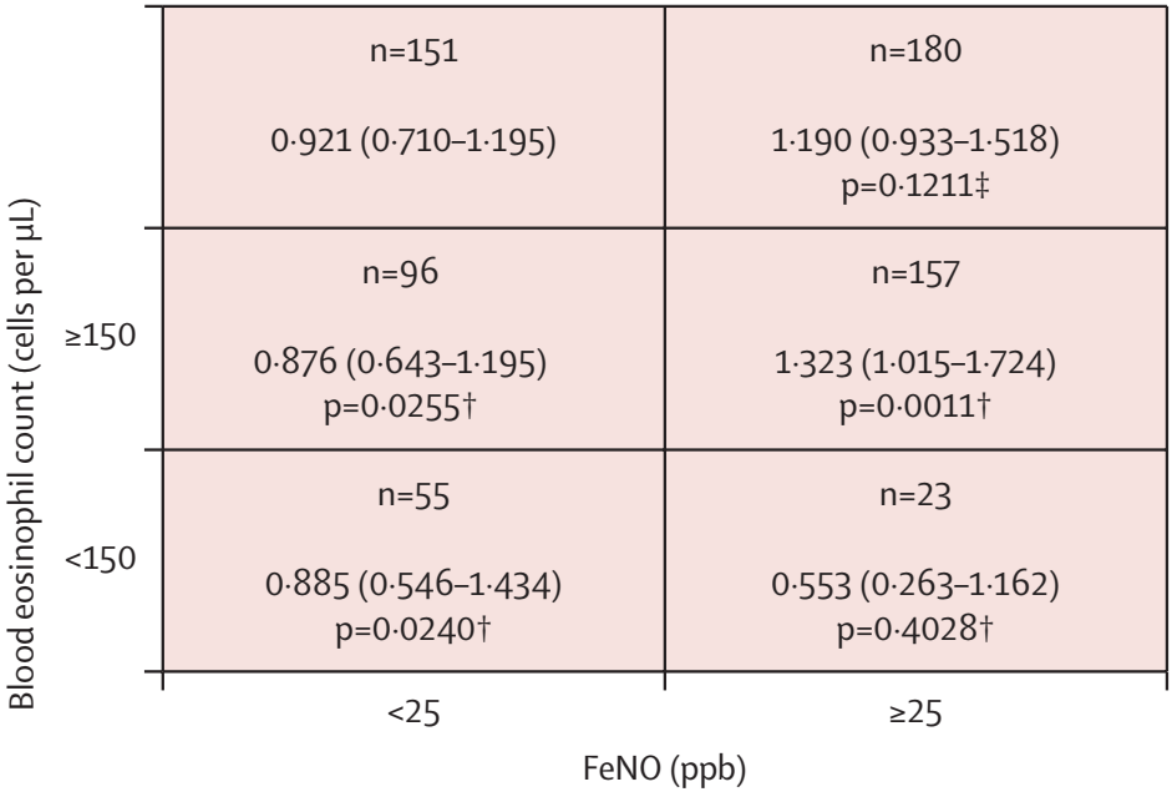
Busse WW, et al. Lancet Respir Med 2021;9:1165-73.

FENO as a prognostic biomarker

In patients with one prior exacerbation



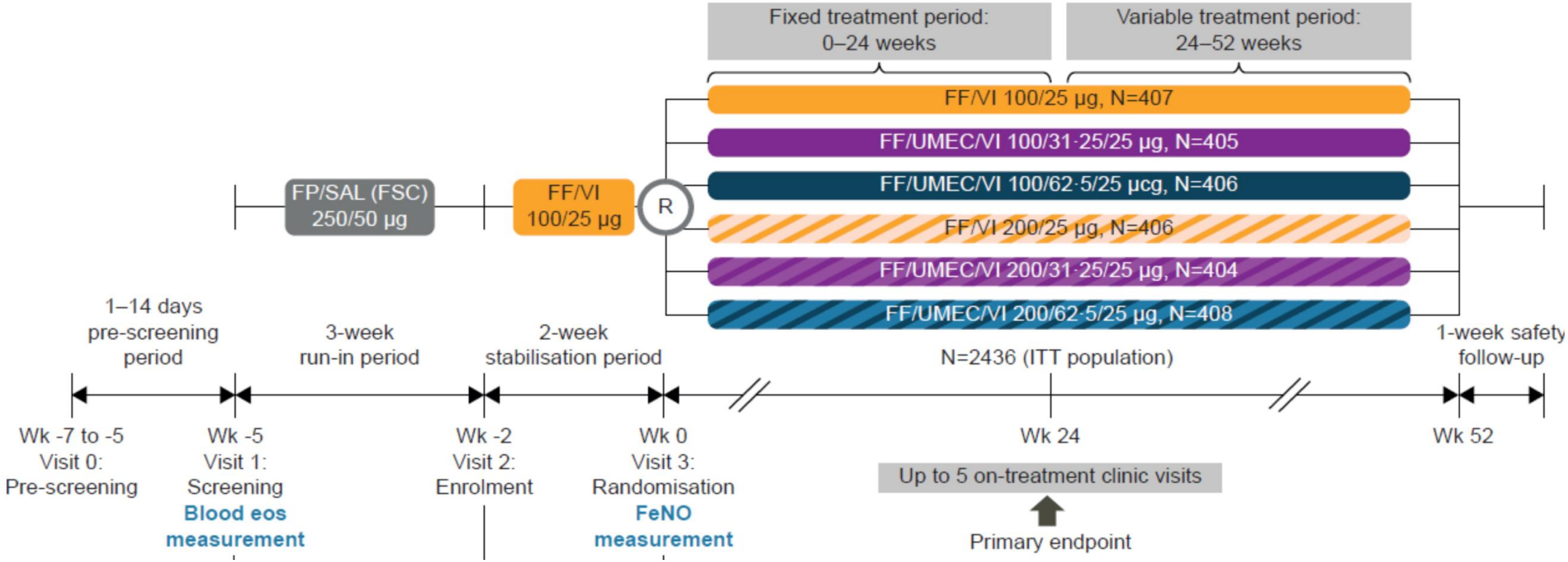
In patients with ≥ 2 prior exacerbation



Busse WW, et al. Lancet Respir Med 2021;9:1165-73.

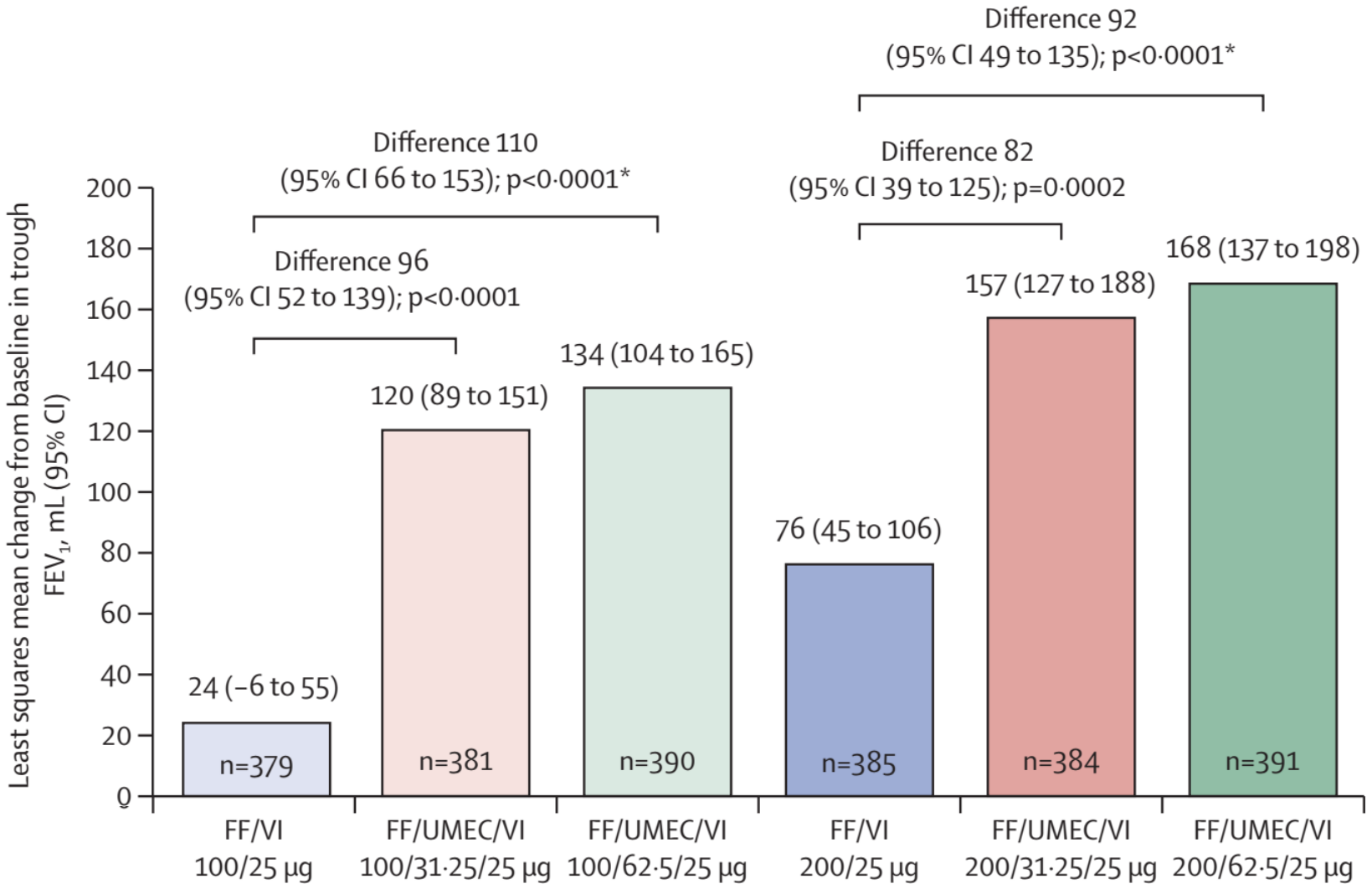
Once-daily single-inhaler triple therapy

- 2,439 patients with uncontrolled, moderate or severe asthma with ICS/LABA
- Fluticasone/umeclidinium/vilanterol (FF/UMEC/VI) vs. FF/VI, phase 2A study (CAPTAIN)
- via Ellipta DPI



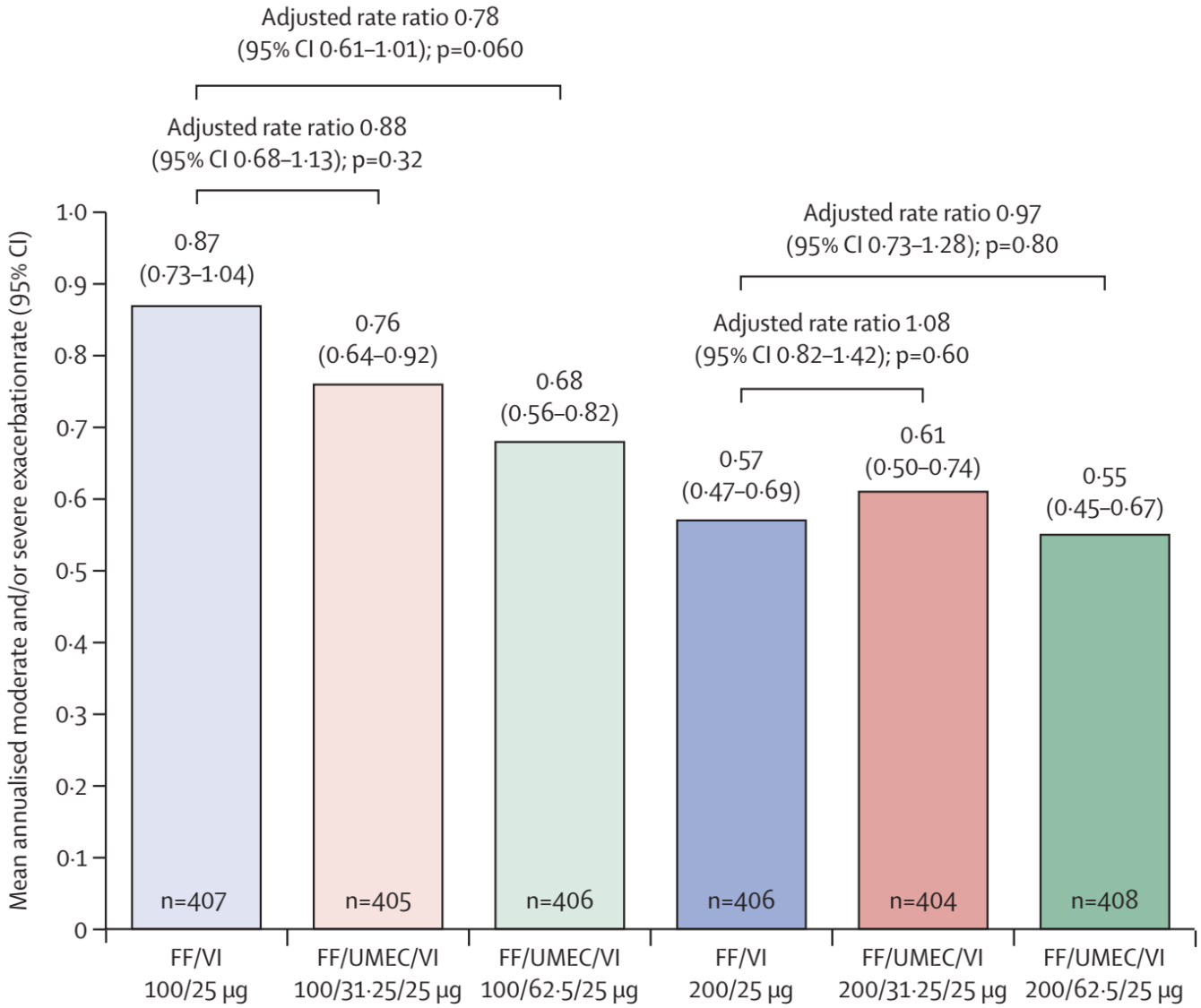
Lee LA, et al. Lancet Respir Med 2021;9:69-84.

Lung function improvement with triple therapy



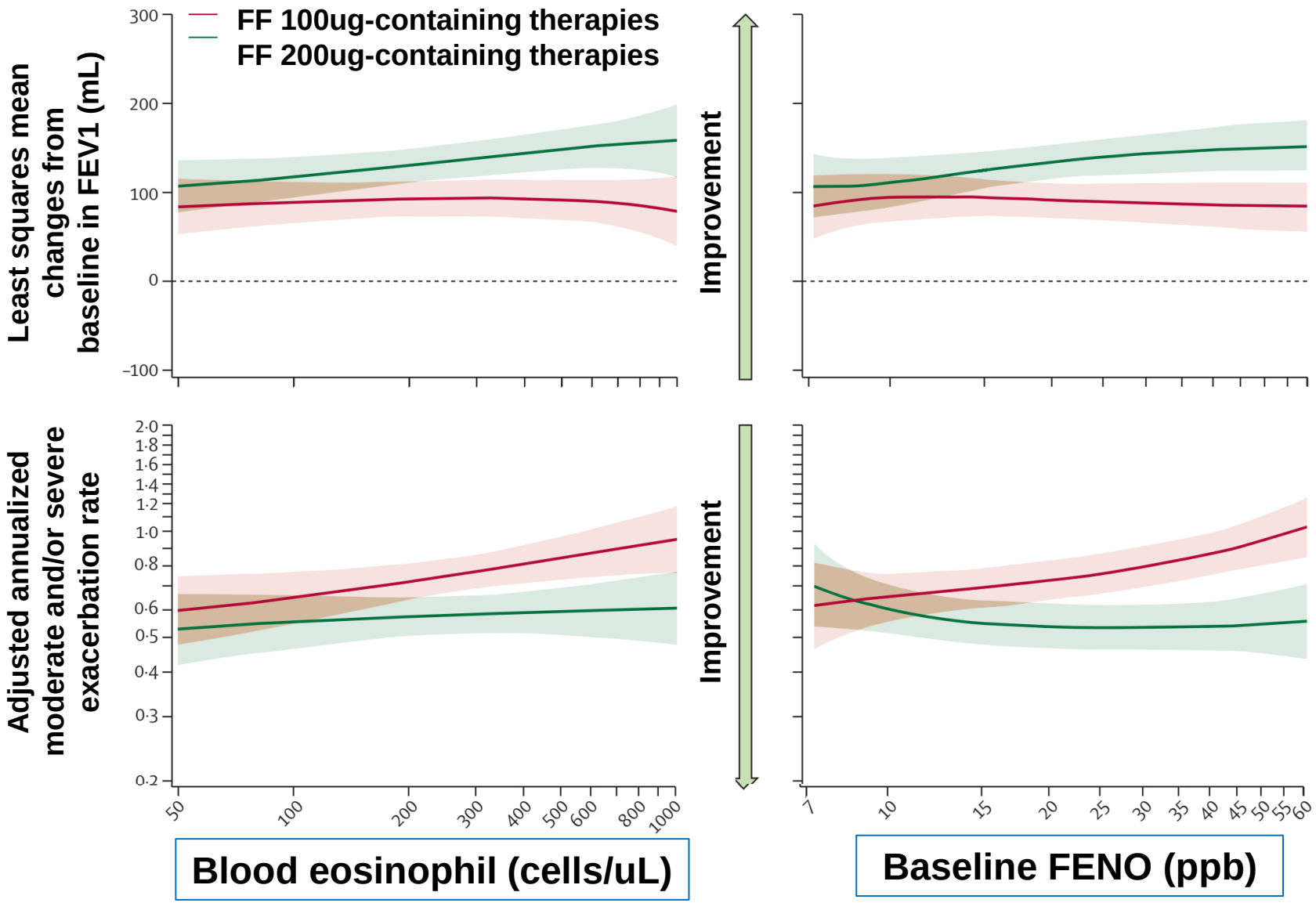
Lee LA, et al. Lancet Respir Med 2021;9:69-84.

Acute exacerbation with triple therapy



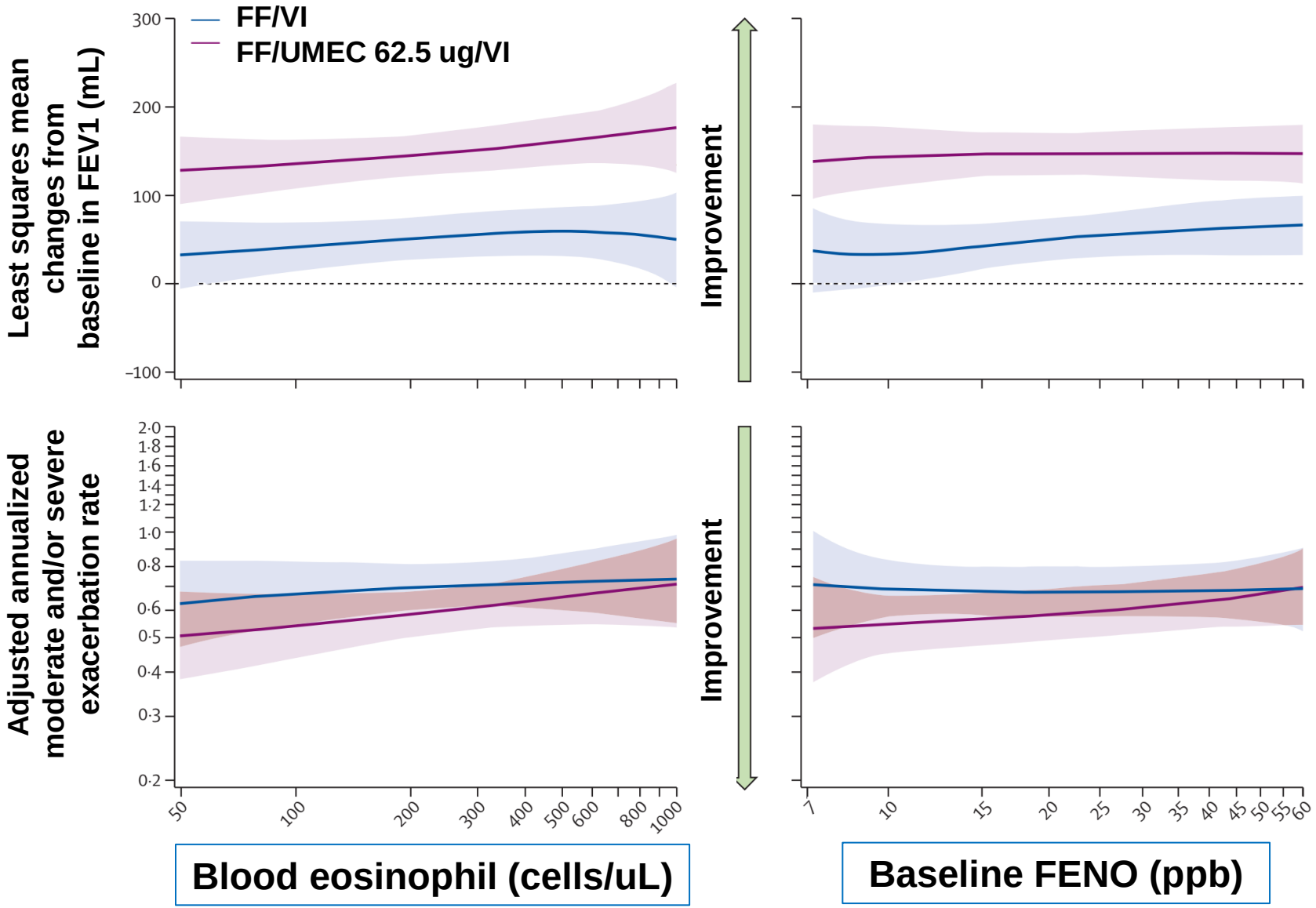
Lee LA, et al. Lancet Respir Med 2021;9:69-84.

Post-hoc analysis according to type 2 biomarker



Lee LA, et al. Lancet Respir Med 2021;9:69-84.

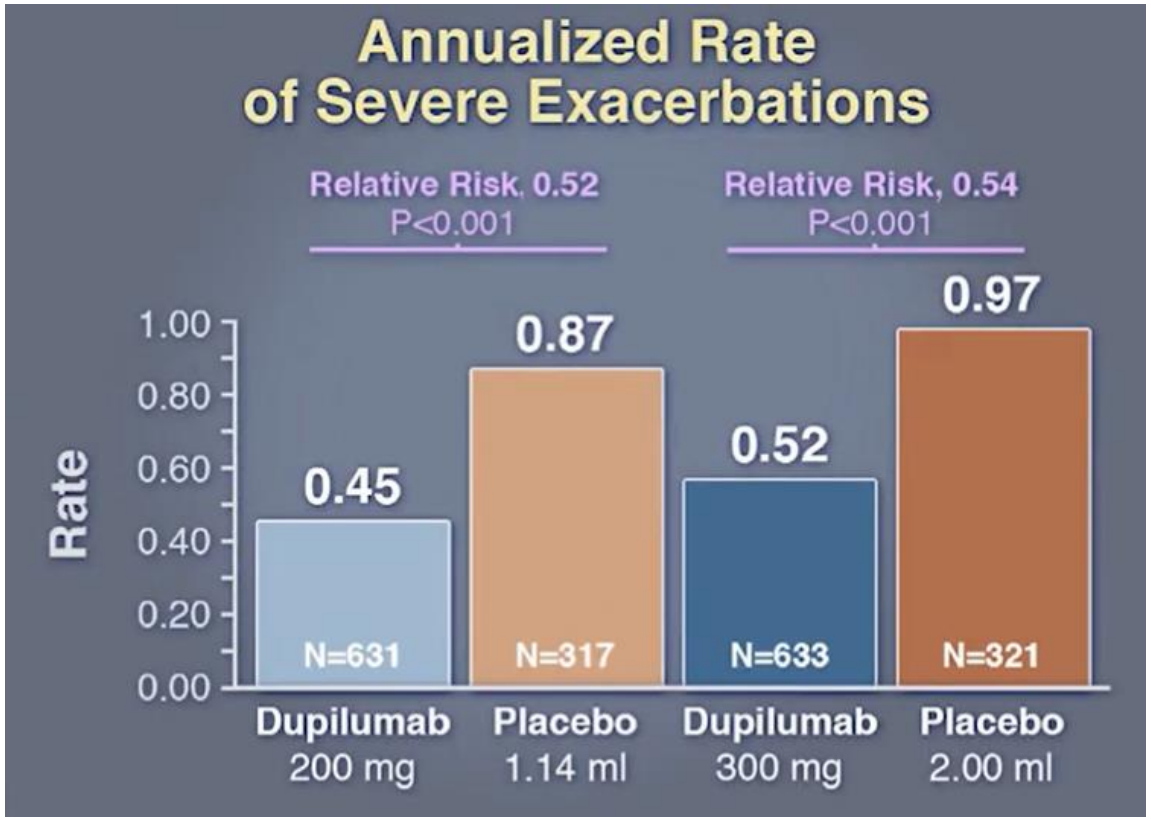
Post-hoc analysis according to type 2 biomarker

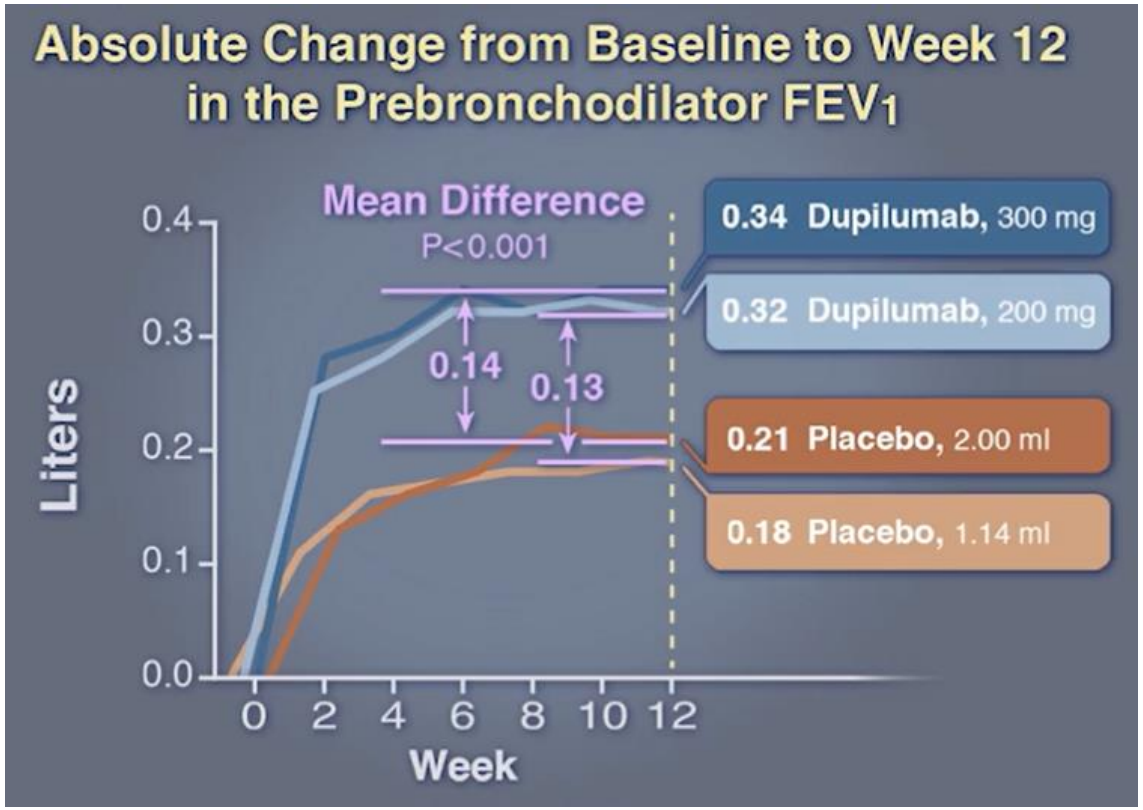


Lee LA, et al. Lancet Respir Med 2021;9:69-84.

Dupilumab in uncontrolled asthma

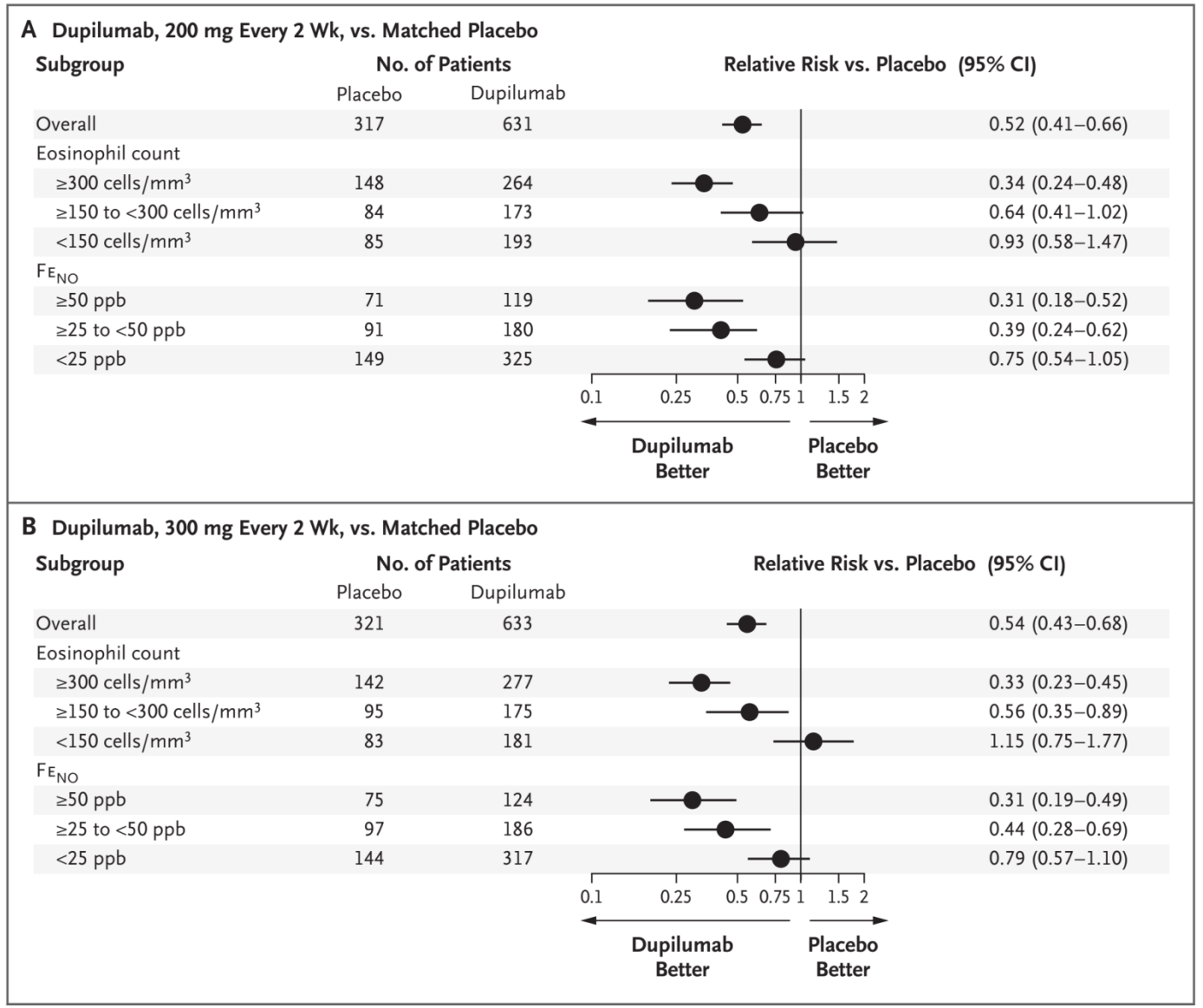
- 1,902 patients with moderate-to-severe asthma, refractory to maximized standard-of-care controller therapy, phase 3 LIBERTY ASTHMA QUEST study
- Dupilumab 200mg vs. 300mg vs. matched placebo, SC, q2wk, 52wk





Castro MJ, et al. N Engl J Med 2018;378(26):2486-96.

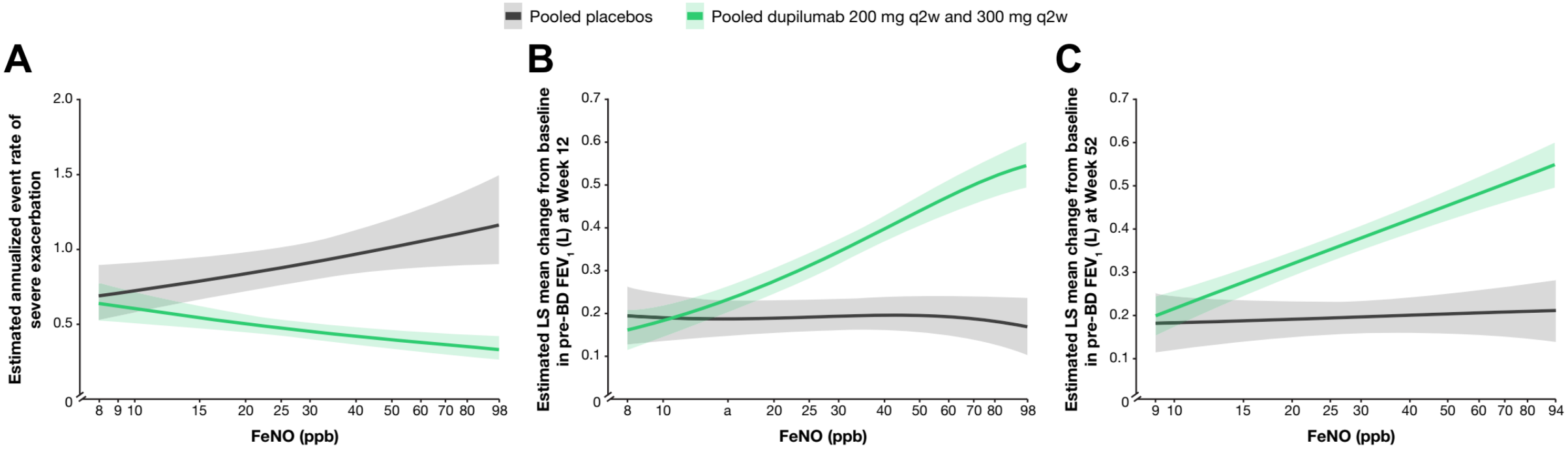
Dupilumab according to type 2-high phenotype



Castro MJ, et al. N Engl J Med 2018;378(26):2486-96.

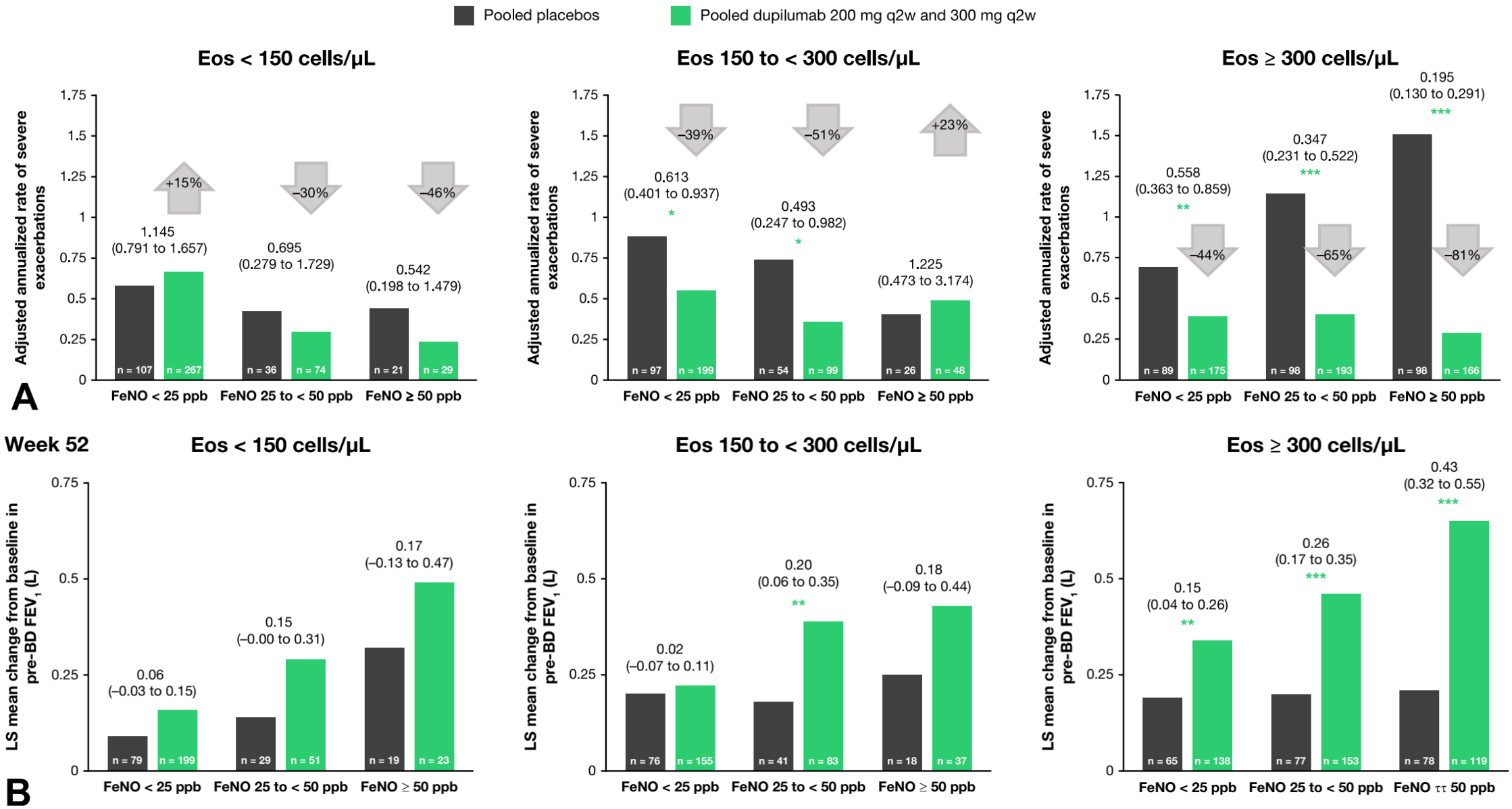
Effect of dupilumab according to baseline FENO

- Post-hoc analysis of LIBERTY ASTHMA QUEST
- Relationship to baseline FENO, adjusted for eosinophils and other clinical characteristics



Pavord ID, et al. J Allergy Clin Immunol Pract 2023;11:1213-20.

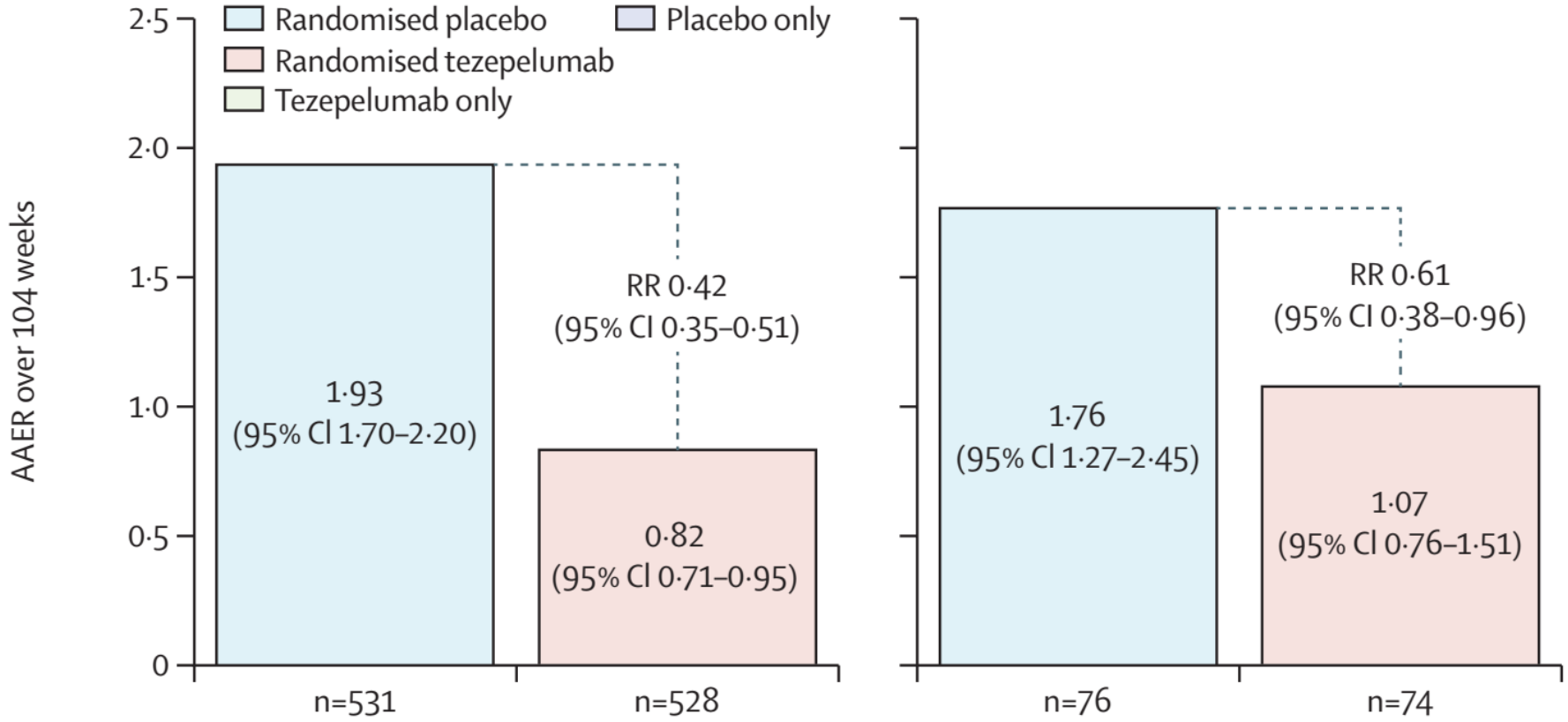
Effect of dupilumab according to baseline FENO



Pavord ID, et al. J Allergy Clin Immunol Pract 2023;11:1213-20.

Long-term efficacy of tezepelumab in severe uncontrolled asthma

- Severe uncontrolled asthma patients, 12-80 years, medium-to-high does ICS with ≥1 additional asthma controller with or without OCS, DESTINATION
- Recruited from NAVIGATOR(52-wk)/SOURCE(48-wk), till 104 weeks

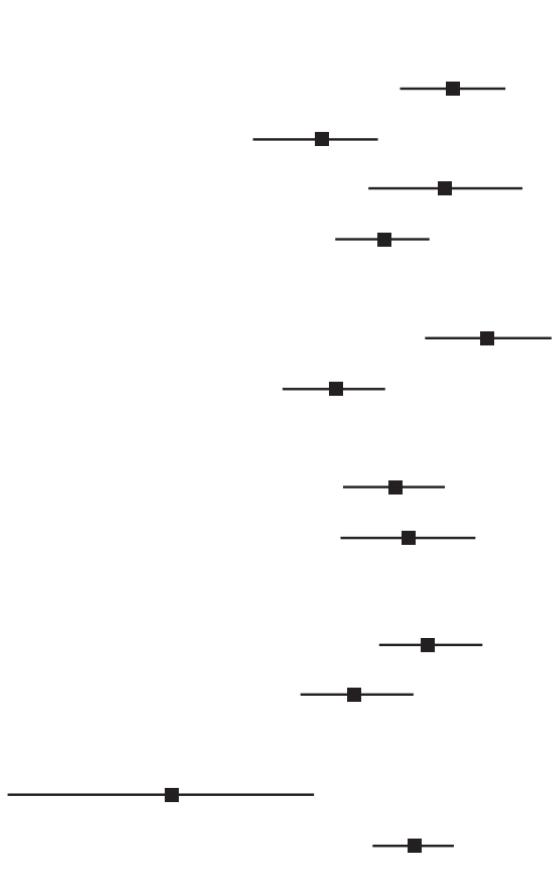


*AAER=annualized asthma exacerbation rate

Mezies-Gow A, et al. Lancet Respir Med 2023;11:425-38.

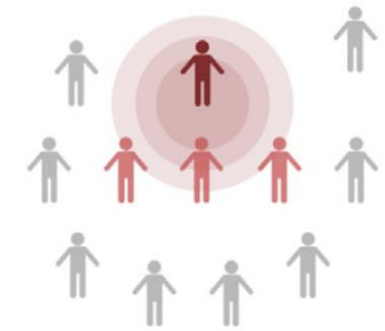
Long-term efficacy of tezepelumab: sub-group analysis

	Randomised tezepelumab n/estimate	Randomised placebo n/estimate	Rate ratio (95% CI)
Baseline blood eosinophil count			
<300 cells per µL	309/0·88	309/1·60	0·55 (0·44–0·70)
≥300 cells per µL	219/0·73	222/2·46	0·30 (0·22–0·39)
<150 cells per µL	138/0·82	138/1·55	0·53 (0·37–0·76)
≥150 cells per µL	390/0·82	393/2·08	0·40 (0·32–0·49)
Baseline FeNO level			
<25 ppb	213/0·90	220/1·40	0·64 (0·48–0·86)
≥25 ppb	309/0·75	307/2·37	0·32 (0·25–0·40)
Allergy status			
FEIA positive for any perennial aeroallergen	339/0·77	341/1·84	0·42 (0·33–0·53)
FEIA negative for all perennial aeroallergens	184/0·94	177/2·09	0·45 (0·33–0·61)
Number of asthma exacerbations in the year before study entry			
≤2	310/0·61	325/1·23	0·49 (0·39–0·63)
>2	218/1·10	206/1·11	0·35 (0·27–0·46)
Nasal polyps in the 2 years before randomisation			
Yes	42/0·39	41/2·65	0·15 (0·07–0·29)
No	486/0·86	490/1·88	0·46 (0·38–0·55)



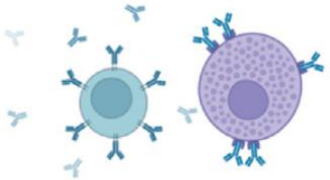
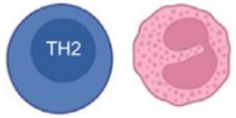
Mezies-Gow A, et al. Lancet Respir Med 2023;11:425-38.

Selection of biomarker to select biological therapies



Adults and children with poorly controlled asthma

40%-60% patients with asthma

Inflammatory pathway	Diagnostic biomarkers	Biological	Treatment responses
 Allergen-mediated B cells/mast cells	Total IgE > 30-150 IU/mL	Omalizumab	IgE bound < Exacerbations ± FEV_1
 IL-4/IL-5/IL-5ra TH2 cells/eosinophils	Blood eosinophils ≥ 300 cells/µL	Mepolizumab Reslizumab Benralizumab	Lower Eos < Exacerbations ± FEV_1
 IL-4/IL-5/IL-13 TH2 cells/eosinophils/ mast cells	FeNO > 15 ppb ± Blood eos count *(independent predictors)*	Dupilumab	Lower FeNO Higher Eos Lower IgE < Exacerbations higher FEV_1
 TSLP dendritic/epithelial cells	FEV_1 < 80% irrespective of type-2 markers	Tezepelumab	Lower FeNO Lower Eos Lower IgE < Exacerbations higher FEV_1

Alving K, et al. J Allergy Clin Immunol Pract 2023;11;1221-3.

Type 2 biomarker strategy for steroid dose adjustment

- 301 patients with severe asthma (GINA 4 and 5) and FENO <45ppb, q8wk, 48wk
- Composite type-2 biomarker strategy (n=240) vs. symptom-risk-based algorithm (n=61)

Composite biomarker scoring system

	0	1	2
FENO, ppb	<15	≥15–29	≥30
Blood eosinophil count, n/μL	<150	≥150–299	≥300
Periostin, ng/mL	<45	≥45–54	≥55

Symptom-risk-based treatment adjustment

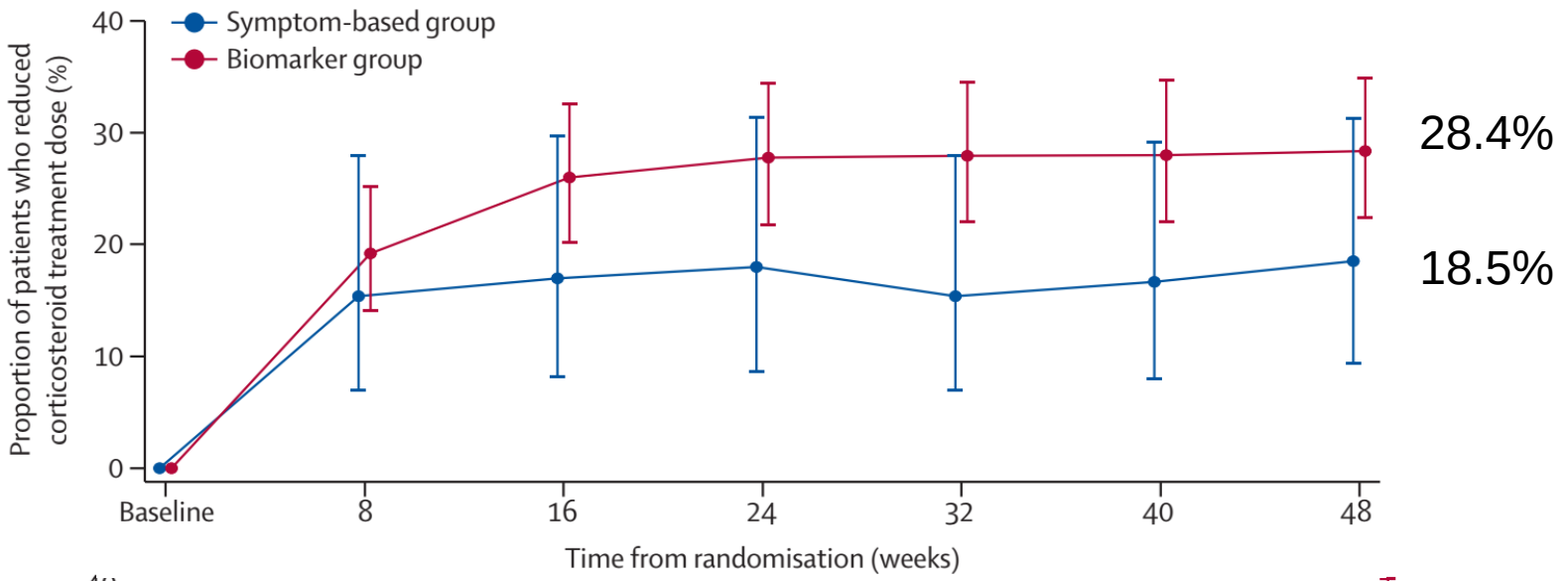
	Score
ACQ-7 ≥1·5 and ≥1 change from baseline score or a severe exacerbation since last study visit (previous 8 weeks at baseline randomisation visit)	2
ACQ-7 is 1·0 to <1·5 or ACQ-7 ≥1·5 and <1 change from baseline score AND no severe exacerbation since last study visit (previous 8 weeks at baseline randomisation visit)	1
ACQ-7 <1·0 and no severe exacerbation since last study visit (previous 8 weeks at baseline randomisation visit)	0

* Treatment advice
0 → Reduction
1 → Maintenance
2 → Increase

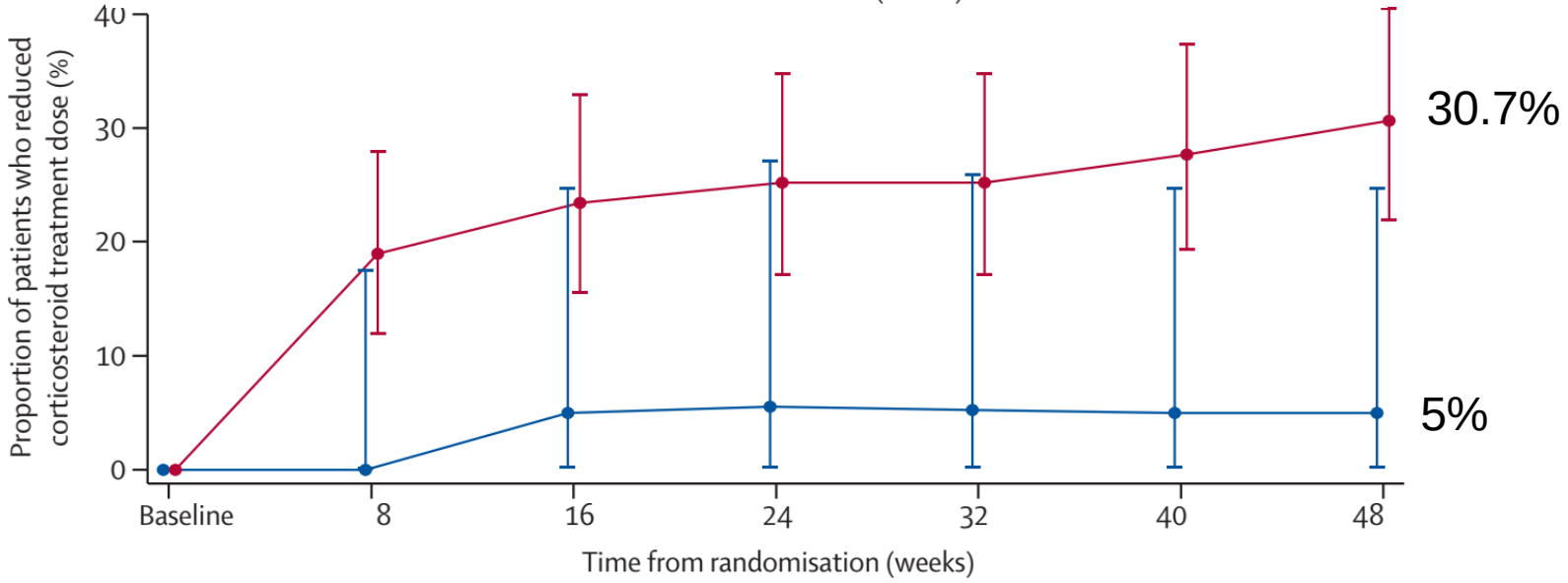
Heaney LG, et al. Lancet Repir Med 2021;9:57-68.

Steroid reduction with type 2 biomarker strategy

ITT population



PP population

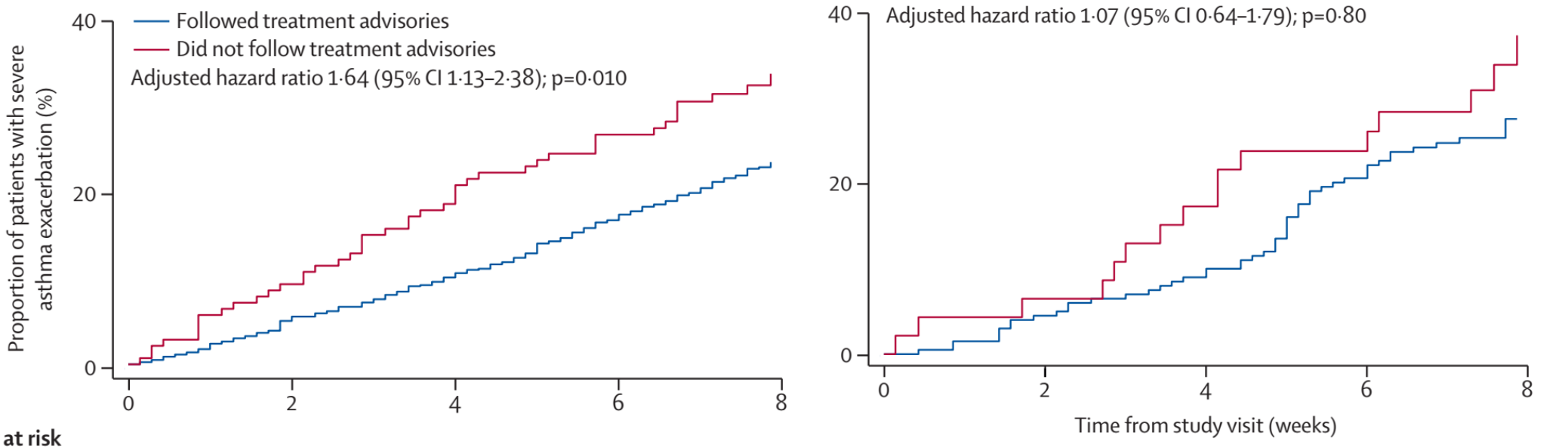


Heaney LG, et al. Lancet Repir Med 2021;9:57-68.

Asthma exacerbation in type 2 biomarker strategy

Biomarker strategy group

Symptom-based strategy group



Number at risk (number censored)										
Followed treatment advisories	790	750 (0)	705 (5)	636 (22)	0 (611)	199	190 (0)	180 (1)	155 (3)	0 (146)
Did not follow treatment advisories	139	126 (0)	111 (2)	97 (5)	0 (94)	46	43 (0)	38 (0)	33 (2)	0 (30)

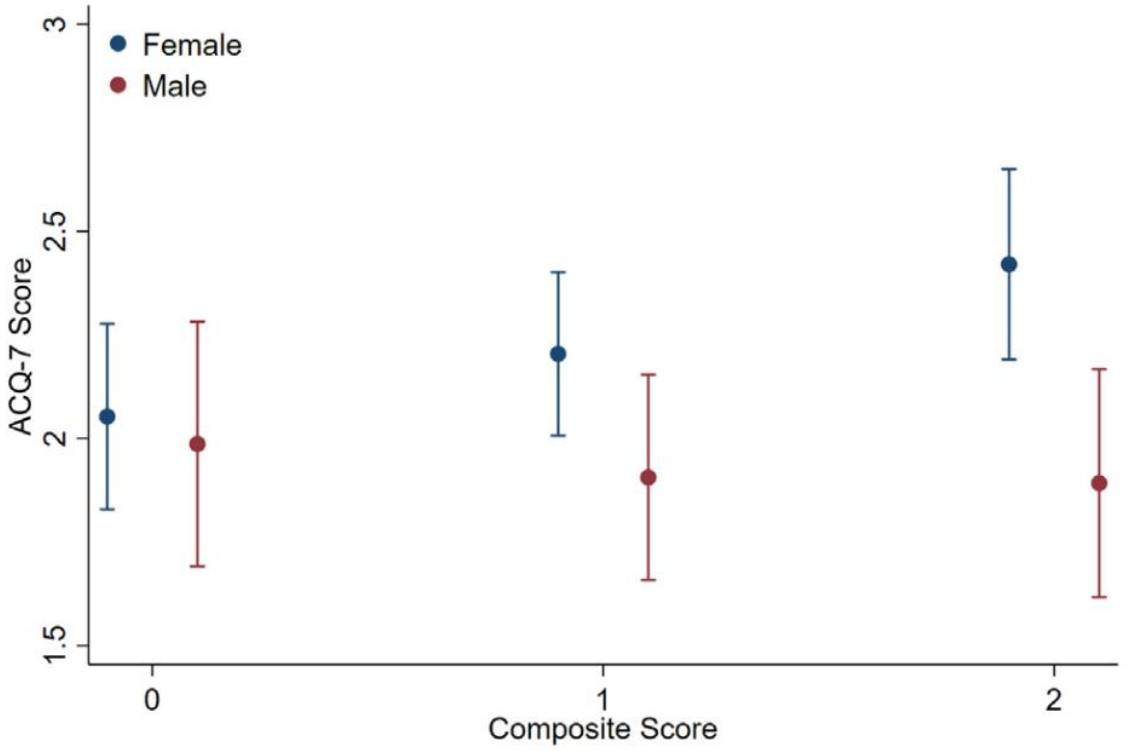
Heaney LG, et al. Lancet Repir Med 2021;9:57-68.

Biomarker and symptom concordance according to sex

- Symptom high/T2-biomarker low → more female (22.8% vs 15.6%; P = 0.0002)
- Symptom low/T2-biomarker high → more males (22.3% vs 11.4%; P < 0.0001)

TABLE III. Biomarker and symptom concordance in males and females by composite scores*

Sex	Biomarkers		
Females	Score 0	Score 1	Score 2
Symptoms			
Score 0	31 (2.6%)	*109 (9.1%)*	*28 (2.3%)*
Score 1	131 (11.0%)	467 (39.1%)	101 (8.5%)
Score 2	**76 (6.4%)**	**196 (16.4%)**	54 (4.5%)
Males	Score 0	Score 1	Score 2
Symptoms			
Score 0	22 (3.4%)	*93 (14.3%)*	*52 (8.0%)*
Score 1	50 (7.7%)	230 (35.4%)	82 (12.6%)
Score 2	**29 (4.5%)**	**72 (11.1%)**	20 (3.1%)%)



Eastwod MC, et al. J Allergy Clin Immunol Pract 2023;11:1233-42.

Summary

- **IOS**
  - ✓ Basic principal of IOS test
  - ✓ Association with asthma severity, control and exacerbation
  - ✓ Additional role of IOS to spirometry
  - ✓ MICD
  - ✓ Pitfall:

- **FENO**
  - ✓ Asthma phenotype
  - ✓ Prognostic biomarker
  - ✓ Prediction of treatment response: inhaler, biologics
  - ✓ Index for adjustment of maintenance treatment

Thank You for Your Attention